Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP)

Draft for Public Comment

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Agency for Toxic Substances and Disease Registry

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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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the 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 toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, 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 the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; 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. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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 is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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Centers for Disease Control and Prevention

VERSION HISTORY

Date	Description
December 2019	Draft for public comment toxicological profile released
September 2002	Final toxicological profile released
April 1993	Final toxicological profile released
June 1989	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Di(2-ethylhexyl)phthalate, commonly referred to as DEHP, is not found naturally in the environment. Approximately 97% of commercial DEHP is used as a plasticizer in the production of flexible polyvinyl chloride (PVC) products (CPSC 2010). Because DEHP is used in PVC, it is present in many common items such as wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, toys, shoes, automobile upholstery and tops, packaging film and sheets, sheathing for wire and cable, medical tubing, and blood storage bags. It has been detected in children's products such as pacifiers at levels of up to 42% by weight (Lay and Miller 1987); however, the U.S. Congress banned many that contain DEHP at levels >0.1% by weight (CPSIA 2008). DEHP also has nonplasticizer uses, and has been reported in several other consumer products, such as cosmetics, lubrication oil, and paint (CPSC 2010; Mannsville Chemical Products Corporation 1990; NTP 1989). Because of concerns regarding potential health effects from DEHP exposure, many manufacturers have discontinued use of DEHP in their products. For instance, the use of DEHP has been discontinued in domestically produced baby teethers, rattles, and food packaging (CDC 2016; CPSC 1999; Wilkinson and Lamb 1999). In 2008, Congress permanently banned DEHP in any amount >0.1% in children's toys and certain child care articles, such as those to help sleeping, feeding, sucking, or teething of children ≤3 years old (CPSIA 2008).

DEHP is a widely-used chemical that enters the environment predominantly through disposal of industrial and municipal wastes in landfills. To a much lesser extent, it is volatized into air (from industrial and end uses of DEHP), carried in wastewater from industrial sources, and in effluent from municipal wastewater treatment plants (Bauer and Herrmann 1997; Clara et al. 2010; EPA 1981). It tends to sorb strongly to soils and sediments and to bioconcentrate in aquatic organisms (Staples et al. 1997; Wolfe et al. 1980a); however, potential for DEHP to biomagnify in the food chain is expected to be minimized by metabolism (EPA 1979; Johnson et al. 1977; Mackintosh et al. 2004; Staples et al. 1997; Wofford et al. 1981). Biodegradation can occur under aerobic conditions (Sugatt et al. 1984). Sorption, bioaccumulation, and biodegradation are likely to be competing processes, with the dominant fate determined by local environmental conditions. DEHP is found at low levels (<5 ng/m^3) in ambient air (Eisenreich et al. 1981; Ligocki et al. 1985a). It is very difficult to determine these low levels accurately since DEHP is ubiquitously present in laboratory equipment, potentially leading to false identification of elevated phthalate concentrations due to sample contamination (Howard et al. 1985).

1. RELEVANCE TO PUBLIC HEALTH

The principal route of human exposure to DEHP is oral. In adults and children, ingestion of food (including food from containers that leach DEHP) accounts for approximately 95% of total oral exposure, with the remaining exposure attributed to dust ingestion (Clark et al. 2011). In toddlers and infants, ingestion of food and dust particles containing DEHP have approximately equal contributions to total oral DEHP intake (Clark et al. 2011). Occupational exposures may be significant in some settings. For all age groups, the highest exposures to DEHP result from medical procedures such as blood transfusions (upper bound limit of 8.5 mg/kg/day) or hemodialysis (upper bound limit of 0.36 mg/kg/day), during which DEHP may leach from plastic equipment directly into the blood (FDA 2001). Exposures of neonatal children to DEHP can be especially high as a result of some medical procedures (Doull et al. 1999; FDA 2001; Huber et al. 1996). For example, upper-bound doses of DEHP have been estimated to be as high as 2.5 mg/kg/day during total parenteral nutrition (TPN) administration and 14 mg/kg/day during extracorporeal membrane oxygenation (ECMO) procedures (FDA 2001). These historical values may not apply to current exposures.

People residing near hazardous waste disposal sites or municipal landfills may be subject to higher than average levels of DEHP in ambient air and drinking water (Thurén and Larsson 1990). Even so, the concentrations of DEHP in these media will be greatly limited by the low volatility and water solubility of DEHP, and subpopulations living in the vicinity of hazardous waste sites are exposed to levels much lower than those exposed to DEHP during medical procedures.

Changes in use patterns and restrictions on the use of DEHP in children's products, such as the Consumer Protection Safety Act (CPSA) of 2008, have likely changed human exposure patterns to DEHP over the past 20 years (CPSIA 2008; Wilkinson and Lamb 1999). In support, the National Health and Nutrition Examination Survey (NHANES) data show an overall decrease in urinary levels for all DEHP metabolites by approximately 2-fold or greater between 1999 and 2014 for a broad mix of the general public (CDC 2018; CPSIA 2008). Estimates for average total daily intake for all U.S. populations were 3–30 µg/kg/day (NTP 2006). Clark et al. (2011) estimated DEHP exposures in the United States for different age groups. These ranged from 5.0–7.3 µg/kg/day (0–0.5 year) to 25.8 µg/kg/day (0.6–4 years). These intake approximations indicate that the general population is exposed to DEHP at levels that are 3–4 orders of magnitude lower than those observed to cause adverse health effects in animal studies (Section 1.2).

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of DEHP comes primarily from a large database of oral studies in laboratory animals, with the addition of a limited number of inhalation studies in laboratory animals. Although many epidemiology studies have examined potential associations between DEHP exposure and various adverse health effects, the available studies are limited by reliance on biomarkers in spot urine samples to assess exposure; urine samples, while preferred over other biomarkers, do not provide long-term exposure estimates, nor do they provide information on the route(s) of exposure. In addition, the epidemiological database consists largely of studies of the general population, whose exposure is to a variety of phthalate esters. Many phthalates have similar effects and also produce some of the same urinary metabolites (e.g., phthalic acid is a metabolite of several phthalate esters including dibutyl phthalate, butyl benzyl phthalate, etc.). Thus, human epidemiology studies evaluating potential adverse effects from exposure to phthalates (including DEHP) are insufficient to draw firm conclusions regarding cause and effect or dose-response for individual phthalate esters. Due to their similarity of effects, the National Academy of Sciences (NAS) recommends applying a cumulative risk assessment model to phthalates as a chemical group rather than conducting separate assessments on individual phthalates (EPA 2012; NAS 2008).

Limited data in animal studies indicate that health effects in animals following inhalation exposure include alterations in the immune system and the developing and mature reproductive systems at low concentrations (<1 ppm), with respiratory and developmental effects at higher concentrations (Figure 1-1). In oral animal studies, effects consistently reported at low doses (≤50 mg/kg/day) include altered development or function of several systems following *in utero* and/or early life exposure (i.e., developmental effects), altered immune responses, damage to the sexually mature male reproductive system, renal effects, and hepatic effects (Figure 1-2). Effects on body weight and the neurological, hematological, sexually mature female reproductive, and non-reproductive endocrine systems were observed at higher DEHP doses.

Below are the primary health effects in laboratory animals following exposure to DEHP.

- Altered immune responses
- Developmental effects (altered glucose homeostasis and impaired development/function of the reproductive, renal, hepatic, and nervous systems)
- Male and female reproductive effects in post-pubertal animals (altered hormones, testicular toxicity, male infertility)
- Liver and kidney toxicity

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to DEHP

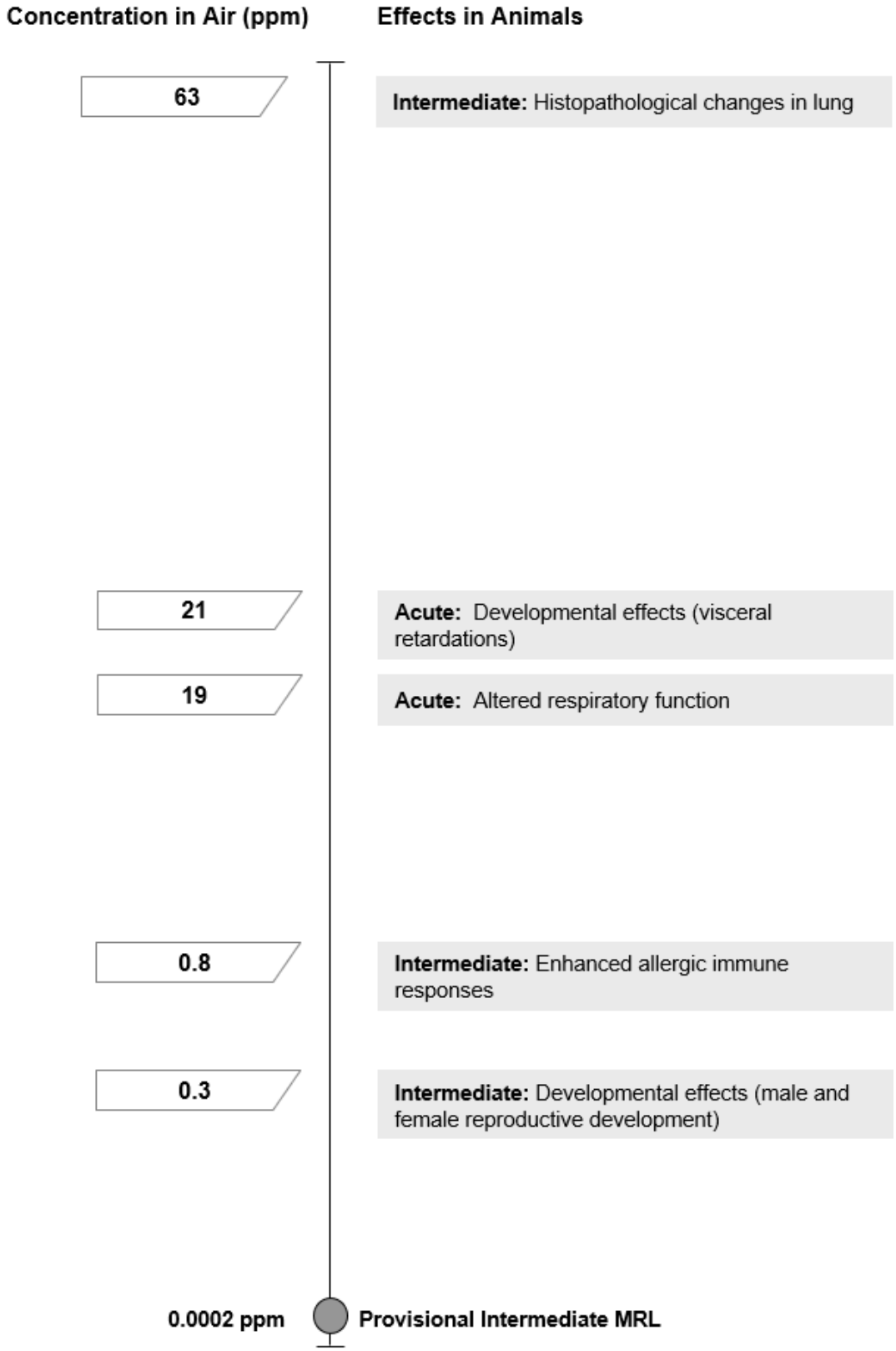
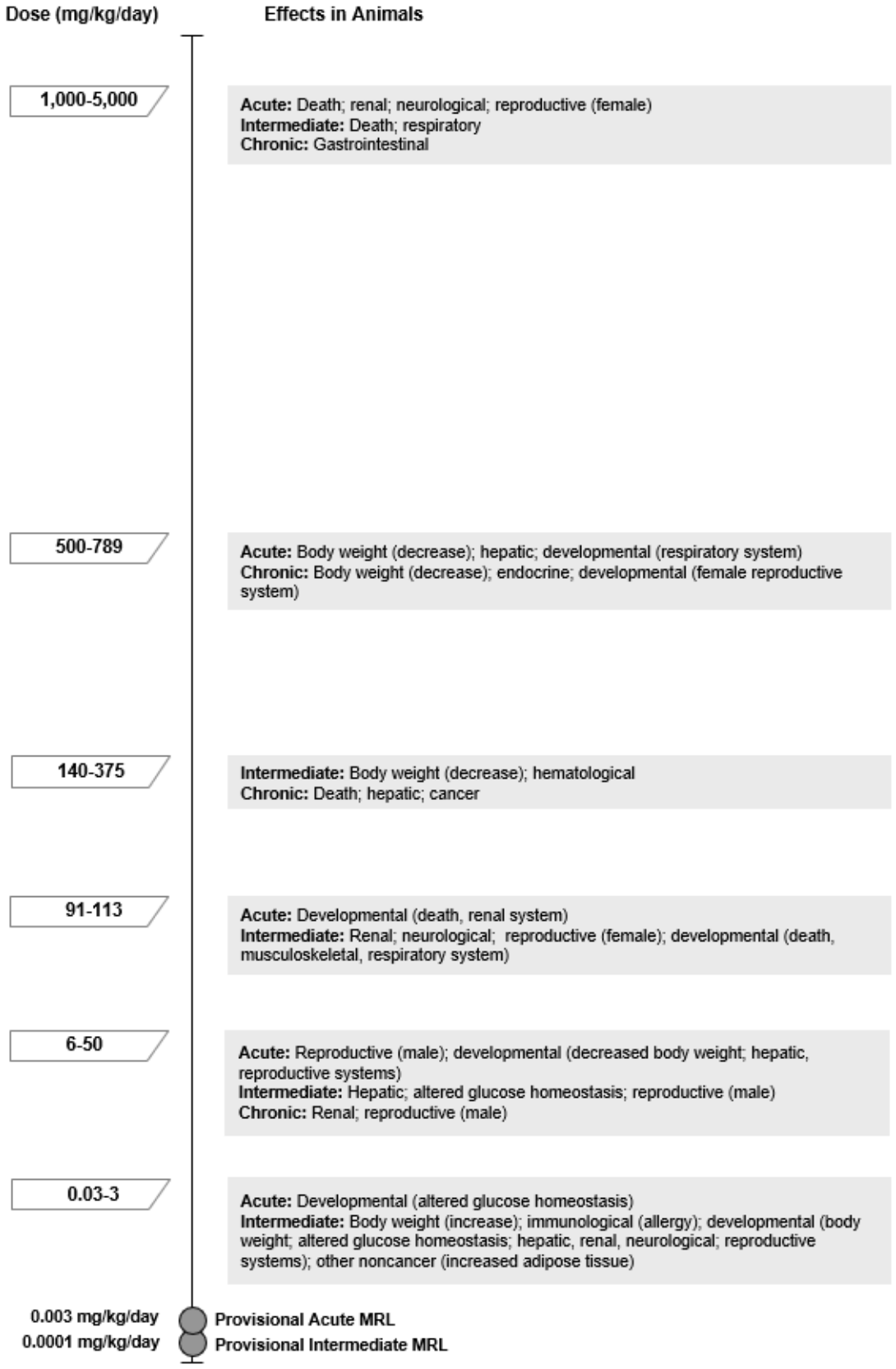


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to DEHP



Immune Effects. Limited human data provide inconsistent findings regarding increased risk of asthma, wheeze, and elevated immunoglobulin E (IgE) levels in childhood (Gascon et al. 2015a; Ku et al. 2015; Wang et al. 2014). In animals, repeated exposure to DEHP had an adjuvant effect on the mouse immune system response to the allergen ovalbumin (OVA) in sensitized animals at oral doses ≥0.03 mg/kg/day (lowest dose evaluated) (Guo et al. 2012; Han et al. 2014; Yang et al. 2008) and after exposure to air concentrations of 0.81 ppm, but not concentrations up to 0.11 ppm (Larsen et al. 2007). In these studies, enhanced immune responses included increases in immune cells in bronchoalveolar lavage (BAL) fluid and lymph nodes, immunoglobulins, cell infiltration and airway remodeling in the lungs, and airway responsiveness.

Developmental Effects. Human epidemiological studies suggest potential associations between maternal exposure to DEHP and preterm birth (Ferguson et al. 2014a, 2014b), male genital anomalies (Sathyanarayana et al. 2016b; Swan 2008), decreased anogenital distance (AGD) in male infants (Barrett et al. 2016; Suzuki et al. 2012; Swan 2008; Wenzel et al. 2018), altered timing of puberty (Ferguson et al. 2014c; Watkins et al. 2014; Wolff et al. 2014), delayed mental and psychomotor development in young children (Kim et al. 2011; Polanska et al. 2014; Tellez-Rojo et al. 2013), and alterations in gender-related play behavior (Swan et al. 2010).

The developing reproductive system appears to be a sensitive developmental target for DEHP in rodents, particularly in males. In inhalation studies, altered reproductive development was observed in both male and female weanling rats following intermittent exposure to ≥0.3 ppm for 3–8 weeks (Kurahashi et al. 2005; Ma et al. 2006). In oral studies, effects associated with the lowest identified lowest-observed-adverse-effect levels (LOAELs) include potentially transient changes in reproductive organ weight and sperm parameters in mouse offspring at maternal doses of 0.05 mg/kg/day (Pocar et al. 2012) and evidence for severe and permanent reproductive tract malformations and lesions in rat offspring at maternal doses of 3–10 mg/kg/day (Arcadi et al. 1998; Christiansen et al. 2010; Klinefelter et al. 2012; Lin et al. 2008, 2009). In studies evaluating prepubertal exposure in nonhuman primates, no changes in testes/epididymides weights or testicular histology were observed following gavage exposure to 500 mg/kg/day for 14 days (Pugh et al. 2000) or serum testosterone, male reproductive organ weight or histology, or sperm parameters following gavage exposure to 2,500 mg/kg/day for 65 weeks (Tomonari et al. 2006).

Data from oral rodent studies indicate the alteration of several organ systems in addition to the reproductive system with early life DEHP exposure. Developmental exposure has resulted in kidney

damage and impaired renal function in rats at maternal doses ≥0.25 mg/kg/day (Arcadi et al. 1998; Wei et al. 2012). Additionally, several studies indicate that DEHP exposure may also impair development of the non-reproductive endocrine system following gestational and/or early postnatal exposure. The lowest doses associated with impaired pancreatic function and adrenal damage in young rats were 1 and 10 mg/kg/day, respectively (Christiansen et al. 2010; Mangala Priya et al. 2014; Rajesh and Balsubramanian 2014a).

Other studies report transient liver damage in rats and mice at maternal or early postnatal doses ≥3 mg/kg/day (Arcadi et al. 1998; Maranghi et al. 2010). Impaired reflexes and altered neurobehavior were also observed in rat and mouse offspring. The lowest maternal effects associated with these neurodevelopmental effects were 20–30 mg/kg/day (Arcadi et al. 1998; Carbone et al. 2013; Tanaka 2002). In both rats and mice, maternal doses ≥95 mg/kg/day produced fetotoxicity and teratogenic effects (Schilling et al. 2001; Shiota and Nishimura 1982; Shiota et al. 1980; Tanaka 2002; Tomita et al. 1982a; Yagi et al. 1980).

Reproductive Effects. Cross-sectional studies suggest associations between levels of urinary DEHP metabolites in humans and decreased serum testosterone (Chang et al. 2015; Jurewicz et al. 2013; Wang et al. 2016) and reduced sperm motility and/or concentration (Axelsson et al. 2015; Bloom et al. 2015a, 2015b) in adult men. However, three prospective cohort studies did not observe associations between DEHP exposure and prolonged time to pregnancy (Buck Louis et al. 2014; Jukic et al. 2016; Thomsen et al. 2017).

Numerous studies in rodents have shown that the male reproductive system, particularly the testis, is susceptible to DEHP toxicity following oral exposure. The lowest exposures associated with male reproductive effects were oral doses of 10–20 mg/kg/day (Guo et al. 2013; Kitaoka et al. 2013; Lee and Koo 2007). Several oral studies have also evaluated reproductive performance in rodents, with reported decreases in male fertility at doses ≥447 mg/kg/day in rats and ≥130 mg/kg/day in mice (Blystone et al. 2010; Dalgaard et al. 2000; Lamb et al. 1987; Morrissey et al. 1988; NTP 1984, 2005; Schilling et al. 1999, 2001). However, limited data indicate that nonhuman primates are not susceptible to male reproductive toxicity following exposure to DEHP at oral doses of 100–2,500 mg/kg/day (Kurata et al. 1998; Rhodes et al. 1986).

Epidemiological data on potential female reproductive effects following exposure to DEHP are limited. In rodents, there are some data suggesting that the female reproductive system may be susceptible to

DEHP toxicity. Decreased fertility was reported in females in a cross-over mating study in mice at doses ≥130 mg/kg/day (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984). However, cross-over mating trials in rats did not indicate decreased female fertility at doses up to 659 mg/kg/day (Blystone et al. 2010; NTP 2005). In pregnant animals, increased resorptions, postimplantation loss, and/or complete litter loss were observed in some studies. The lowest gestational exposure levels associated with these effects are 500 mg/kg/day in rats (Dalsenter et al. 2006) and 95 mg/kg/day in mice (Price et al. 1988b).

Hepatic Effects. The human data on hepatic effects of DEHP exposure are limited. One study showed increased serum enzyme levels in occupationally exposed individuals in China (Wang et al. 2015). Cross-sectional studies of the association between DEHP metabolites in urine and serum triglycerides or cholesterol levels in humans (James-Todd et al. 2016b; Lin et al. 2016; Trasande et al. 2015, 2013b; Yaghjyan et al. 2015a, 2015b) did not indicate consistent relationships.

In rodents, there is clear evidence of hepatomegaly (increased liver weight, hepatocellular hypertrophy) associated with peroxisomal proliferation and induction of hepatic enzymes following DEHP exposure, most likely mediated via the peroxisome proliferator-activated receptor-α (PPARα). The lowest reported doses associated with these effects in adult, non-pregnant rats and mice were 50–60 and 180 mg/kg/day, respectively (Blystone et al. 2010; Mitchell et al. 1985; NTP 2005; Sasaki et al. 2003). These effects have also been reported in pregnant mice at 5 mg/kg/day (Pocar et al. 2012). However, dogs exposed to 56.6 mg/kg/day for 1 year (Carpenter et al. 1953) and monkeys exposed to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998) did not have these changes. On their own, increased liver weight, induction of hepatic enzymes, and peroxisome proliferation may reflect adaptation to xenobiotic exposure, with uncertain relevance to prediction of adverse effects in humans (Hall et al. 2012). Thus, these effects were not considered critical effects for no-observed-adverse-effect level (NOAEL)/LOAEL determinations and are not included in Figure 1-1. This is discussed in further detail in Section 2.9 (Hepatic).

Additional hepatic effects (centrilobular necrosis and inflammation, hepatocyte cytoplasmic eosinophilia, bile duct lesions, altered foci) were observed in some rodent studies, but LOAEL doses generally exceeded 1,000 mg/kg/day (Berman et al. 1995; Exxon Chemical Americas 1990; Schilling et al. 2001). Increased incidences of hepatocellular eosinophilia were reported in F1 rats in one 2-generation study at doses ≥340 mg/kg/day (Schilling et al. 2001), but not at doses up to 1,040 mg/kg/day in another 2-generation study (Schilling et al. 1999).

Renal Effects. Limited data are available in humans. Human studies show no differences in serum urea or creatinine levels in workers exposed to DEHP (Wang et al. 2015) or children exposed to DEHP via contaminated food (Wu et al. 2013). However, two studies suggest increases in the ratio of albumin to creatinine (ACR) in urine with increasing levels of DEHP metabolites in urine (Trasande et al. 2014; Tsai et al. 2016).

Most oral animal studies indicate that the kidney is not a very sensitive target of DEHP toxicity. Exposure-related kidney lesions occurred following chronic or multigenerational exposure to DEHP doses ≥447 mg/kg/day in rats (Blystone et al. 2010; NTP 2005; Rao et al. 1990; Schilling et al. 1999, 2001) and ≥292.2 mg/kg/day in mice (David et al. 2000a, 2000b; Kluwe et al. 1982a; NTP 1982). However, one chronic study in male SV/129 mice showed mild glomerulonephritis and cell proliferation in the kidney at doses ≥9.5 mg/kg/day (Kamijo et al. 2007). Kidney lesions were only reported in a few intermediate-duration studies at exposure levels >1,000 mg/kg/day (Myers 1992a, 1992b; Toyosawa et al. 2001).

There is some evidence of impaired renal function following repeated exposure to DEHP. Rats experienced elevated serum blood urea nitrogen (BUN) when exposed to ≥261.2 mg/kg/day for 13 weeks (Myers 1992b). There was reduced renal concentrating and diluting ability in rats exposed to 1,414 mg/kg/day for 17 weeks (Gray et al. 1977), and increased protein in the urine of mice exposed to ≥9.5 mg/kg/day for 22 months (Kamijo et al. 2007). However, no other studies reported altered renal clinical chemistry or urinalysis findings following DEHP exposure. Renal toxicity has not been observed in guinea pigs, dogs, or young or sexually mature nonhuman primates (Carpenter et al. 1953; ICI Americas Inc. 1982; Kurata et al. 1998; Pugh et al. 2000; Rhodes et al. 1986; Satake et al. 2010).

Cancer Effects. Epidemiology studies of cancer endpoints in humans exposed to DEHP are limited to three case-control studies (Holmes et al. 2014; Lopez-Carillo et al. 2010; Martinez-Nava et al. 2013) in which exposure (as urinary biomarker levels) was measured after the outcome; these studies are not useful for hazard assessment. There is no information (qualitative or quantitative) on exposures prior to incidence/diagnosis that could have been involved in tumor induction. Furthermore, cancer treatments could increase exposure to, and excretion of, phthalates from medical equipment and supplies, especially disposable plastic items.

The carcinogenic potential of DEHP has been evaluated in several chronic-duration oral studies in rats and mice. Studies in F344 rats and B6C3F1 mice have consistently reported increased incidences of liver

tumors following chronic oral exposure to DEHP at doses >350 mg/kg/day (Cattley et al. 1987; David et al. 1999, 2000a, 2000b; Hayashi et al. 1994; Kluwe et al. 1982a, 1982b, 1985; NTP 1982; Rao et al. 1987, 1990). Only David et al. (1999, 2000a) reported an increased incidence of hepatocellular tumors in male F344 rats at lower doses, observing a dose-related increase in tumors at dietary doses ≥147 mg/kg/day, but not ≤29 mg/kg/day (David et al. 1999, 2000a). There is limited evidence of an increased incidence of pancreatic adenomas following chronic exposure to DEHP; however, these tumors were only observed in male F344 rats at high dose levels (≥789 mg/kg/day) (David et al. 2000a; Rao et al. 1990). Additionally, one study reported a significant increase in the incidence of rats with any Leydig cell tumor (unilateral, bilateral, or multifocal) in Sprague-Dawley rats following lifetime exposure to DEHP at doses of 300 mg/kg/day (Voss et al. 2005).

Various U.S. and international agencies have assessed the potential carcinogenicity of DEHP, concluding that it is “reasonably anticipated to be a human carcinogen” (NTP 2016), a “probable human carcinogen” (Group B2) (IRIS 1988), a “confirmed animal carcinogen with unknown relevance to humans” (Group A3) (ACGIH 2001, 2016), or “possibly carcinogenic to humans” (Group 2B) (IARC 2013, 2017). These determinations were based on sufficient evidence of carcinogenicity in experimental animals.

1.3 MINIMAL RISK LEVELS (MRLs)

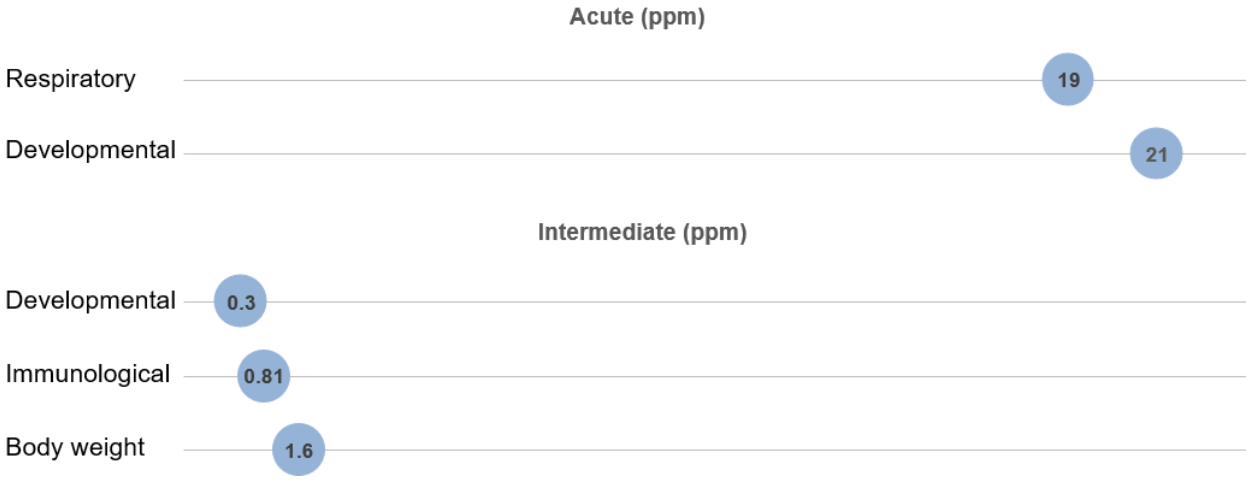
Human studies were not considered for MRL derivation due to limitations discussed in Section 1.2, including lack of information regarding route(s) of exposure, lack of long-term exposure estimates, exposure to multiple phthalate esters, and inadequate dose-response information.

The inhalation database for animals was considered adequate for derivation of a provisional intermediate-duration MRL, but inadequate for derivation of acute- or chronic-duration MRLs. As presented in Figure 1-3, the available inhalation data for DEHP from animal studies suggest that the immune and prepubertal reproductive systems are sensitive targets of toxicity, with body weight effects and respiratory system damage observed at much higher concentrations. However, other potentially sensitive endpoints, particularly indices of glucose homeostasis and development of the reproductive system following early life exposure, have not been adequately examined for this exposure route.

Figure 1-3. Summary of Sensitive Targets of DEHP – Inhalation

Limited data indicate that the developing fetus/neonate and the immune system are the most sensitive targets of DEHP.

Based on the lowest LOAELs (ppm) for all health effects in animals; no human data were identified.



The oral database for animals was considered adequate for derivation of provisional acute- and intermediate-duration oral MRLs for DEHP. As with inhalation exposure, the immune and adult reproductive systems are sensitive targets in animals following oral exposure to DEHP (Figure 1-4). Additional sensitive endpoints identified in animal oral studies include the adult and developing renal system, developing and pubescent reproductive system, and glucose homeostasis in developing animals. While several chronic-duration animal studies were identified, the lowest identified LOAEL of 9.5 mg/kg/day for renal effects was much higher than the LOAELs identified for the most sensitive endpoints in intermediate-duration studies (0.03–0.04 mg/kg/day; immune function and development); see Figure 1-4. Based on available animal data, the chronic-duration point of departure (POD) would be orders of magnitude greater than the POD used to derive the provisional intermediate oral MRL; no chronic MRL was developed.

The provisional MRL values are summarized in Table 1-1.

Figure 1-4. Summary of Sensitive Targets of DEHP – Oral

The developing fetus/neonate and the immune, male reproductive, and renal systems are the most sensitive targets of DEHP

Based on the lowest LOAELs (mg/kg/day) for all health effects in animals; no reliable dose-response data were available for humans.

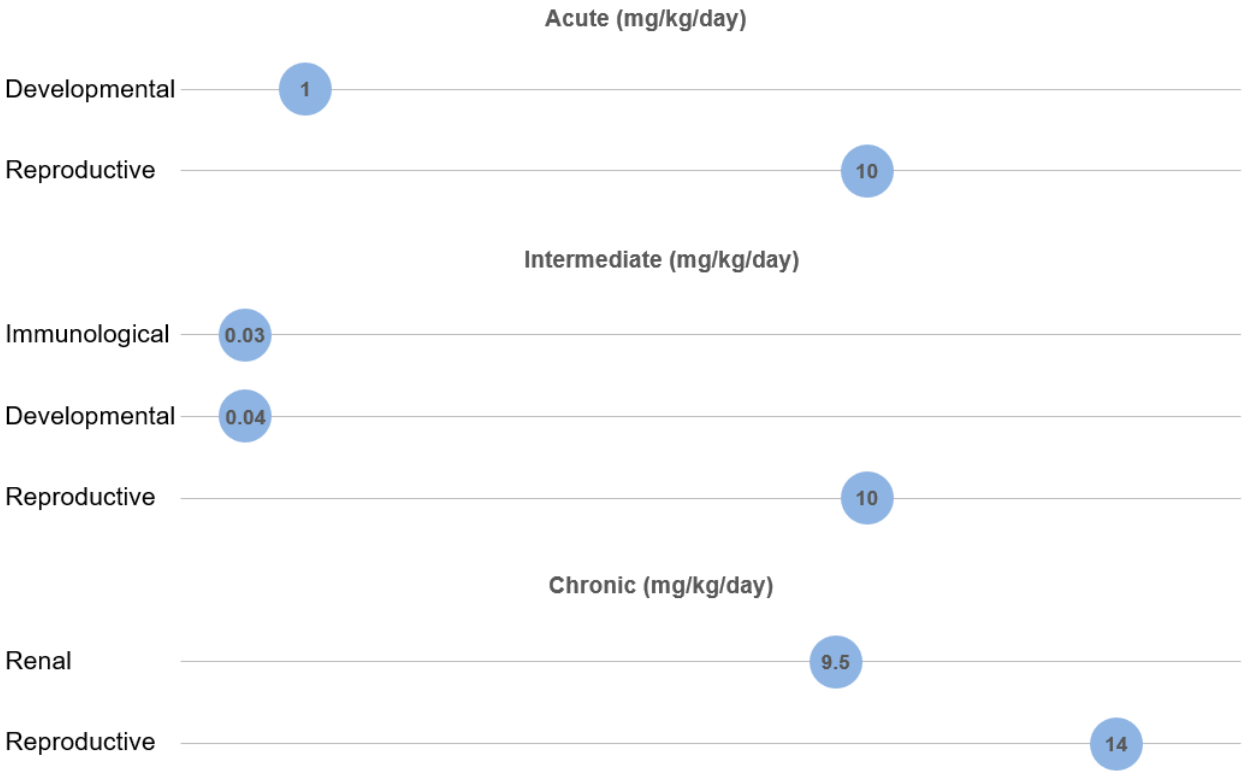


Table 1-1. Minimal Risk Levels (MRLs) for DEHP[a]

Exposure duration	Provisional MRL	Critical effect(s)	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation; the provisional intermediate-duration MRL should be protective of acute exposures				
Intermediate	0.0002	Developmental effects (reproductive system)	0.05 ($LOAEL_{HEC}$)	300	Kurahashi et al. 2005; Ma et al. 2006
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	0.003	Developmental effects (altered glucose homeostasis)	1 (LOAEL)	300	Rajesh and Balasubramanian 2014a
Intermediate	0.0001	Developmental effects (reproductive system)	0.04 (LOAEL)	300	Zhang et al. 2015
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

DEHP = di(2-ethylhexyl)phthalate; GD = gestation day; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; PND = postnatal day

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of DEHP. 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. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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 by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to DEHP, but is not inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) 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 endpoint 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 endpoints. 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. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of DEHP are indicated in Table 2-2 and Figure 2-3.

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

A comprehensive literature search was conducted to identify epidemiological studies of DEHP and its metabolites, as shown in Figure 3-1 and discussed in Appendix B. The literature search revealed an extensive epidemiological database. For endpoints with large numbers of epidemiological studies, a series of inclusion criteria (Table B-1) were defined to narrow the evaluation to those studies of greatest utility to hazard identification, and only studies meeting the criteria were included in the Toxicological Profile. Selected studies were tabulated and discussed in subsequent sections of this chapter. Recent (since 2011) reviews and systematic reviews of specific health effects, when available, were used to ensure complete coverage of the key literature. However, since urinary metabolites represent the preferred biomarkers for DEHP exposure in human epidemiological studies (Section 3.3.1), and many systematic reviews included studies using metabolite levels in biological media other than urine, the reviews themselves were generally not evaluated in detail. Additional considerations employed in the assessment of the effects suggested by the epidemiological data include consistency in the direction of effect, number of urinary metabolites measured, and size of study population, as well as corroborating information from animal or mechanistic studies. The epidemiological database for DEHP is extensive, but is largely focused on a small number of endpoints: body weight (body mass index [BMI] and waist circumference), cardiovascular (blood pressure), hepatic (serum lipids), endocrine (diabetes), immunological (allergy and asthma), and reproductive and developmental endpoints. There are important limitations in the human epidemiological literature for DEHP. In particular, many of the epidemiological studies used a single spot urine sample to assess DEHP exposure. DEHP is rapidly metabolized and excreted, and urinary metabolite levels vary over time within an individual. Thus, a single urine sample may not correlate with long-term exposure patterns unless exposure levels remain very consistent. It is

worth noting, however, that exposure to DEHP was probably relatively consistent for many years due to its ubiquitous presence in foods, packaging, and personal care products, until recent efforts to reduce or ban its use were initiated.

As presented in Figure 2-1, most of the available studies on the health effects of DEHP in laboratory animals used oral administration, with a few inhalation studies and two dermal exposure studies identified. The most commonly examined endpoints were developmental, reproductive, body weight, and hepatic. Data presented under individual organ systems are specific to post-pubertal adult animals, while studies evaluating effects following prenatal or early life (pre-pubertal) exposures are considered developmental. Due to the large size of the oral database, oral animal studies were prioritized for efficient review. Studies with inadequate design or reporting and those not meeting certain dose criteria (e.g., high-dose or single-dose studies for well-studied endpoints/durations) were not included in Chapter 2 or Figure 2-1. For example, only acute- and intermediate-duration oral reproductive/ developmental studies that evaluated at least one dose <100 mg/kg/day were included because reproductive/developmental effects have been consistently observed in numerous studies at doses <100 mg/kg/day; for other endpoints, only acute- and intermediate-duration oral studies that evaluated at least one dose <1,000 mg/kg/day were included. Further details can be found in the Prioritization of Animal Data section of Appendix B. For the included studies, the highest NOAELs and all LOAELs can be found in Tables 2-1 and 2-2.

The results of the selected animal studies, along with limited human data, suggest potential associations between DEHP exposure and the following health outcomes:

- **Hepatic effects.** Human data regarding hepatotoxicity are limited and do not show consistent findings. In rodents, high DEHP doses resulted in degenerative and necrotic hepatic changes. At lower DEHP doses, there is evidence of liver enlargement (increased liver weight, hepatocellular hypertrophy) associated with peroxisomal proliferation in rodents; however, these responses are considered adaptive and human relevance is unclear due to association with the nuclear receptors, particularly PPARα (Hall et al. 2012). Thus, doses associated with hepatomegaly were not considered adverse effect levels unless hepatocellular degenerative or necrotic changes or evidence of biliary or other liver cell damage were also present. The lowest doses associated with the liver weight increases and hepatocellular hypertrophy are noted in Tables 2-1 and 2-2 even though the dose levels are considered NOAELs. Studies that evaluated parameters associated with hepatomegaly only (and not clinical chemistry and/or histopathology) were not included in Tables 2-1 and 2-2 because they were considered inadequate to assess hepatic toxicity; however, these studies are discussed briefly in Section 2.9.

- **Renal effects.** Human data regarding renal effects following DEHP exposure are extremely limited, and do not report consistent findings. In animals, there is some evidence that the kidney

is a sensitive target of DEHP toxicity following oral exposure. However, most of the available studies observed kidney damage only at high doses.

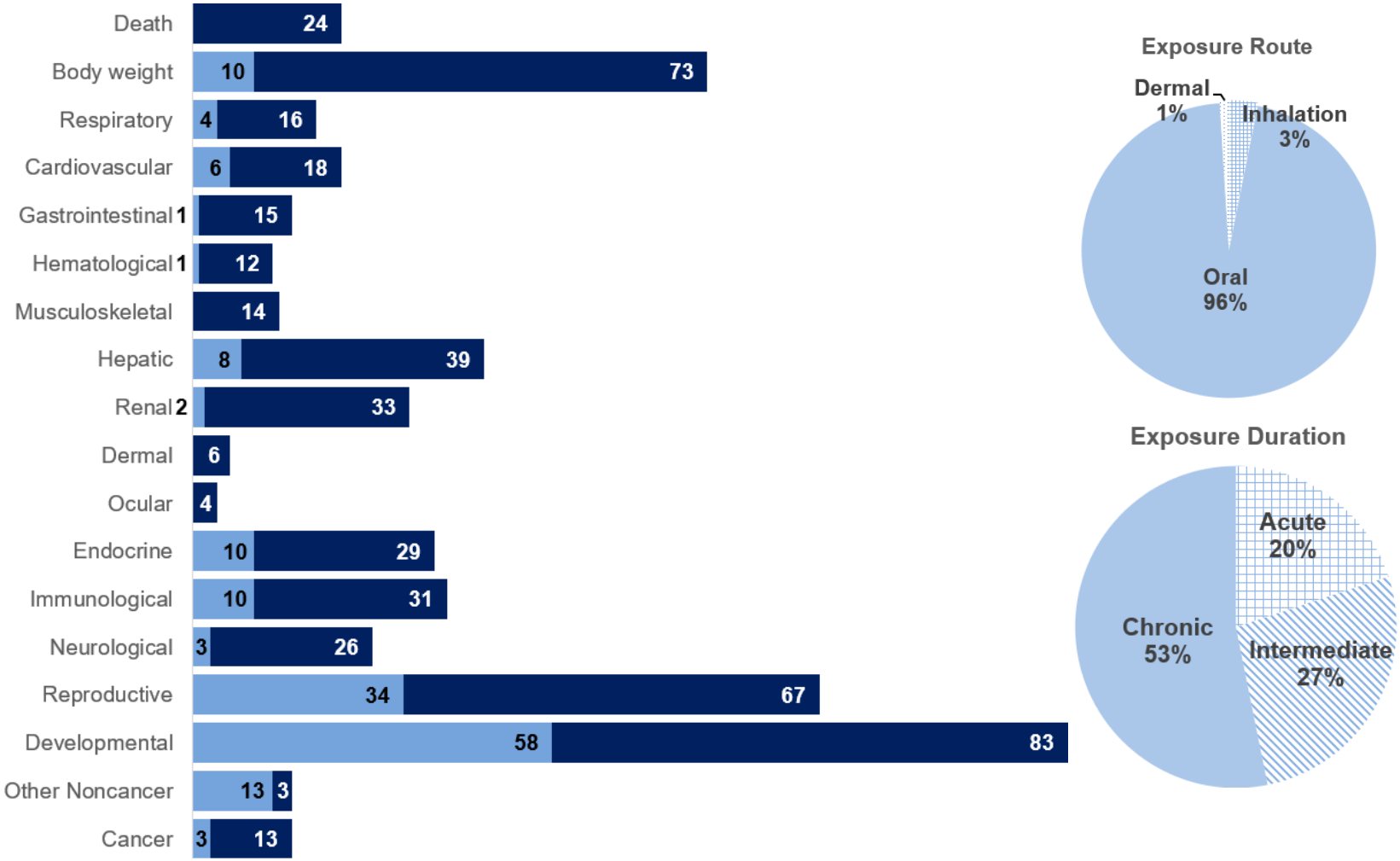
- **Immunological effects.** Human data regarding immunological effects following DEHP exposure are extremely limited. Results from studies evaluating potential associations between prenatal exposure and childhood risk of wheezing or increased IgE were inconsistent. However, some animal studies provide evidence that DEHP is an immune adjuvant in sensitized animals at low exposure levels.

- **Reproductive effects.** Epidemiological studies suggest a potential association between DEHP exposure and decreased serum testosterone and altered sperm parameters in males. Available studies on fertility effects in humans are limited to a single study in 439 couples and do not indicate an association between DEHP exposure and infertility. In animals, the available oral and inhalation studies provide evidence that the male reproductive system, particularly the testes, is susceptible to DEHP toxicity. Evidence from animal studies indicates decreased male and female fertility at high oral doses.

- **Developmental effects.** Epidemiological studies suggest a potential association between reduced AGD and testicular decent in male infants and prenatal DEHP exposure. In addition, human epidemiological studies provide mixed results for potential relationships between exposure to DEHP and preterm birth, early puberty, and delayed mental and psychomotor development in children. Studies in animals indicate that altered glucose homeostasis and development of the reproductive system following early life exposure are particularly sensitive targets of DEHP toxicity.

Figure 2-1. Overview of the Number of Studies Examining DEHP Health Effects

Most studies examined the potential body weight, reproductive, and developmental effects of DEHP
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 285 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to DEHP – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Rat (Wistar) 25 F	10 days GDs 6–15 6 hours/day (WB)	0, 0.6, 3, 21	BW, DX, FX, MX, TG	Develop	3	21		Increased percent of litters with visceral “retardations” (mostly renal pelvis dilatation)
Merkle et al. 1988									
2	Mouse (BALB/c) 8 F	60 minutes (WB)	0.2, 1.2, 2, 19	OF	Resp	2	19		Decreased tidal volume, increased respiratory rate
Larsen et al. 2007 [OVA-sensitized mice]									
INTERMEDIATE EXPOSURE									
3	Rat (Wistar) 27 M, 12 F	4 weeks 5 days/week 6 hours/day (N)	0, 0.6, 3, 63	BW, BC, CS, HE, HP, OW, OF	Bd wt	63			
					Resp	3	63		Transient increases in lung weight, foam cell proliferation, and thickening of alveolar septa
					Cardio	63			
					Hemato	63			
					Musc/skel	63			
					Hepatic	63			Increased relative liver weight at 63 ppm[b]
					Renal	63			
					Endocr	63			
					Immuno	63			
					Neuro	63			
					Repro	63			
Klimisch et al. 1991, 1992									

Table 2-1. Levels of Significant Exposure to DEHP – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
4	Rat (Wistar) 6 M	4 weeks (PNDs 28–56) 6 hours/day 5 days/week (WB)	0, 0.3, 1.6	DX	Develop		0.3[c]		Increased plasma testosterone
Kurahashi et al. 2005									
5	Rat (Wistar) 6 M	8 weeks (PNDs 28–84) 6 hours/day 5 days/week (WB)	0, 0.3, 1.6	DX	Develop		0.3[c]		Increased plasma testosterone, increased relative seminal vesicle weight
Kurahashi et al. 2005									
6	Rat (Wistar) 10 F	21 days (PNDs 22–42) 6 hours/day 5 days/week (WB)	0, 0.3, 1.6	DX	Develop		0.3[c]		Accelerated vaginal opening and first estrus at ≥0.3 ppm; increased serum estradiol and LH at 1.6 ppm
Ma et al. 2006									
7	Rat (Wistar) 10 F	63 days (PNDs 22–84) 6 hours/day 5 days/week (WB)	0, 0.3, 1.6	DX	Develop		0.3[c]		Accelerated vaginal opening and first estrus at ≥0.3 ppm; irregular estrous cycles and ~10% decrease in terminal body weight at 1.6 ppm
Ma et al. 2006									

Table 2-1. Levels of Significant Exposure to DEHP – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
8	Mouse (BALB/c) 9–10 F	14 weeks; 20 minutes/ day 5 days/week for 2 weeks + 1 day/week for 12 weeks (WB)	0, 0.001, 0.006, 0.11, 0.81	BW, OF, OW	Bd wt	0.81			
					Hepatic	0.81			
					Immuno	0.11	0.81		Enhanced immune response to OVA challenge in sensitized animals
Larsen et al. 2007 [OVA-sensitized mice]									

[a]The number corresponds to entries in Figure 2-2.
[b]Hepatic effects associated with hepatomegaly (elevated liver weight, hypertrophy, enzyme induction, and/or peroxisome proliferation) are not considered adverse unless hepatocellular degenerative or necrotic changes or evidence of biliary or other liver cell damage were also present (Hall et al. 2012). The lowest doses associated with hepatomegaly endpoints are noted in the LSE tables even though the dose levels are considered NOAELs.
[c]Used to derive a provisional intermediate-duration inhalation minimal risk level (MRL). The LOAEL of 0.3 ppm was adjusted for continuous exposure and was converted to a human equivalency concentration using the default animal:human blood gas partition coefficient ratio of 1 (0.3 ppm × 6 hours/24 hours × 5 days/7days × 1 = 0.05 ppm), and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human after dosimetric adjustment, and 10 for human variability), resulting in a provisional MRL of 0.0002 ppm.

BC = serum (blood) chemistry; Bd Wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; DEHP = di(2-ethylhexyl)phthalate; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FX = fetal toxicity; GD = gestational day; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; LSE = levels of significant exposure; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; (N) = nose-only; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OF = organ function; OVA = ovalbumin; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; TG = teratogenicity; (WB) = whole-body

Figure 2-2. Levels of Significant Exposure to DEHP – Inhalation
Acute (≤14 days)

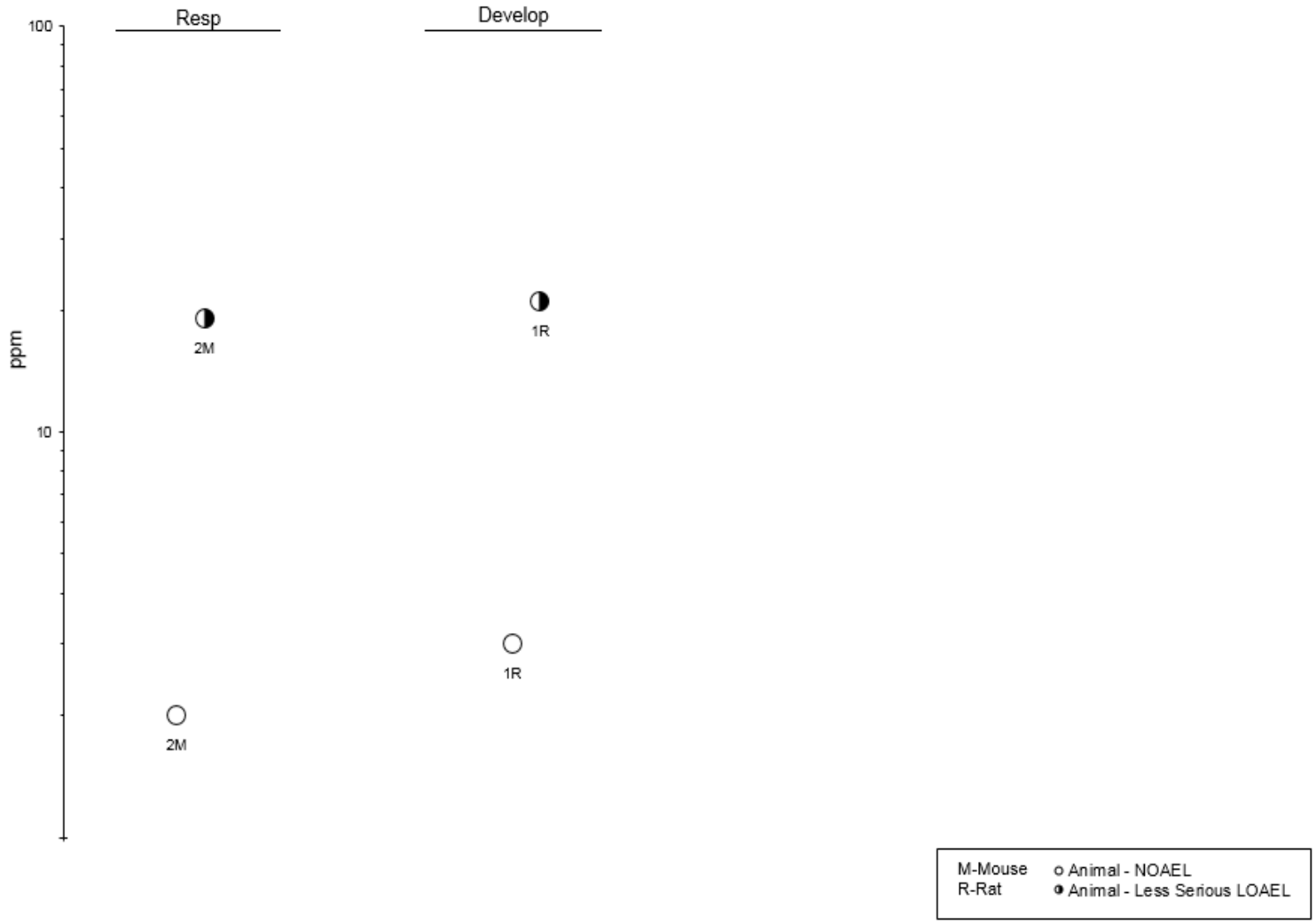


Figure 2-2. Levels of Significant Exposure to DEHP – Inhalation
Intermediate (15-364 days)

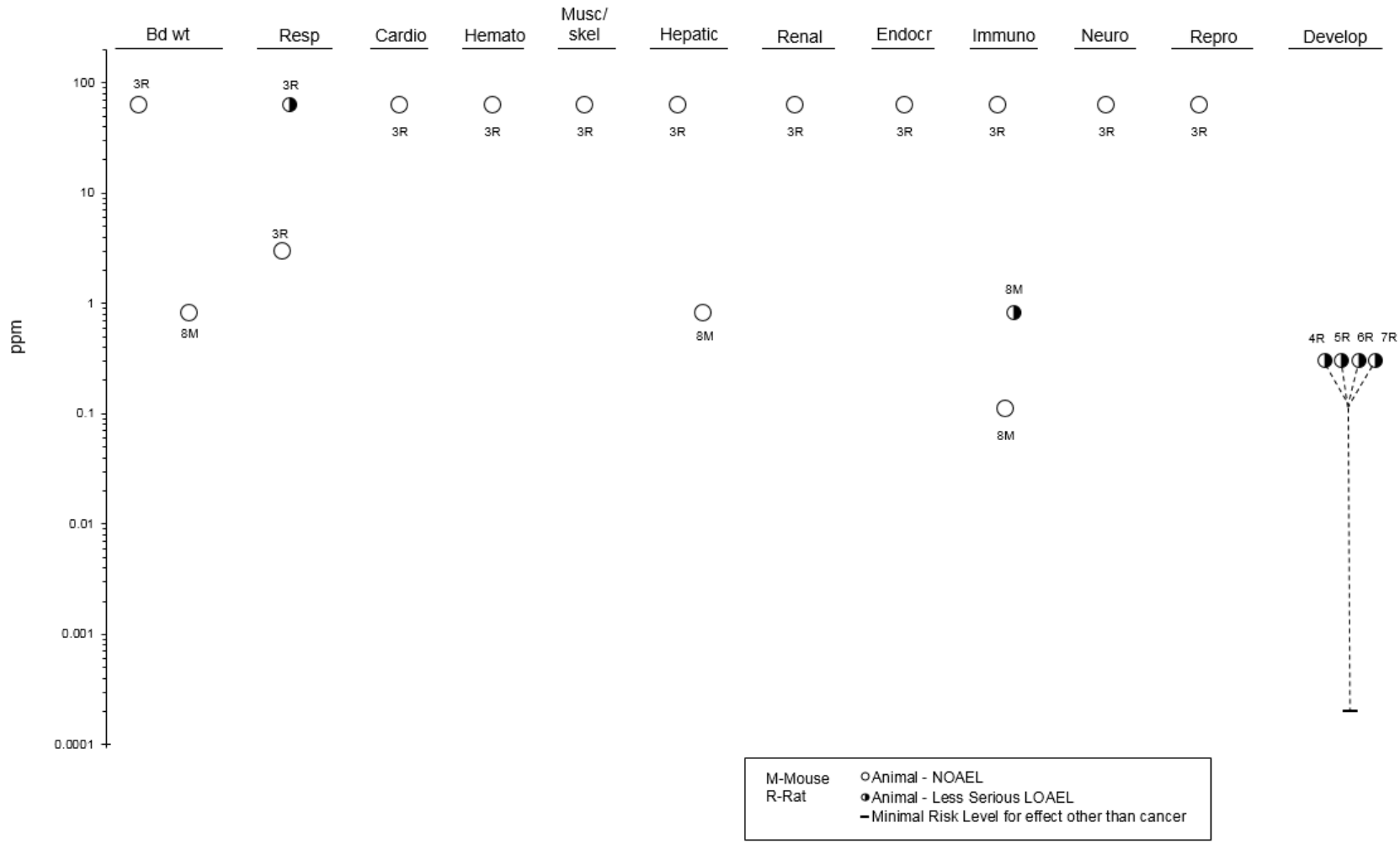


Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	Human 1 M	Once (C)	71.4, 142.9	CS	Gastro	71.4	142.9		Gastrointestinal distress
Shaffer et al. 1945									
2	Monkey (Cynomol-gus) 4 M	14 days (G)	0, 500	CS, BC, BI, BW, HE, HP, OW, UR	Develop	500			
Pugh et al. 2000 [exposure prior to sexual maturity]									
3	Monkey (Marmoset) 5 M, 5 F	14 days (GO)	0, 2,000	BC, BI, BW, HE, HP, OW	Hemato	2,000			
					Hepatic	2,000			
					Renal	2,000			
					Neuro	2,000			
					Repro	2,000			
ICI Americas Inc. 1982; Rhodes et al. 1986									
4	Rat (Long-Evans) 10 M	14 days PNDs 21–34 (GO)	0, 1, 10, 100, 200	DX	Develop	10	100		Reduced testosterone production in Leydig cells
Akingbemi et al. 2001									
5	Rat (Long-Evans) 10 M	14 days PNDs 35–48 (GO)	0, 1, 10, 100, 200	DX	Develop	1	10		Reduced testosterone production in Leydig cells; reduction in androgen biosynthesis enzymes
Akingbemi et al. 2001									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
6	Rat (Fischer-344) 4 M, 4 F	1 week (F)	M: 0, 85, 530, 1,100 F: 0, 86, 570, 940	BC, BI, BW, EA, FI, HP, OW	Bd wt	1,100			
					Hepatic	85	530		Decreased serum lipids, increased absolute and relative liver weight, enzyme induction at ≥530 mg/kg/day; increased hepatocellular hypertrophy in males at 1,100 mg/kg/day
					Musc/skel	1,100			
					Renal	1,100			
					Endocr	1,100			
					Immuno	1,100			
					Neuro	1,100			
					Repro	1,100			
Astill et al. 1986									
7	Rat (Fischer-344) 8 F	Once (GO)	0, 150, 500, 1,500, 5,000	HP, OW	Hepatic	500	1,500		Centrilobular necrosis or inflammation at ≥1,500 mg/kg/day; increased liver weight and hepatocellular hypertrophy at all doses[b]
					Endocr	5,000			
					Immuno	5,000			
Berman et al. 1995									
8	Rat (Fischer-344) 8 F	14 days (GO)	0, 50, 150, 500, 1,500	BW, HP, OW	Hepatic	500	1,500		Centrilobular necrosis and inflammation at ≥1,500 mg/kg/day; Increased relative liver weight and hepatocellular hypertrophy at ≥150 mg/kg/day[b]
					Endocr	1,500			
					Immuno	1,500			
Berman et al. 1995									
9	Rat (Sprague-Dawley) 8–10 F	10 days GD 12–PND 0 (GO)	0, 10, 100, 750	BW, DX	Bd wt	100		750	Maternal weight loss during exposure period
					Develop	10	100	750	~7% decrease in pup birth weight at 100 mg/kg/day; 12% decrease in pup birth weight, increased thickness of alveolar septa, and increased interstitial lung tissue proportion in offspring at 750 mg/kg/day
Chen et al. 2010									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
10	Rat (Fischer-344) NS F	7 days PNDs 1–21 (GO)	0, 500, 1,000, 2,500, 5,000	DX, HP, OW	Death			5,000	25% maternal mortality
Cimini et al. 1994									
11	Rat (Sprague-Dawley) 6–10 M	5 days PNDs 6–10, 14–18, 16–20, 21–25, or 42–46, (GO)	0, 10, 100, 1,000, 2,000	LE, DX	Death			1,000	68% mortality in rats treated on PNDs 14–18; 98% mortality in rats with initiation at or before PND 21 with 2,000 mg/kg/day
					Develop	100	1,000		Increased relative kidney weight; slight decrease absolute kidney weight
Dostal et al. 1987									
12	Rat (Sprague-Dawley) 6–10 M	5 days PNDs 86–90 (GO)		BI, OW	Renal	100	1,000		Increased relative kidney weight; slight decrease absolute kidney weight
Dostal et al. 1987									
13	Rat (Sprague-Dawley) 7–10 M	5 days PNDs 6–10 (GO)	0, 10, 100, 1,000, 2,000	DX	Develop	100	1,000		Reduced absolute and relative testes weight and number of Sertoli cells
Dostal et al. 1988									
14	Rat (Sprague-Dawley) 7–10 M	5 days PNDs 14–18 (GO)	0, 10, 100, 1,000, 2,000	DX	Develop	100	1,000		Reduced testes weight; reduced number of spermatocytes
Dostal et al. 1988									
15	Rat (Sprague-Dawley) 7–10 M	5 days PNDs 21–25 (GO)	0, 10, 100, 1,000, 2,000	DX	Develop	100	1,000		Decreased testicular weight; reduced number of spermatocytes
Dostal et al. 1988									
16	Rat (Sprague-Dawley) 7–10 M	5 days PNDs 42–46 (GO)	0, 10, 100, 1,000, 2,000	DX	Develop	100	1,000		Reduced absolute and relative testicular weight; reduced number of spermatids and spermatocytes
Dostal et al. 1988									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
17	Rat (Sprague-Dawley) 7–10 M	5 days PNDs 86–90 (GO)	0, 10, 100, 1,000, 2,000	BI, HP, OW	Repro	100	1,000		Reduced number of spermatids and spermatocytes; decreased testicular zinc
Dostal et al. 1988									
18	Rat (Long-Evans) 19–38 M	14 d PNDs 21–34 (GO)	0, 10, 500	DX	Develop	10	500		Decreased testes weight, serum testosterone, and Leydig cell testosterone production
Ge et al. 2007									
19	Rat (Long-Evans) 6 M	7 days (GO)	0, 10, 750	BW, HP	Bd wt	750			
					Repro		10		Increased Leydig cell number in testes
Guo et al. 2013									
20	Rat (Long-Evans) 6 M	11 days (GO)	0, 10, 750	BC, EA, HP	Repro		10		Increased Leydig cell proliferation following EDS elimination of Leydig cells
Guo et al. 2013									
21	Rat (Sprague-Dawley) 3–6 F	5 days GDs 14–18 (GO)	0, 100, 300, 500, 625, 750, 875	BW, DX	Bd wt	500		625	>50% decrease in maternal body weight gain
					Develop	100	300		Decreased fetal testicular testosterone production
Hannas et al. 2011									
22	Rat (Wistar) 3–6 F	5 days GDs 14–18 (GO)	0, 100, 300, 500, 625, 750, 875	BW, DX	Bd wt	500		625	>30% decrease in maternal body weight gain
					Develop	100	300		Decreased fetal testicular testosterone production
Hannas et al. 2011									
23	Rat (Sprague-Dawley) 6–8 F	5 days GDs 14–18 (GO)	0, 100, 300, 600, 900	DX	Develop		100		Decreased fetal testicular testosterone production
Furr et al. 2014; Hannas et al. 2011									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
24	Rat (Wistar) 9–10 F	9 days GDs 6–15 (GO)	0, 40, 200, 1,000	BW, CS, DX, OW, TG	Bd wt	1,000			
					Renal	200	1,000		Increased relative maternal kidney weight
					Repro	200	1,000		Increased resorptions and post-implantation loss; vaginal hemorrhage in 2/9 dams; decreased maternal uterine weight
					Develop	200		1,000	34% decrease in the number of live fetuses/dam; increased number of fetuses/litter with malformations (70.1%), variations (80.2%), and retardations (58.3%)
Hellwig et al. 1997									
25	Rat (Sprague-Dawley) 4 F	11 days GDs 8–18 (GO)	0, 100, 300, 600, 900	BW, DX	Bd wt	900			
					Develop	100	300		Decreased fetal testicular testosterone production
Howdeshell et al. 2008									
26	Rat (Sprague-Dawley) 8 F	7 days GDs 13–19 (GO)	0, 10, 100	DX	Develop		10		Leydig cell clustering in fetal testes at ≥10 mg/kg/day; dysgenic seminiferous cords and decreased fetal testicular testosterone production at 100 mg/kg/day
Klinefelter et al. 2012									
27	Rat (Sprague-Dawley) 5 M	2 weeks (GO)	0, 25, 100, 250, 1,000	EA, HP, OW	Hepatic	1,000			Increased relative liver weight and peroxisomal markers at ≥100 mg/kg/day; enzyme induction and increased peroxisomal proliferation at higher doses[b]
Lake et al. 1984									
28	Rat (Sprague-Dawley) 6 M	10 days (GO)	0, 20, 100, 500	BC, BW, CS, OW	Bd wt	500			
					Renal	500			
					Endocr	500			
					Repro		20		Decreased ventral prostate weight at ≥20 mg/kg/day; decreased seminal vesicle weight and increased serum LH at ≥100 mg/kg/day; decreased LABC muscle weight at 500 mg/kg/day
Lee and Koo 2007 [Hershberger Assay; castrated rats supplemented with testosterone]									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
29	Rat (Sprague-Dawley) 5 M	Once PND 3 (GO)	0, 20, 100, 200, 500	DX	Develop	20	100		Multinucleated gonocytes and reduced Sertoli cell proliferation on PND 4
Li et al. 2000									
30	Rat (Long-Evans) 8 M	14 days (GO)	0, 10, 750	BC, OF	Bd wt	750			
					Repro		10		Increased Leydig cell number/proliferation following EDS elimination of Leydig cells
Li et al. 2012a									
31	Rat (Sprague-Dawley) 3 F	8 days GD 14–PND 0 (GO)	0, 20, 50, 100, 300, 750	DX	Develop	50 M	100 M		Decreased serum testosterone and aldosterone at ≥100 mg/kg/day; reduced adrenal weight at 750 mg/kg/day
						100 F	300 F		Decreased serum estradiol and increased serum aldosterone at ≥300 mg/kg/day; reduced adrenal weight at 750 mg/kg/day
Martinez-Arguelles et al. 2011 [Effects measured in adult (PND 60) offspring]									
32	Rat (Sprague-Dawley) NS F	8 days GD 14–PND 0 (GO)	0, 300	DX	Develop		300		Decreased serum aldosterone and mild decreases in systolic blood pressure at PND 200; decreased nighttime locomotor activity at PNDs 60 and 200
Martinez-Arguelles et al. 2013									
33	Rat (Fischer-344) 8 F	Once (GO)	0, 150, 500, 1,500, 5,000	BH, CS	Neuro	1,500	5,000		Signs of general debilitation
Moser et al. 1995									
34	Rat (Fischer-344) 8 F	14 days (GO)	0, 50, 150, 500, 1,500	BH, CS	Neuro	1,500			
Moser et al. 1995									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
35	Rat (Fischer-344) 10 F	10 days (GO)	0, 50, 100, 150, 200	BH, BW, CS	Bd wt Neuro	200 200			
Moser et al. 2003									
36	Rat (Fischer-344) 5 M, 5 F	14 days PNDs 38.5–52.5 (F)	M: 0, 670, 1,300, 2,700, 5,700, 12,000 F: 0, 730, 1,500, 3,000, 6,200, 12,000	DX, LE	Death Develop			12,000	2/5 males and 4/5 females died 22–53% decrease in body weight at ≥5,700 mg/kg/day; food consumption not measured
NTP 1982									
37	Rat (Wistar) 6 F	13 days GDs 9–21 (GO)	0, 1, 10, 100	DX	Develop		1[c]	10	Altered glucose homeostasis at ≥1 mg/kg/day; 12–21% decreased body weight and increased adipose tissue at ≥10 mg/kg/day in adult offspring
Rajesh and Balasubramanian 2014a									
38	Rat (Fischer-344) 4–7 M	1 week (F)	0, 500, 4,000	BC, EA, OW	Hepatic		500		Decreased serum triglycerides at ≥500 mg/kg/day; decreased serum cholesterol, increased relative liver weight, markers of peroxisomal proliferation at 4,000 mg/kg/day
Reddy et al. 1976									
39	Rat (Sprague-Dawley) 8–12 F	8 days GDs 12–19 (GO)	0, 50, 625	DX	Develop		50		Decreased fetal testosterone production
Saillenfait et al. 2013									
40	Rat (Wistar) 10 NS	Once (G)	≤79,500	CS, BW, LE	Death			30,600	LD_{50}; 8/10 died at 79,500 mg/kg/day
Shaffer et al. 1945									
41	Rat (Wistar) 8 M	10 days (GO)	0, 4, 20, 100, 200, 400, 600, 800, 1,000	BW, OW	Bd wt Repro	1,000 20	 100		 Decreased LABC muscle weight at ≥100 mg/kg/day; decreased prostate weight at ≥200 mg/kg/day; decreased seminal vesicles weight at ≥400 mg/kg/day
Stroheker et al. 2005 [Hershberger Assay; castrated rats supplemented with testosterone]									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
42	Rat (Sprague-Dawley) 8 F	11 days GDs 11–21 (GO)	0, 10, 100, 500	DX	Develop		10	500	Effects at PNDs 13–63: Sperm effects at ≥10 mg/kg/day; decreased AGD at 100 mg/kg/day; increased nipple retention, hypospadias, and cryptorchidism at 500 mg/kg/day Effects at GD 21: 14% decrease in fetal body weight; decreased serum testosterone and LH at 500 mg/kg/day
Vo et al. 2009a									
43	Rat (Sprague-Dawley) 10 F	4 days ~PNDs 26–30 (GO)	0, 20, 200, 2,000	DX	Develop	2,000			
Zacharewski et al. 1998 [immature ovariectomized rats]									
44	Rat (Sprague-Dawley) 10 F	4 days (GO)	0, 20, 200, 2,000	BW, OW	Bd wt Repro	2,000 2,000			
Zacharewski et al. 1998 [mature ovariectomized rats]									
45	Mouse (CD-1) 9–20 F	10 days GDs 9–18	0, 0.0005, 0.001, 0.005, 0.5, 50, 500 (micropipette)	BC, DX, MX	Repro Develop	500 0.5	 50		 Decreased fetal testes weight
Do et al. 2012									
46	Mouse (A/J) 10 M	2 weeks (F)	0, 12.3, 125	BW, FI, HP, OF, WI	Bd wt Repro	125	 12.3		 Sertoli cell vacuolation at ≥12.3 mg/kg/day; germ cell sloughing in seminiferous tubules at 125 mg/kg/day
Kitaoka et al. 2013									
47	Mouse (C57BL/6) 10 F	6 days GDs 12–17 (GO)	0, 100, 200, 500	DX	Develop		100		Increased incidence of hypospadias and decreased AGD on GD 19 at ≥100 mg/kg/day; decreased anterior urethra length at ≥200 mg/kg/day
Liu et al. 2008									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
48	Mouse (CD-1) 10 F	9 days GDs 11–19 (GO)	0, 25, 100	BW, DX, FI, HP, OW	Bd wt	100			
					Hepatic	100			
					Repro	100			
					Develop		25		Transient liver lesions in PND 21 offspring (pyknotic nuclei, hepatocyte vacuolization)
Maranghi et al. 2010									
49	Mouse (C57BL/6N 5 M	7 days (F)	0, 385, 1,250, 3,850	BI, BW, OW	Bd wt				17% decrease in final body weight at 3,850 mg/kg/day; food consumption not measured
Muhlenkamp and Gill 1998									
50	Mouse (B6C3F1) 5 M, 5 F	14 days PNDs 44–58 (F)	M: 0, 1,200, 2,400, 4,900, 10,000, 20,000 F: 0, 1,400, 2,700, 5,300, 11,000, 23,000	DX, LE	Death			11,000 F	4/5 died at 11,000 mg/kg/day, 5/5 died at 20,000 mg/kg/day
								20,000 M	5/5 died
					Develop				17–29% decrease in male body weight at ≥4,900 mg/kg/day and female body weight at ≥11,000 mg/kg/day; food consumption not measured
NTP 1982									
51	Mouse (C57BL/6) 6 M	10 days (F)	0, 180, 360	BW, OW, OF	Bd wt	360			
					Immuno	360			
Sasaki et al. 2003									
52	Mouse (ddY-Slc) 3–8 F	Once GD 6, 7, 8, 9, or 10 (G)	0, 50, 100, 1,000, 2,500, 5,000, 7,500, 10,000, 30,000	BW, DX	Develop	50		100	11.2% fetal lethality
Nakamura et al. 1979; Tomita et al. 1982a; Yagi et al. 1980									
53	Hamster (Syrian) 5 M	2 weeks (GO)	0, 25, 100, 250, 1,000	EA, HP, OW	Hepatic	1,000			Increased relative liver weight and peroxisomal proliferation at 1,000 mg/kg/day[b]
Lake et al. 1984									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
54	Rabbit (NS) 4-5 M	7 days (GO)	0, 2,000	LE	Death			2,000	50% died
Parmar et al. 1988									
55	Rabbit (NS) NS	Once (G)	NS	CS, BW	Death			33,900	LD_{50}
Shaffer et al. 1945									
INTERMEDIATE EXPOSURE									
56	Monkey (Marmoset) 4 M, 4 F	13 weeks (GO)	0, 100, 500, 2,500	BC, BI, BW, CS, EA, GN, HE, HP, OW	Bd wt	2,500			
					Resp	2,500			
					Cardio	2,500			
					Gastro	2,500			
					Hemato	2,500			
					Musc/skel	2,500			
					Hepatic	2,500			
					Renal	2,500			
					Dermal	2,500			
					Ocular	2,500			
					Endocr	2,500			
					Repro	2,500			
Kurata et al. 1998									
57	Monkey (Cynomol-gus) 3 M, 3–4 F	28 days (GO)	0, 1,000	BC, EA, HE, HP, OW	Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
Satake et al. 2010									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
58	Rat (Fischer-344) 24 M	60 days (F)	0, 17.5, 69.2, 284.1, 1,156.4	BC, BW, FI, HP, OF, OW	Bd wt	284.1	1,156.4		10–15% decrease in body weight; no change in food consumption
					Hepatic	17.5	69.2		Decreased serum lipids at ≥69.2 mg/kg/day; increased liver weight at ≥284.1 mg/kg/day
					Repro	284.1	1,156.4		Testicular atrophy, decreased reproductive organ weights, sperm decrements and abnormalities
Agarwal et al. 1986									
59	Rat (Long-Evans) 10 M	28 days PNDs 21–48 (GO)	0, 1, 10, 100, 200	DX	Develop	1	10		Increased serum testosterone and LH; increased Leydig cell testosterone production
Akingbemi et al. 2001									
60	Rat (Long-Evans) 10 M	28 days PNDs 62–89 (GO)	0, 1, 10, 100, 200	BC, BW, HP, OF	Bd wt	200			
					Repro	200			
Akingbemi et al. 2001									
61	Rat (Long-Evans) 10 M	28 days PNDs 21–48 (GO)	0, 10, 100	DX	Develop		10		Increased serum estradiol and Leydig cell estradiol production
Akingbemi et al. 2004									
62	Rat (Long-Evans) 10 M	70 days PNDs 21–90 (GO)	0, 10, 100	DX	Develop		10		Increased serum testosterone and LH, decreased Leydig cell testosterone and estradiol production, Leydig cell proliferation
Akingbemi et al. 2004									
63	Rat (Long-Evans) 10 M	100 days PNDs 21–120 (GO)	0, 10, 100	DX	Develop		10		Leydig cell proliferation at ≥10 mg/kg/day; increased serum testosterone and decreased Leydig cell testosterone production at 100 mg/kg/day
Akingbemi et al. 2004									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
64	Rat (Long-Evans) 12 F	42 days GD 1 – PND 21 (W)	0, 3, 30	BM, BW, DX, MX, OF	Bd wt	30			
					Repro	30			
					Develop			3	PNDs 21–56: permanent testes damage and reversible liver and kidney damage at ≥3 mg/kg/day, impaired learning in females at 30 mg/kg/day
Arcadi et al. 1998									
65	Rat (Fischer-344) 5 M, 5 F	3 weeks (F)	M: 0, 75, 470, 950 F: 0, 79, 490, 930	BC, BI, BW, EA, FI, HP, OW	Bd wt	950			
					Musc/skel	950			
					Hepatic		75		Decreased serum lipids, increased liver weight, enzyme induction at ≥75 mg/kg/day; hepatocellular hypertrophy and peroxisomal proliferation at 470 mg/kg/day
					Renal	470	930		Increased absolute and relative kidney weight
					Endocr	950			
					Immuno	950			
					Neuro	950			
					Repro	950			
Astill et al. 1986									
66	Rat (Fischer-344) 5 M, 5 F	21 days (F)	M: 0, 11, 105, 667, 1,224, 2,101 F: 0, 12, 109, 643, 1,197, 1,892	BC, BI, BW, FI, HP, OW	Bd wt	1,224			38–44% decrease in body weight and 48–60% decreased in food consumption at ≥1,892 mg/kg/day
					Hepatic	11	105		Reduced serum lipids at ≥105 mg/kg/day; increased liver weight and peroxisome proliferation, decreased cytoplasmic basophilia, increased cytoplasmic eosinophilia at ≥643 mg/kg/day
					Renal	2,101			
					Repro	1,224 M	2,101 M		Decreased testicular weight and testicular atrophy
Barber et al. 1987; CMA 1984 [female reproductive organs not assessed]									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
67	Rat (Sprague-Dawley) 17 M, 17 F	24 weeks (3-generation) 6 weeks premating through 3 weeks post-weaning of 3rd litter (F)	0.1, 0.58, 1.7, 5.9, 17, 57, 447, 659	BW, DX, FI, HP, OF, OW	Bd wt	57 M	447 M		10–19% decreased F1/F2 body weight; no change in food consumption
						447 F	659 F		12–24% decreased F0/F1 body weight; no change in food consumption
					Hepatic	659			Increased liver weight and hepatocellular hypertrophy in all generations at ≥57 mg/kg/day[b]
					Renal	57	447		Increased kidney weight, medullary mineralization, and tubular dilation in parental animals
					Endocr	447 M	659 M		Increased relative adrenal gland weight in parental males; adrenal cortical vacuolation in F0 males
						659 F			
					Neuro	659			
					Repro	5.9 M	17 M	659 M	Reproductive tract malformations in F1 and F2 adults at ≥17 mg/kg/day; male reproductive organ and sperm damage at higher doses; decreased F1/F2 pregnancy rate at 447 mg/kg/day; complete loss of F1 male fertility at 659 mg/kg/day
						659 F			
					Develop	57	447		Decreased birth weight in F2 pups at ≥464.44 mg/kg/day and F1 pups at 658.82 mg/kg/day; decreased AGD in males in all generations; delayed maturation in all generations
Blystone et al. 2010; NTP 2005 [3-generation, continuous breeding study with cross-over mating]									
68	Rat (Wistar) 8 F	15 days GDs 7–21 (GO)	0, 10, 30, 100, 300	DX	Develop	30	100		Increased gonocyte number and centralized and multinucleated germ cells in fetal testes at ≥100 mg/kg/day; Leydig cell clustering, Sertoli cell vacuolization, decreased testicular testosterone content and production in fetal testes at 300 mg/kg/day
Borch et al. 2006									
69	Rat (Wistar) 3 F	42 days GD 1–PND 21 (W)	0, 3, 30	DX	Develop	3	30		Decreased serum FSH and reduced absolute testis weight on PND 30 in male offspring
Carbone et al. 2010									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
70	Rat (Wistar) 3 F	36 days GD 1–PND 15 (W)	0, 3, 30	DX, MX	Repro	30			
					Develop	3	30		Decreased testes weight and increased serum LH and FSH at PND 15
Carbone et al. 2012									
71	Rat (Wistar) 5 F	30 days PNDs 1–21 (via dam) PNDs 22–30 (W)	0, 30	DX	Develop	30			
Carbone et al. 2013									
72	Rat (Wistar) 5 F	45 days PNDs 1–21 (via dam) PND 22-45 (W)	0, 30	DX	Develop	30F	30 M		Increased anxiety-like behavior in elevated plus maze
Carbone et al. 2013									
73	Rat (Wistar) 5 F	60 days PNDs 1–21 (via dam) PNDs 22–60 (W)	0, 30	DX	Develop	30 F	30 M		Increased anxiety-like behavior in elevated plus maze, decreased serum testosterone, and increased serum LH
Carbone et al. 2013									
74	Rat (Sprague-Dawley) 8–10 F	31 days GD 12–PND 21 (GO)	0, 10, 100, 750	BW, DX	Bd wt	750			
					Develop			10	>10% decrease in body weight at PND 21 at ≥10 mg/kg/day; >10% decrease in birth weight, increased thickness of alveolar septa, and increased interstitial lung tissue proportion at ≥100 mg/kg/day
Chen et al. 2010									
75	Rat (Wistar) 8–16 F	31 days GD 7–PND 16 (GO)	0, 3, 10, 30, 100	BI, BW, DX, MX, OF	Bd wt	100			
					Repro	100			
					Develop		3		Mild external genital dysgenesis in males at ≥3 mg/kg/day; decreased LABC muscle weight at ≥10 mg/kg/day; decreased AGD at 100 mg/kg/day
Christiansen et al. 2010									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
76	Rat (Wistar) 8–16 F	31 days GD 7–PND 16 (GO)	0, 10, 30, 100, 300, 600, 900	BI, BW, DX, MX, OF	Bd wt	900			
					Repro	900			
					Develop		10		Decreased AGD, increased nipple retention, decreased adrenal gland and LABC muscle weight at ≥10 mg/kg/day; mild external genital dysgenesis, decreased reproductive organ weights, and Leydig cell hyperplasia at ≥300 mg/kg/day
Christiansen et al. 2010									
77	Rat (Wistar) 8–10 M	4 weeks (G)	0, 1,000, 5,000, 10,000	BH, BW, CS, FI, LE, HP, OF, OW, WI	Death			10,000	2/8 deaths due to emaciation
					Bd wt	1,000	5,000	10,000	9% decrease in terminal body weight at 5,000 mg/kg/day; 32% decrease in terminal body weight at 10,000 mg/kg/day
					Cardio	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000		5,000	Decreased fertility, decreased testicular weight, severe atrophy of seminiferous tubules, and diffuse Leydig cell hyperplasia
Dalgaard et al. 2000									
78	Rat (Wistar) 10 M	9 weeks (GO)	0, 125, 250, 500, 1,000	BH, BW, CS, FI, HP, OW, WI	Bd wt	1,000			
					Cardio	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000			
Dalgaard et al. 2000									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
79	Rat (Wistar) 10–12 F	42 days GD 1–PND 21 (GO)	0, 20, 100, 500	BW, DX, MX	Bd wt	500			
					Repro	100		500	Increased post-implantation loss, decreased litter size
					Develop	20	100	500	Decreased plasma testosterone in adult offspring at ≥100 mg/kg/day; altered sexual behavior, decreased sperm production, and decreased reproductive organ weights at 500 mg/kg/day
Dalsenter et al. 2006									
80	Rat (Fischer-344) 5–10 M	28 days (F)	0, 23.8, 51.7, 115, 559, 1,093, 2,496	BW, FI, EA, HP, OW	Bd wt	1,093			35% decrease in body weight and 52% decrease in food consumption at 2,496 mg/kg/day
					Hepatic	1,093	2,496		Increased hepatocyte cytoplasmic eosinophilia Increased liver weight and peroxisome proliferation at ≥115 mg/kg/day[b]
					Repro	1,093	2,496		Decreased testes weight, bilateral testicular atrophy
Exxon Chemical Americas 1990									
81	Rat (Long-Evans) 19–38 M	28 d PNDs 21–48 (GO)	0, 10, 500, 750	DX	Develop		10		Decreased age of PPS, increased seminal vesicle weight, and increased serum testosterone at 10 mg/kg/day; opposite reproductive effects observed at 750 mg/kg/day (biphasic response); 13% decrease in body weight at 750 mg/kg/day
Ge et al. 2007									
82	Rat (Wistar) 11–16 F	37 days GD 6–PND 21 (GO)	0.015, 0.045, 0.135, 0.405, 1.215, 5, 15, 45, 135, 405	BW, MX, DX, OW	Bd wt	405			
					Renal	405			
					Endocr	405			
					Immuno	405			
					Neuro	405			
					Repro	405			
					Develop	5	15		Delayed PPS and vaginal opening and decreased sperm production at ≥15 mg/kg/day; testicular lesions at ≥135 mg/kg/day; increased nipple retention and decreased AGD in males and increased tertiary atretic follicles in females at 405 mg/kg/day
Andrade et al. 2006a, 2006b, 2006c; Grande et al. 2006, 2007									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
83	Rat (Sprague-Dawley) 15 M, 15 F	17 weeks (F)	M: 0, 142, 737, 1,440 F: 0, 154, 797, 1,414	BC, BW, CS, FI, HE, HP, OW, UR, WI	Bd wt	154	797 F		10 decrease in terminal body weight in females with no significant change in mean food consumption; body weight decreases in males at ≥737 mg/kg/day attributed to decreased food consumption
					Resp	1,440			
					Cardio	1,440			
					Gastro	1,440			
					Hemato	142	737		Decreased PCV and hemoglobin
					Musc/skel	1,440			
					Hepatic	1,440			Increased liver weight at ≥142 mg/kg/day[b]
					Renal	142	737		Increased relative kidney weight at ≥737 mg/kg/day; mild renal impairment at 1,414 mg/kg
					Endocr	142 M	737 M		Vacuolation of basophils in the pars distalis in the pituitary gland (“castration cells”) in males
						1,414 F			
					Immuno	1,440			
					Neuro	1,440			
					Repro		142 M		Testicular lesions at ≥147 mg/kg/day; decreased testicular weight at ≥747 mg/kg/day
						1,414 F			
					Other noncancer	797 F	1,414 F		Extensive fur loss on head and ventral body surface
Gray et al. 1977									
84	Rat (Sprague-Dawley) 13–14 F	31–78 days GD 8–PND 17 (via dam) PNDs 18–64 (direct) (GO)	0, 11, 33, 100, 300	BW, DX, MX, OF	Bd wt	300			
					Repro	300			
					Develop			11	Reproductive tract malformations and nipple retention in adult male offspring at ≥11 mg/kg/day; decreased AGD at PND 2 and decreased reproductive organ weights and sperm count in adult offspring at ≥100 mg/kg/day
Gray et al. 2009									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
85	Rat (Fischer-344) 10 M, 10 F	13 weeks (F)	M: 0, 62.7, 261.2, 850.1, 1,724.0 F: 0, 72.5, 301.8, 918.4, 1,857.6	CS, BW, CS, FI, HE, HP, OP, OW, UR	Bd wt	301.8 F	918.4 F		7% decrease in terminal body weight (22% decrease in body weight gain) with no significant changes in food consumption at 918.4 mg/kg/day; 20% decrease in terminal body weight (55% decrease in body weight gain) and 8% decrease in food consumption at 1.857.6 mg/kg/day
						850.1 M	1,724 M		17% decrease in terminal body weight (38% decrease in body weight gain) with no significant changes in food consumption
					Resp	1,857.6			
					Cardio	1,857.6			
					Gastro	1,857.6			
					Hemato	261.2 M	850.1 M		Decreased RBCs, hemoglobin, and hematocrit and increased platelets
						918.4 F	1,857.6 F		Decreased hemoglobin, hematocrit, segmented neutrophils, and myeloid/erythroid ratio
					Musc/skel	1,857.6			
					Hepatic	850.1	1,724		Cellular pigmentation Increased liver weight at ≥62.7 mg/kg/day; hepatocellular enlargement at ≥261.2 mg/kg/day[b]
					Renal	62.7 M	261.2 M		Increased BUN at ≥261.2 mg/kg/day; increased kidney weight at ≥850.1 mg/kg/day; cellular pigmentation at 1,724 mg/kg/day
						301.8 F	918.4 F		Increased kidney weight and BUN at ≥918.4 mg/kg/day; cellular pigmentation at 1,857.6 mg/kg/day
					Ocular	1,857.6			
					Endocr	261.2	850.1		Increased serum glucose at ≥850.1 mg/kg/day; vacuolation in the zona glomerulosa in adrenal gland and increased “castration cells” in pituitary gland (males only) at high dose
					Immuno	1,857.6			
					Neuro	1,857.6			

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro	850.1 M	1,724 M		Decreased testis weight, bilateral atrophy and focal mineralization in the testes, and aspermia in the epididymides
						918.4 F	1,857.6 F		Decreased uterus weight
Myers 1992b									
86	Rat (Sprague-Dawley) 8 F	36 days GD 6–PND 20 (GO)	0, 25, 100, 400	BW, DX	Bd wt	400			
					Repro	400			
					Develop	400			
Kobayashi et al. 2006									
87	Rat (Long-Evans) 8 M	21 days (GO)	0, 10, 750	BC, OF	Bd wt	750			
					Repro		10		Increased serum LH, increased number and proliferation of Leydig cell precursors following elimination of mature Leydig cells using EDS
Li et al. 2012a									
88	Rat (Long-Evans) 8 M	35 days (GO)	0, 10, 750	BC, OF	Bd wt	750			
					Repro		10		Decreased serum testosterone, increased number of Leydig cell precursors following elimination of mature Leydig cells using EDS
Li et al. 2012a									
89	Rat (Long-Evans) 2–6 F	19 days GDs 2–20 (GO)	0, 10, 100, 750	BW, DX, MX, OF	Bd wt	750			
					Repro	750			
					Develop		10		PND 1 males: altered distribution of Leydig cells, decreased testicular testosterone; reduced testes weight and Leydig cell number/volume at ≥100 mg/kg/day; decreased AGD at 750 mg/kg/day
Lin et al. 2008									
90	Rat (Long-Evans) 11–13 F	31 days GD 12.5–PND 21.5 (GO)	0, 10, 750	BW, DX, OF	Bd wt	750			
					Repro	750			
					Develop		10		Birth (males): altered Leydig cell clustering in males PND 21 males: decreased serum testosterone at ≥10 mg/kg/day; decreased AGD at 750 mg/kg/day
Lin et al. 2009									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
91	Rat (Wistar) 10–12 F	42 days GD 0–PND 21 (GO)	0, 1.25, 6.25	BC, BW, DX, MX	Endocr	6.25			
					Repro	6.25			
					Develop			1.25	≥10% decrease in body weight; decreased adipose tissue; pancreatic damage with impaired glucose homeostasis in adult offspring
Lin et al. 2011									
92	Rat (Wistar) 3 F	21 days PNDs 1–21 (GO)	0, 1, 10, 100	DX	Develop		1		Altered glucose homeostasis in PND 60 offspring
Mangala Priya et al. 2014									
93	Rat (Wistar) 20 M, 20 F	9 months (F)	0, 50, 200, 1,000	BI, BW, FI, HP, OW	Bd wt	200	1,000		12–15% decreased body weight gain; no change in food consumption
					Hepatic		50		Morphological changes in bile ducts; increased liver weight, hepatocellular hypertrophy, enzyme induction
Mitchell et al. 1985									
94	Rat (Sprague-Dawley) 7–8 M	22 days PNDs 23–44 (GO)	0, 100, 300, 900	DX	Develop		100		Decreased Cowper's gland and adrenal weight at ≥100; delayed PPS, increased LH, decreased testicular testosterone production, and decreased weight of male reproductive organs at ≥300 mg/kg/day
Noriega et al. 2009									
95	Rat (Sprague-Dawley) 6 M	35 days PNDs 23–57 (GO)	0, 10, 100, 300, 900	DX	Develop	10	100	900	Decreased prostate weight at ≥100 mg/kg/day; decreased male reproductive organ weights and hypospermia/aspermia at ≥300 mg/kg/day; delayed PPS, decreased serum LH, and testicular/epididymal degeneration at 900 mg/kg/day
Noriega et al. 2009									
96	Rat (Long-Evans) 6 M	35 days PNDs 23–57 (GO)	0, 10, 100, 300, 900	DX	Develop	10	100	900	Decreased Cowper's gland weight at ≥100 mg/kg/day; decreased male reproductive organ weights at ≥300 mg/kg/day; delayed PPS, hypospermia/aspermia, testicular/epididymal degeneration, and decreased adrenal gland weight at 900 mg/kg/day
Noriega et al. 2009									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
97	Rat (Sprague-Dawley) 8 M	42 days PNDs 23–64 (GO)	0, 100, 300, 900	DX	Develop		100		Decreased Cowper's gland weight at ≥100 mg/kg/day; increased LH, decreased testicular testosterone production, delayed PPS, and decreased weight of male reproductive organs at ≥300 mg/kg/day
Noriega et al. 2009									
98	Rat (Sprague-Dawley) 4 M	76 days PNDs 23–98 (GO)	0, 10, 100, 300, 900	DX	Develop	300		900	Delayed PPS, testicular degeneration, 70% decrease in sperm count, decreased testes and epididymides weight, increased serum LH
Noriega et al. 2009									
99	Rat (Long-Evans) 4 M	76 days PNDs 23–98 (GO)	0, 10, 100, 300, 900	DX	Develop	100	300		Delayed PPS at ≥300 mg/kg/day; increased kidney weight at 900 mg/kg/day
Noriega et al. 2009									
100	Rat (Fischer-344) 10 M, 10 F	13 weeks (F)	M: 0, 150, 300, 620, 1,300, 2,600 F: 0, 180, 340, 700, 1,400, 3,000	BW, CS, HP	Bd wt				20–30% decrease in body weight at 2,600 mg/kg/day; food consumption not measured
					Resp	3,000			
					Cardio	3,000			
					Gastro	3,000			
					Musc/skel	3,000			
					Hepatic	3,000			
					Renal	3,000			
					Endocr	3,000			
					Immuno	3,000			
					Neuro	3,000			
					Repro	620 M 3,000 F	1,300 M		Testicular atrophy
NTP 1982									
101	Rat (Wistar) 6 M	15 days (F)	0, 2000	LE	Death			2,000	50% mortality after 3 weeks with subsequent 100% mortality
Parmar et al. 1987									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
102	Rat (Wistar) 6 M	30 days PNDs 25–54 (GO)	0, 50, 100, 250, 500	DX	Develop		50	250	Decreased absolute testes weight at ≥50 mg/kg/day, decreased relative testes weight at ≥100 mg/kg/day, testicular germ cell damage at ≥250 mg/kg/day
Parmar et al. 1995									
103	Rat (Sprague-Dawley) 12 F	16 days (GO)	0, 37.5, 75, 150, 300	BI, BW, HP, OW, OF	Bd wt	300			
					Immuno	300			
Piepenbrink et al. 2005									
104	Rat (Sprague-Dawley) 12–13 F	16 days GDs 6–21 (GO)	0, 37.5, 75, 150, 300	DX, MX	Repro	300			
					Develop		37.5		Increased AGD
Piepenbrink et al. 2005									
105	Rat (Sprague-Dawley) 10 M, 10 F	13 weeks (F)	M: 0, 0.4, 3.7, 37.6, 375.2 F: 0, 0.4, 4.2, 42.2, 419.3	BC, BI, BW, CS, EA, FI, GN, HE, HP, OW	Bd wt	419.3			
					Resp	419.3			
					Cardio	419.3			
					Gastro	419.3			
					Hemato	37.6 M	375.2 M		Decreased RBCs and hemoglobin
						419.3 F			
					Musc/skel	419.3			
					Hepatic	37.6	375.2		Decreased serum cholesterol; increased liver weight, mild hypertrophy, and peroxisomal proliferation
					Renal	37.6	375.2		Increased kidney weight
					Dermal	419.3			
					Ocular	419.3			
					Endocr	419.3			
					Neuro	419.3			

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Repro	3.7 M 419.3 F	37.6 M	375.2 M	Mild vacuolation of Sertoli cells at ≥37.6 mg/kg/day; testicular atrophy and lack of spermatogenesis at 375.2 mg/kg/day
Poon et al. 1997									
106	Rat (Wistar) 6 M	30 days (G)	0, 10, 100	BC, BI	Other noncancer		10		Altered glucose metabolism/homeostasis
Rajesh et al. 2013									
107	Rat (Wistar) 10 M, 10 F	~19 weeks (2-generation) (F)	0, 130, 380, 1,040	BW, CS, DX, FI, HP, OF, OW	Death			1,040	3/9 F1 males and 2/9 F1 females died
					Bd wt	380 F 1,040 M			Decreased F0 and F1 body weight and food consumption at 1,040 mg/kg/day
					Hepatic	1,040			Increased liver weights in adult females at ≥130 mg/kg/day and adult males at ≥380 mg/kg/day[b]
					Renal	1,040			
					Endocr	1,040			
					Repro	380	1,040		Observed in one or both generations: decreased pups/dam, postimplantation loss, decreased reproductive organ weight, testicular lesions
					Develop	130	380	1,040	Decreased spermatocytes in F1 males at ≥380 mg/kg/day; decreased F1 postnatal survival, decreased pup weight, increased nipple retention and decreased AGD in males, and delayed sexual maturation at 1,040 mg/kg/day
Schilling et al. 1999									
108	Rat (Wistar) 25 M, 25 F	19 weeks (2-generation) ~10 weeks premating–PND 21 (F)	0, 113, 340, 1,088	BH, BW, CS, FI, HP, OF, OW, LE	Death			1,088 F	6/25 deaths in F1 adult females
					Bd wt	340			Decreased body weight and food consumption in F0 females and adult F1 males and females at 1,088 mg/kg/day
					Hepatic	113	340		F1 adults: hepatocellular eosinophilia, increased liver weight at ≥340 mg/kg/day; focal bile duct proliferation and altered hepatic foci at 1,088 mg/kg/day

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal		113		Increased relative kidney weight in F0 and F1 adults at ≥113 mg/kg/day; renal tubule dilation and renal pelvis calcification in F1 adults at 1,088 mg/kg/day
					Endocr	1,088			
					Immuno	1,088			
					Neuro	1,088			
					Repro		113 M		Focal tubular atrophy in testis in F1 males at ≥113 mg/kg/day and F0 males at 1,088 mg/kg/day; aspermia and decreased fertility in F1 at 1,088 mg/kg/day
						340 F	1,088 F		Increased post-implantation loss in F0 females; decreased growing ovarian follicles and corpora lutea in F0 and F1 females
					Develop	113		340	Decreased pup survival, decreased pup weight gain, decreased AGD/AGI, and increased nipple retention at ≥340 mg/kg/day; delayed F1 sexual maturation at 1,088 mg/kg/day; increased pup liver weight at ≥113 mg/kg/day[b]
Schilling et al. 2001									
109	Rat (Wistar) 5 M	90 days (F)	0, 200, 400, 900, 1,900	BC, BW, HP	Cardio	1,900			
					Hemato	1,900			
					Hepatic	1,900			
					Renal	1,900			
					Immuno	1,900			
					Repro	400		900	Tubular atrophy and degeneration
Shaffer et al. 1945									
110	Rat (Fischer-344) 5 M	21 days (F)	0, 11, 105, 667, 1,223, 2,100	BI, BW	Bd wt				No weight gain during study at 2,100 mg/kg/day; food consumption not measured
Short et al. 1987									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
111	Rat (Sprague-Dawley) 4 M	15 d PNDs 21–35 (GO)	0, 10, 100, 500	DX	Develop		10		Decreased serum testosterone, decreased reproductive organ weights, degeneration of the Leydig cells, and "disorders of germ cells" at ≥10 mg/kg/day; dilation of tubular lumen and germ cell stratification at ≥100 mg/kg/day
Vo et al. 2009b									
112	Rat (Wistar) 10 F	42 days GD 0–PND 21 (GO)	0, 0.25, 6.25	BW, DX, MX	Repro	6.25			
					Develop		0.25	6.25	Kidney lesions and impaired renal development and at PNWs 0–33 at ≥0.25 mg/kg/day; >10% decrease in body weight through adulthood, elevated blood pressure, and increased kidney weight at 6.25 mg/kg/day
Wei et al. 2012									
113	Rat (Wistar) 8 M	30 days (G)	0, 0.7, 70	HP, BI, OF	Immuno		0.7		Enhanced immune response to OVA challenge in sensitized animals; non-sensitized animals showed mild increases in immune response at 70 mg/kg/day (not tested at 0.7 mg/kg/day)
Yang et al. 2008									
114	Mouse (BALB/c) 8 M	52 days (G)	0, 0.03, 0.3, 3	BC, HP, OF	Immuno		0.03		Enhanced immune response to OVA challenge in sensitized animals
Guo et al. 2012									
115	Mouse (BALB/c) 4 M, 4 F	28 days (GO)	0, 0.03, 0.3, 3	OF	Immuno		0.03		Enhanced humoral immune response to OVA challenge in sensitized animals
Han et al. 2014									
116	Mouse (CD-1) 8 F	30 days (GO)	0, 0.02, 0.2, 20, 200	BW, OF, OW	Bd wt	200			
					Repro	20	200		Increased percentage of days spent in estrus
Hannon et al. 2014									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
117	Mouse (B6C3F1) 10 M, 10 F	28 days (F)	M: 0, 245, 1,209, 2,579, 6,922 F: 0, 270, 1,427, 2,888, 7,899	BC, BW, LE, HE, HP, OW	Death			6,922 M	4/10 males died
								7,899 F	3/10 females died
					Bd wt	2,579 M	6,922 M		35% decrease in body weight and 18–20% decrease in food consumption during weeks 1–2 only
						2,888 F		7,899 F	39% decrease in body weight; no change in food consumption
					Resp	7,899			
					Cardio	7,899			
					Gastro	7,899			
					Hemato	245 M	1,209 M		Decreased hemoglobin and hematocrit in males
						1,427 F	2,888 F		Decreased hemoglobin and hematocrit in females
					Hepatic	245	1,209		Slight to moderate focal coagulative necrosis and increased liver weight at ≥1,209 mg/kg/day; increased hepatocellular hypertrophy at ≥2,579 mg/kg/day
					Renal	1,427 F	2,888 F		Tubular necrosis, dilation, and regeneration in females
						2,579 M	6,922 M		Tubular necrosis, dilation, and regeneration in males
					Endocr	7,899			
					Immuno	2,579	6,922		Thymic atrophy
					Neuro	2,579		6,922	Hunched posture in 4/10 males and 10/10 females; hypoactivity in 2/10 females and tremor in 1/10 females
					Repro	1,209 M	2,579 M		Decreased testes weight at ≥2,579 mg/kg/day; testicular atrophy and decreased spermatogenesis at 6,922 mg/kg/day
						7,899 F			
Myers 1992a									
118	Mouse (A/J) 10 M	4 weeks (F)	0, 12.3, 125	BW, FI, HP, OF, WI	Bd wt	125			
					Repro		12.3		Sertoli cell vacuolation and germ cell sloughing in seminiferous tubules
Kitaoka et al. 2013									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
119	Mouse (Cr1:CD-1) 20 M, 20 F	18 weeks (F)	0, 13, 130, 390	DX, FX, HP, MX, OF, OW	Bd wt	390			
					Repro	13	130	390	Decreased fertility and live pups at ≥130 mg/kg/day; male and female infertility, 50% decrease in serum testosterone, and damage to sperm and testes at 390 mg/kg/day
					Develop	13	130		6% decrease in female pup weight
Lamb et al. 1987; Morrissey et al. 1988; NTP 1984 [continuous breeding protocol with crossover mating]									
120	Mouse (B6C3F1) 10 M, 10 F	13 weeks (F)	M: 0, 150, 300, 600, 1,200, 2,500 F: 0, 170, 330, 640, 1,300, 2,600	BW, CS, HP	Bd wt				10–12% decrease in female body weight at ≥1,300 mg/kg/day and a 15% decrease in male body weight at 2,500 mg/kg/day; food consumption not reported
					Resp	2,600			
					Cardio	2,600			
					Gastro	2,600			
					Musc/skel	2,600			
					Hepatic	2,600			
					Renal	2,600			
					Endocr	2,600			
					Immuno	2,600			
					Neuro	2,600			
					Repro	2,600			
NTP 1982									
121	Mouse (CD-1) 7–10 F	42 days GD 0–PND 21 (F)	0, 0.05, 5, 500	DX, OW, OF	Repro	5		500	Complete litter loss in 9/10 dams
					Develop			0.05	>20% decrease body weight, decreased adipose tissue, decrease in sperm count and viability, decrease in seminal vesicle weight, increase in ovary weight
Pocar et al. 2012									
122	Mouse (CD-1) 28–29 F	18 days GDs 0–17 (F)	0, 19, 48, 95	BW, DX, FI, MX	Bd wt	95			
					Repro	48	95		19% decrease in live pups/litter
					Develop	48		95	11% decrease in postnatal viability from PND 1 to PND 4
Price et al. 1988b									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
123	Mouse (NC/Nga) 12 M	4 weeks 1 day/week (GO)	0, 0.0475, 0.095, 19	BC, CS, HP, OF	Immuno	19			
Sadakane et al. 2014 [mite-sensitized mice]									
124	Mouse (C57BL/6) 6 M	20 days (F)	0, 180, 360	BW, OW, OF	Bd wt	360			
					Immuno	360			
Sasaki et al. 2003									
125	Mouse (C3H/N) 15F	8 weeks 7 weeks premating GD1 (F)	0, 0.05, 5, 500	BW, CS, FI, OF	Bd wt		0.05		~20% increase in body weight
					Repro	500			
					Other noncancer		0.05		Increased visceral adipose tissue and adipocyte hypertrophy at ≥0.05 mg/kg/day; increased serum leptin at 500 mg/kg/day
Schmidt et al. 2012									
126	Mouse (C3H/N) 15 F	8 weeks 7 weeks premating–GD 1 (F)	0, 0.05, 5, 500	BW, CS, FI, OF	Repro	500			
					Develop			0.05	>20% increase in offspring body weight at PND 21, increased visceral adipose tissue
					Other noncancer		0.05		Increased visceral adipose tissue and adipocyte hypertrophy at ≥0.05 mg/kg/day; increased serum leptin at 500 mg/kg/day
Schmidt et al. 2012									
127	Mouse (ICR) 7–12 F	18 days GDs 1–18 (F)	0, 85, 170, 341, 683, 1,707	BW, DX, FI, FX, MX, TG	Bd wt	170		341	26% decrease in maternal weight at GD 18; no change in food consumption
					Repro	170		341	62.8% increase in resorptions and fetal mortality (combined); complete litter loss at ≥683 mg/kg/day
					Develop	170		341	14–21% decrease in GD 18 fetal weight; 25.8 % increase in number of malformed fetuses
Shiota et al. 1980; Shiota and Nishimura 1982									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
128	Mouse (CD-1) 10 M, 10 F	17 weeks 4 weeks premating–PNW 9 (F)	0, 20.62, 60.42, 180.77	BH, BW, DX, FI, OF, MX	Bd wt	180.77			
					Neuro	180.77			
					Repro	180.77			
					Develop		20.62 F	180.77 F	Delayed surface righting reflex on PNDs 4 and 7 at ≥20.62 mg/kg/day in females; decreased female survival during lactation at 180.77 mg/kg/day
						60.42 M	180.77 M		Delayed surface righting reflex on PNDs 4 and 7
Tanaka 2002 [reported doses are TWA averages across sex and generation]									
129	Mouse (ICR) 5–6 F	15 days GDs 8–17 (dams) and PNDs 3–7 (pups) (GO)	0, 1	DX	Develop			1	>10% decrease in pup weight at PNW 2; 6–9% decrease in pup weight at PNWs 4–6, increased relative brain weight at PNWs 2 and 4, and decreased number and activity of dopaminergic neurons
Tanida et al. 2009									
130	Mouse (C57bl/6J/BALB/cByJ hybrid) 15 M, 15 F	26 weeks (F)	0, 1,100	BW, CS, FI, HP, OW	Bd wt		1,100		~10% decrease in body weight; no change in food consumption
					Resp		1,100		Increased incidence of eosinophilic bodies in nasal cavities
					Cardio	1,100			
					Gastro	1,100			
					Musc/skel	1,100			
					Hepatic	1,100			Elevated absolute and relative liver weight; liver hypertrophy[b]
					Renal		1,100		Tubular regeneration in both sexes; hydronephrosis in females
					Dermal	1,100			
					Ocular	1,100			
					Endocr	1,100			
					Immuno	1,100			
					Neuro	1,100			
					Repro	1,100 F			
							1,100 M		Decreased testis weight, focal testicular atrophy
Toyosawa et al. 2001									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
131	Mouse (CD-1) 24–25 F	17 days GDs 0–17 (F)	0, 44, 91, 191, 292	BW, CS, DX, GN, FI, MX, OW, TG, WI	Bd wt	91	191		30% decrease in maternal weight gain; no change in food consumption
					Neuro	44	91		Maternal lethargy
					Repro	91	191		Increased resorptions and late fetal deaths, decreased live pups/litter
					Develop	44		91	Increased incidence of external, visceral, and skeletal abnormalities at ≥91 mg/kg/day; decreased fetal weight at ≥191 mg/kg/day
Tyl et al. 1988									
132	Mouse (Sv/129) 15 M	24 weeks (F)	0, 2,400	CS, BW, HP, LE, OF, OW	Death			2,400	100% mortality between weeks 12 and 16
Ward et al. 1998									
133	Mouse (CD-1) 5 F	20 days GDs 0.5–18.5 (NS)	0, 0.04	BC, DX	Develop		0.04[d]		Delayed meiotic progression of germ cells in GD 17.5 F1 fetuses; accelerated folliculogenesis in F1 and F2 PND 21 offspring
Zhang et al. 2015									
134	Guinea pig (NS) 4–5 M	15 days (GO)	0, 2,000	LE	Death			2,000	40% mortality
Parmar et al. 1988									
135	Rabbit (NS) NS M	15 days (GO)	0, 2,000	LE	Death			2,000	100% mortality
Parmar et al. 1988									
CHRONIC EXPOSURE									
136	Monkey (Marmoset) 7–8 M, 5–6 F	65 weeks (GO)	0, 100, 500, 2,500	BC, BI, CS, EA, HP, OW	Develop	100 F	500 F		Increased serum estradiol, elevated ovary weights, and enlarged corpora lutea
Tomonari et al. 2006 [exposed from weaning at 3 months until sexual maturation at 18 months]									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
137	Rat (Sherman) 32 M, 32 F	2 years (F)	0, 20, 65, 200	BC, BW, HP, OW	Bd wt	200			
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Hepatic	200			Increased liver weight at 200 mg/kg/day in F0 and F1 adults
					Renal	65	200		Increased kidney weight in F0 and F1 adults
					Endocr	200			
					Immuno	200			
					Repro	200			
					Cancer				No exposure-related neoplasms in F0 or F1 adults
Carpenter et al. 1953 [combined chronic and reproductive study; high-dose F1 animals maintained for 1 year]									
138	Rat (Fischer-344) 20 F	2 years (F)	0, 15, 50, 600	HP, OW	Cancer			600	CEL: hepatocellular carcinoma
Cattley et al. 1987 [the liver was the only organ evaluated]									
139	Rat (Fischer-344) 50–80 M, 50–80 F	104 weeks (F)	M: 0, 5.8, 29, 147, 789 F: 0, 7.3, 36, 182, 939	BC, BW, CS, FI, HP, OW, UR	Death			147	12% reduction in survival due to mononuclear cell leukemia
					Bd wt	182	789		15% decrease in body weight gain; no changes in food consumption
					Gastro	939			
					Hemato	939			
					Musc/skel	939			
					Hepatic	36 M	147 M		Increased incidence of spongiosis hepatis, increased liver weight, and peroxisome proliferation at ≥147 mg/kg/day; increased cytoplasmic eosinophilia, Kupffer cells, and hepatocyte pigmentation at 789 mg/kg/day
						182 F	939 F		Increased cytoplasmic eosinophilia, Kupffer cells, and hepatocyte pigmentation

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	36	147		Increased kidney weight at ≥147 mg/kg/day; increased severity of renal tubule pigmentation and chronic progressive nephropathy at ≥789 mg/kg/day
					Endocr	147 M	789 M		Vacuolation of basophils in the pars distalis in the pituitary gland ("castration cells") in males
						939 F			
					Immuno	939			
					Neuro	939			
					Repro	5.8 M		29 M	Bilateral testicular aspermatogenesis at ≥29 mg/kg/day; decreased testes weight at 789 mg/kg/day
						939 F			
					Cancer			147 M	CEL: hepatocellular tumors in males at ≥147 mg/kg/day; pancreatic acinar cell adenomas and mononuclear cell leukemia in males at 789 mg/kg/day
								939 F	CEL: hepatocellular tumors in females
David et al. 1999, 2000a									
140	Rat (Sprague-Dawley) 7–18 M	102 weeks (F)	0, 14, 140, 1,400	BW, CS, EA, HP	Bd wt				~8–10% decrease in body weight at 140 mg/kg/day and ~20–27% decreased in body weight at 1,400 mg/kg/day; food consumption was not measured
					Repro		14		"Inhibition" of spermatogenesis and general tubule atrophy (magnitude not reported)
					Cancer				No liver or testicular neoplasms (other organs not evaluated)
Ganning et al. 1991									
141	Rat (Fischer-344) 7–10 M	78 weeks (F)	0, 1,579	BW, HP, OW	Cancer			1,579	CEL: hepatocarcinomas
Hayashi et al. 1994									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
142	Rat (Fischer-344) 50 M, 50 F	2 years (F)	M: 0, 322, 674 F: 0, 394, 774	BW, FI, HP, GN	Bd wt				11–14% decrease in male body weight at ≥322 mg/kg/day and 20% decrease in female body weight at 774 mg/kg/day; 14–15% decrease in food consumption at ≥322 mg/kg/day in both sexes
					Resp	774			
					Cardio	774			
					Gastro	774			
					Musc/skel	774			
					Hepatic		322 M		Increased incidence of clear cell foci in liver
						774 F			
					Renal	774			
					Dermal	774			
					Endocr	322 M	674 M		Anterior pituitary cell hypertrophy
						774 F			
					Immuno	774			
					Neuro	774			
					Repro	322 M		674 M	Severe seminiferous tubular degeneration and testicular atrophy
						774 F			
					Cancer			394 F	CEL: neoplastic liver nodules or hepatocellular carcinoma in females
								674 M	CEL: neoplastic liver nodules or hepatocellular carcinoma in males
Kluwe et al. 1982a, 1982b, 1985; NTP 1982									
143	Rat (Fischer-344) NS M	365 days (F)	0, 930	BW FI OW HP BI	Bd wt				17% decrease in final body weight and 10% decrease in food consumption at 930 mg/kg/day
Marsman et al. 1988									
144	Rat (Wistar) NS	2 years (F)	0, 2,000	HP	Repro			2,000	Testicular atrophy
Price et al. 1987									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
145	Rat (Fischer-344) 8–20 M	95 weeks (F)	0, 1,600	BI, HP	Cancer			1,600	CEL: hepatocellular carcinoma
Rao et al. 1987 [only the liver was examined]									
146	Rat (Fischer-344) 10–14 M	108 weeks (F)	0, 1,600	BW, HP, OW	Bd wt				27% decrease in body weight at 1,600 mg/kg/day; food consumption not measured
					Resp	1,600			
					Gastro		1,600		Pseudoductular lesions and altered acinar cell foci in the pancreas
					Renal		1,600		Lipofuscin pigments in tubular epithelium
					Cancer			1,600	CEL: hepatocellular carcinoma, pancreatic islet-cell adenoma
Rao et al. 1990									
147	Rat (Wistar) 4 M	79 weeks (F)	0, 1,500	BI, BW, OW	Bd wt				21% decrease in body weight gain at 1,500 mg/kg/day; food consumption not measured
Tamura et al. 1990									
148	Rat (Sprague-Dawley) 60–390 M	Lifetime 6 days/week (F)	0, 30, 95, 300	BW, CS, HP, OW	Bd wt	300			
					Resp	300			
					Hepatic	300			
					Endocr	300			
					Immuno	300			
					Neuro	300			
					Repro	95	300		Seminiferous tubule atrophy
					Cancer			300	CEL: Leydig cell tumors
Voss et al. 2005									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
149	Mouse (B6C3F1) 60–70 M, 60–70 F	104 weeks (F)	M: 0, 19.2, 98.5, 292.2, 1,266 F: 0, 23.8, 116.8, 354.2, 1,458	BC, BW, CS, FI, HP, OW, UR	Death			1,266	45% reduced survival due to hepatocellular neoplasia
					Bd wt	292.2 M	1,266 M		9.8% decrease in body weight, no change in food consumption
						1,458 F			
					Gastro	1,458			
					Hemato	1,458			
					Musc/skel	1,458			
					Hepatic	292.2	1,266		Hepatocyte pigmentation and cytoplasmic eosinophilia; increased liver weight, hypertrophy, and peroxisomal proliferation at ≥292.2 mg/kg/day[b]
					Renal	116.8	292.2		Chronic progressive nephropathy
					Endocr	1,458			
					Immuno	1,458			
					Neuro	1,458			
					Repro	98.5 M	292.2 M		Reduced testes weight and hypospermia
						354.2 F	1,458 F		Reduced absolute and relative uterus weight
					Cancer			292.2	CEL: hepatocellular tumors
David et al. 1999, 2000b									
150	Mouse (SV/129) 20–24 M	22 months (F)	0, 9.5, 48.5	BC, BI, BW, HP, OW, UA	Cardio		9.5		Elevated systolic blood pressure (secondary to renal effects)
					Renal		9.5		Mild glomerulonephritis, cell proliferation, proteinuria
Kamijo et al. 2007									
151	Mouse (B6C3F1) 50 M, 50 F	2 years (F)	M: 0, 672, 1,325 F: 0, 799, 1,821	BW, FI, GN, HP	Bd wt	672 M	1,325 M		10% decrease in terminal body weight, no change in food consumption
								799 F	21% decrease in terminal body weight; no change in food consumption
					Resp	1,821			
					Cardio	1,821			
					Gastro	1,821			
					Musc/skel	1,821			
					Hepatic	1,821			

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	672 M	1,325 M		Chronic inflammation of the kidney
						1,821 F			
					Dermal	1,821			
					Endocr	1,821			
					Immuno	1,821			
					Neuro	1,821			
					Repro	672 M		1,325 M	Seminiferous tubular degeneration
						799 F	1,821 F		Suppurative inflammation in the uterus/endometrium
					Cancer			672	CEL: hepatocellular adenoma or carcinoma
Kluwe et al. 1982a, 1982b, 1985; NTP 1982									
152	Guinea pig (NS) 46-47 B	1 year (F)	0, 19, 64	BW, OW, HP	Bd wt	64			
					Hepatic	64			Increased female liver weight at 64 mg/kg/day[b]
					Renal	64			
					Immuno	64			
					Repro	64 M			
					Cancer				No exposure-related neoplasms
Carpenter et al. 1953 [female reproductive organs not assessed]									
153	Dog (NS) 1 M, 1 F	1 year 5 days/ week (C)	0, 56.6	BC, BW, HP, OF, OW	Bd wt	56.6			
					Resp	56.6			
					Cardio	56.6			
					Gastro	56.6			
					Hepatic	56.6			
					Renal	56.6			
					Endocr	56.6			
					Immuno	56.6			
					Repro	56.6			
					Cancer				No exposure-related neoplasms
Carpenter et al. 1953									

Table 2-2. Levels of Significant Exposure to DEHP – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
154	Ferret (albino) 7 M	14 months (F)	0, 1,200	BI, BW, EA, OW, HP	Bd wt				31% decrease in body weight at 1,200; food consumption not measured
					Cardio	1,200			
					Hepatic		1,200		Hepatocellular vacuolation, increased liver weight, hypertrophy, enzyme induction
					Endocr	1,200			
					Neuro	1,200			
					Repro		1,200		3/7 with absence of germinal epithelium in seminiferous tubules

Lake et al. 1976

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Hepatic effects associated with hepatomegaly (elevated liver weight, hypertrophy, enzyme induction, and/or peroxisome proliferation) are not considered adverse unless hepatocellular degenerative or necrotic changes or evidence of biliary or other liver cell damage were also present (Hall et al. 2012). The lowest doses associated with hepatomegaly endpoints are noted in the LSE tables even though the dose levels are considered NOAELs.
[c]Used to derive a provisional acute-duration oral minimal risk level (MRL). The LOAEL of 1 mg/kg/day was divided by an uncertainty factor of 300 (10 for use of a LOAEL; 3 for human variability, and 10 for animal to human extrapolation), resulting in a provisional MRL of 0.0003 mg/kg/day.
[d]Used to derive a provisional intermediate-duration oral MRL. The LOAEL of 0.04 mg/kg/day was divided by an uncertainty factor of 300 (10 for use of a LOAEL; 3 for human variability, and 10 for animal to human extrapolation), resulting in a provisional MRL of 0.0001 mg/kg/day.

AGD = anogenital distance; AGI = anogenital index; B = both males and females (number per sex not reported); BC = serum (blood) chemistry; Bd Wt or BW = body weight; BH = behavioral; BI = biochemical changes; BM = blood metabolites; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Derm = dermal; DEHP = di(2-ethylhexyl)phthalate; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; EDS = ethane dimethanesulphonate; Endocr = endocrine; (F) = feed; F = female(s); F0 = parental generation; F1 = first generation; F2 = second generation; FI = food intake; FSH = follicle stimulating hormone; FX = fetal toxicity; (G) = gavage; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LABC = levator ani/bulbocavernosus; LE = lethality; LH = luteinizing hormone; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; LSE = levels of significant exposure; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OVA = ovalbumin; OW = organ weight; PCV = packed cell volume; PND = postnatal day; PNW = postnatal week; PPS = preputial separation; RBC = red blood cell; Repro = reproductive; Resp = respiratory; TG = teratogenicity; TWA = time-weighted average; UR = urinalysis; (W) = drinking water; WI = water intake

Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Acute (≤14 days)

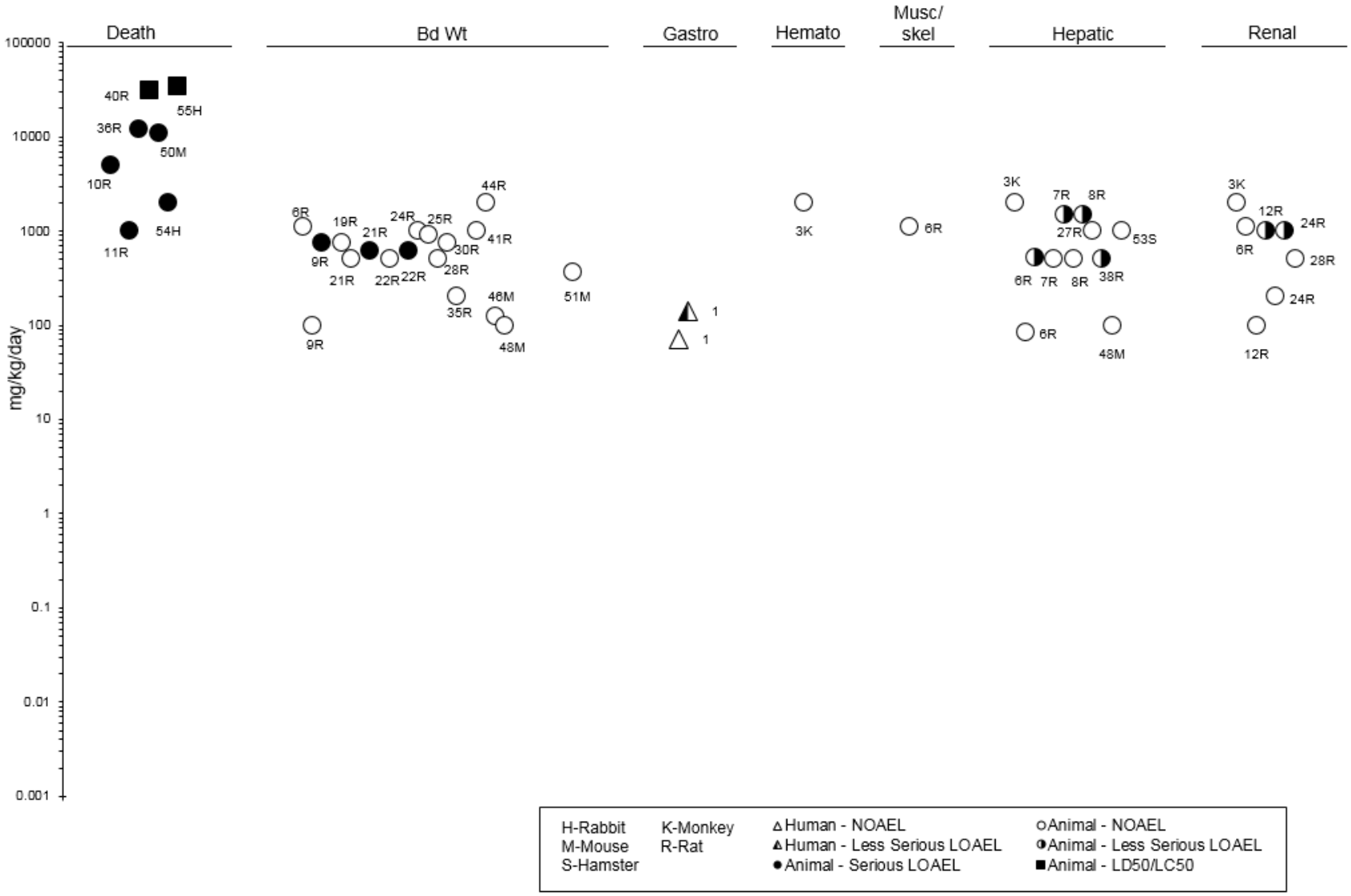


Figure 2-3. Levels of Significant Exposure to DEHP - Oral
Acute (≤14 days)

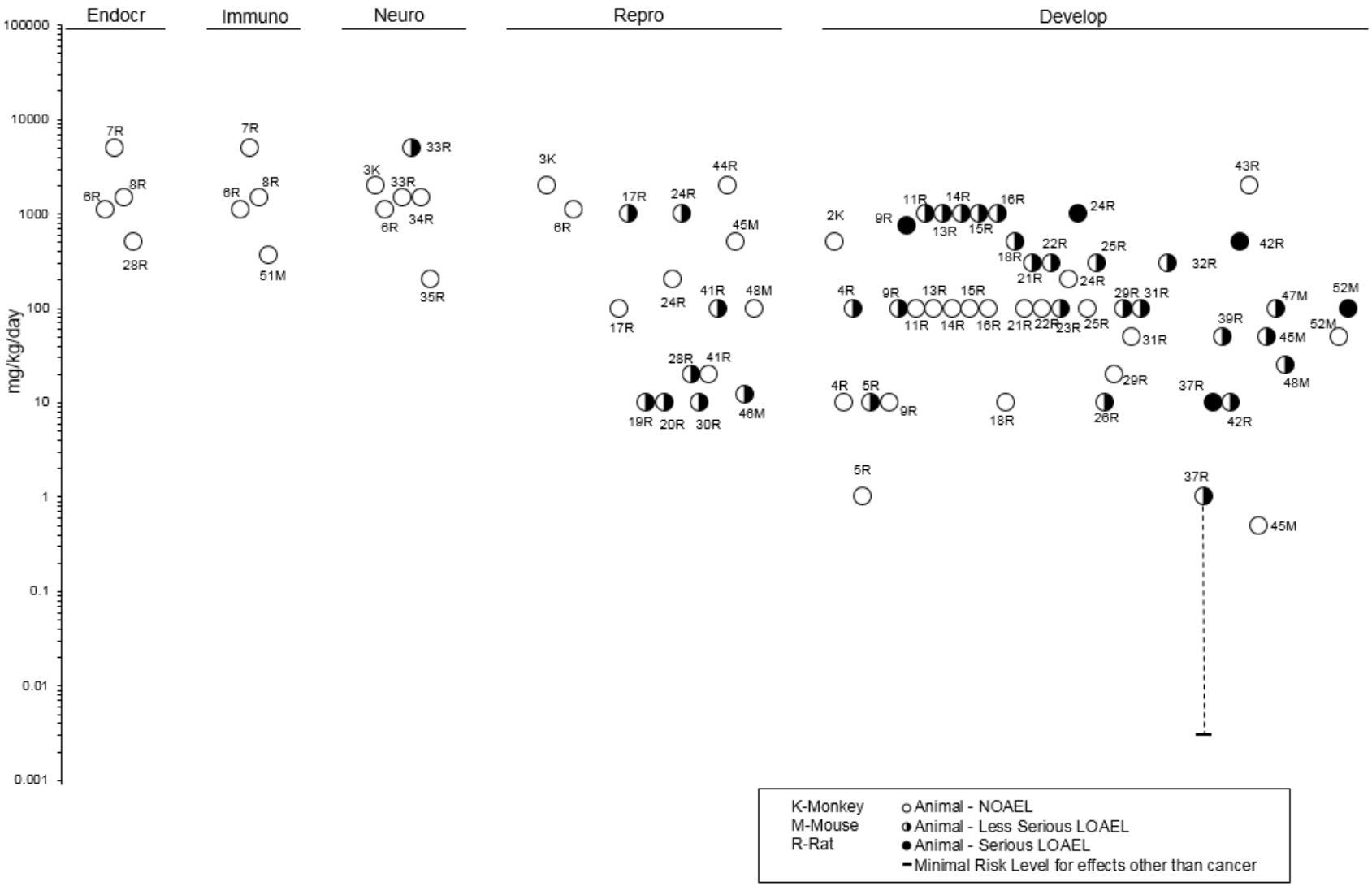


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

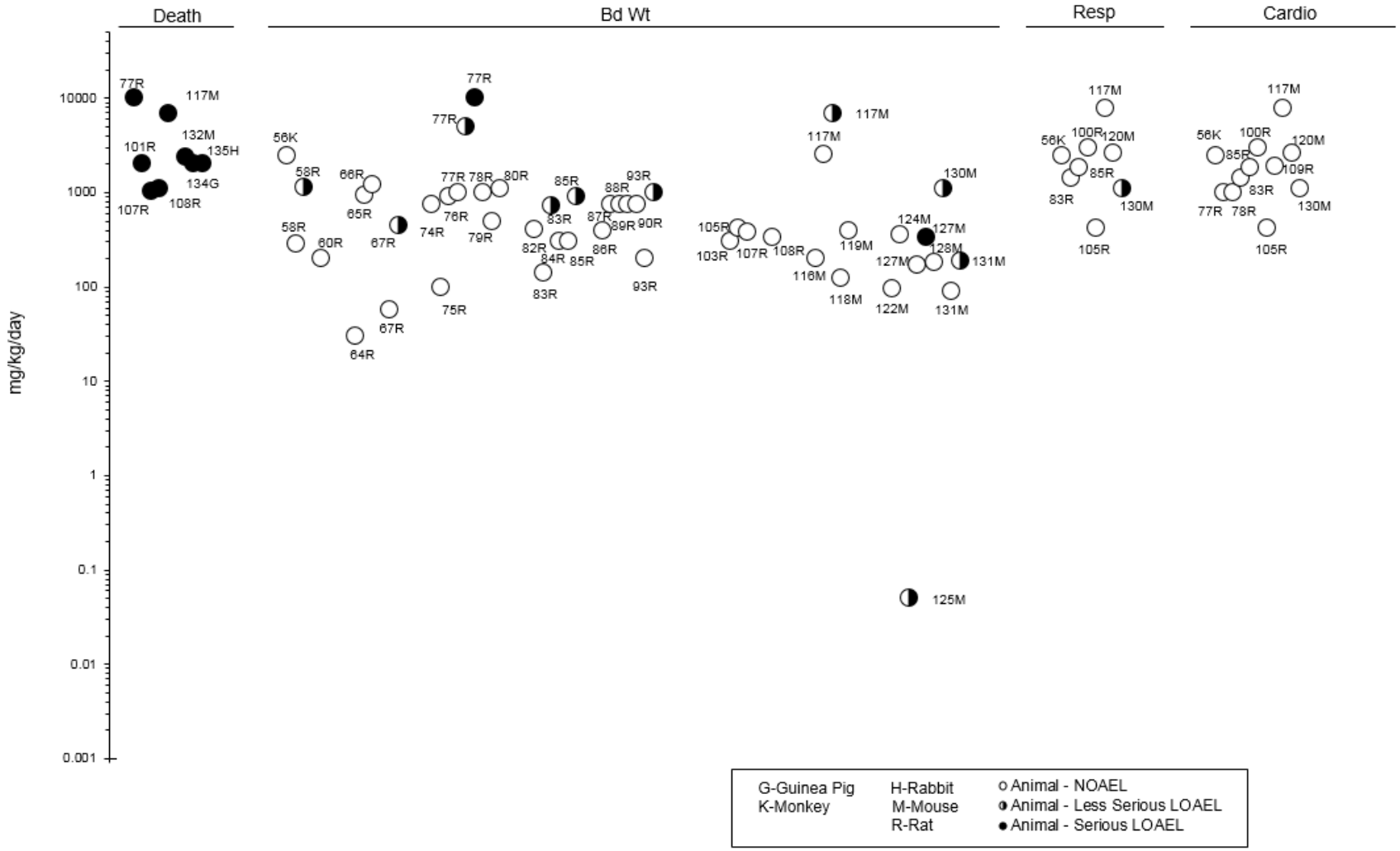


Figure 2-3. Levels of Significant Exposure to DEHP - Oral
Intermediate (15-364 days)

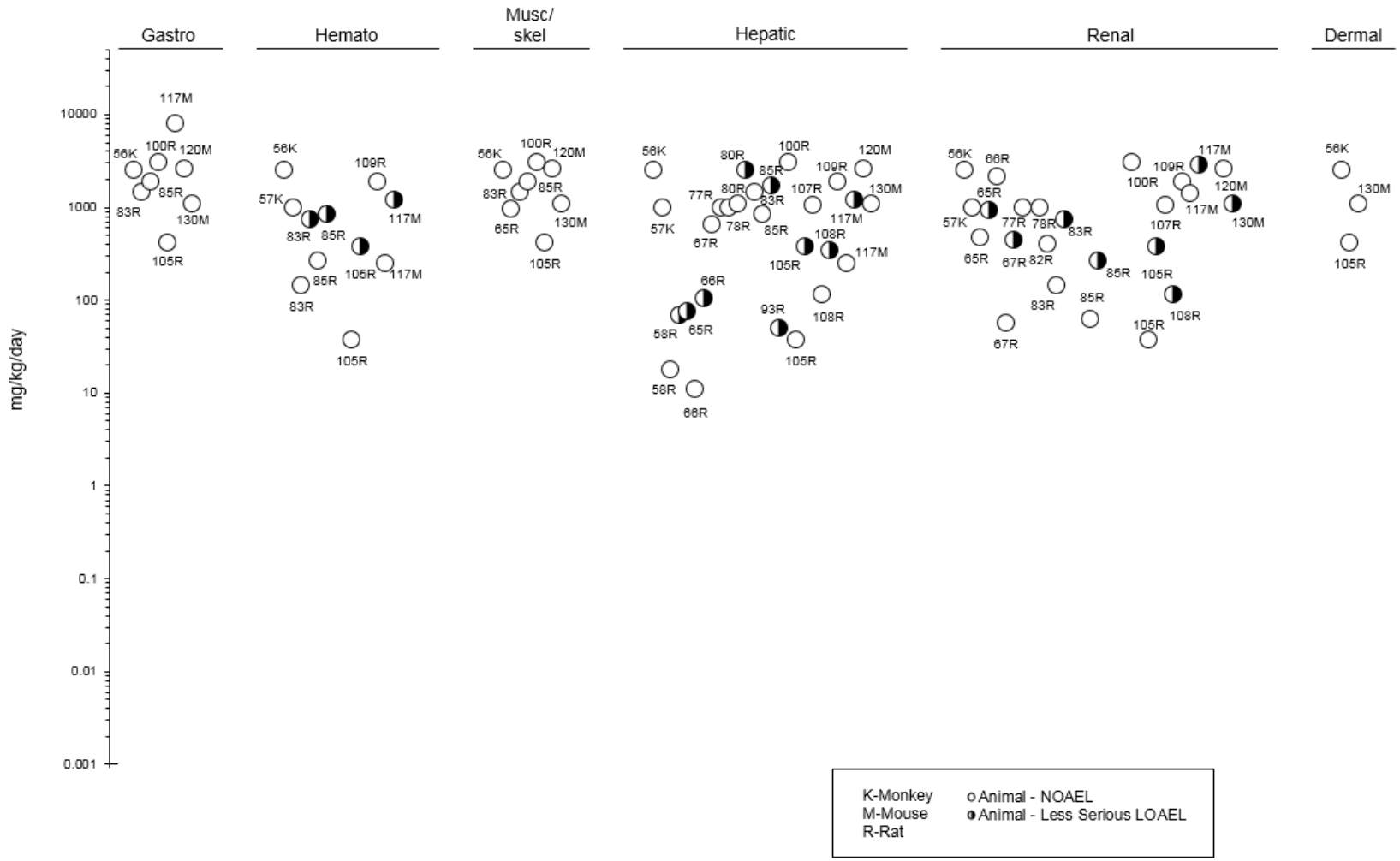


Figure 2-3. Levels of Significant Exposure to DEHP - Oral
Intermediate (15-364 days)

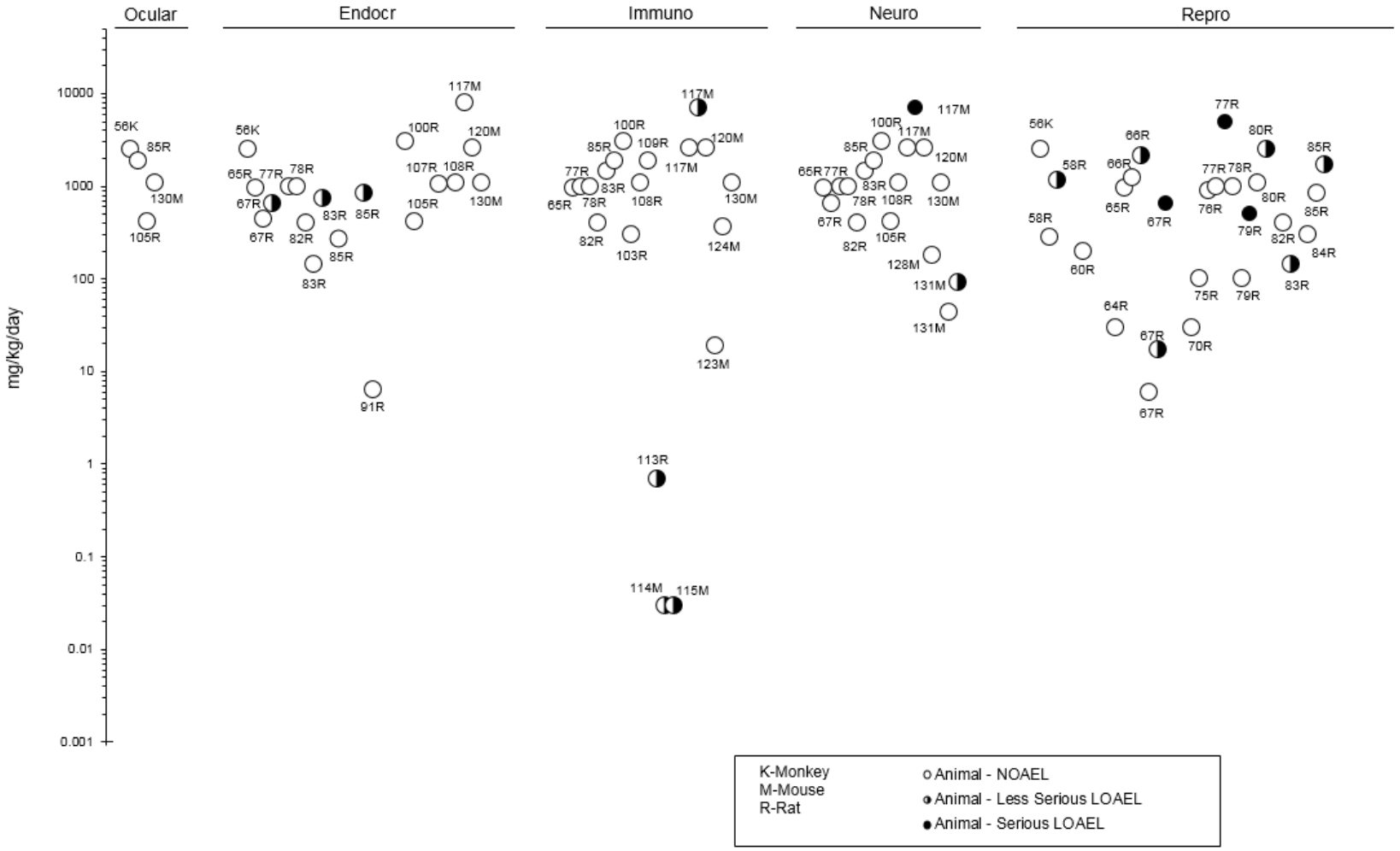


Figure 2-3. Levels of Significant Exposure to DEHP - Oral
Intermediate (15-364 days)

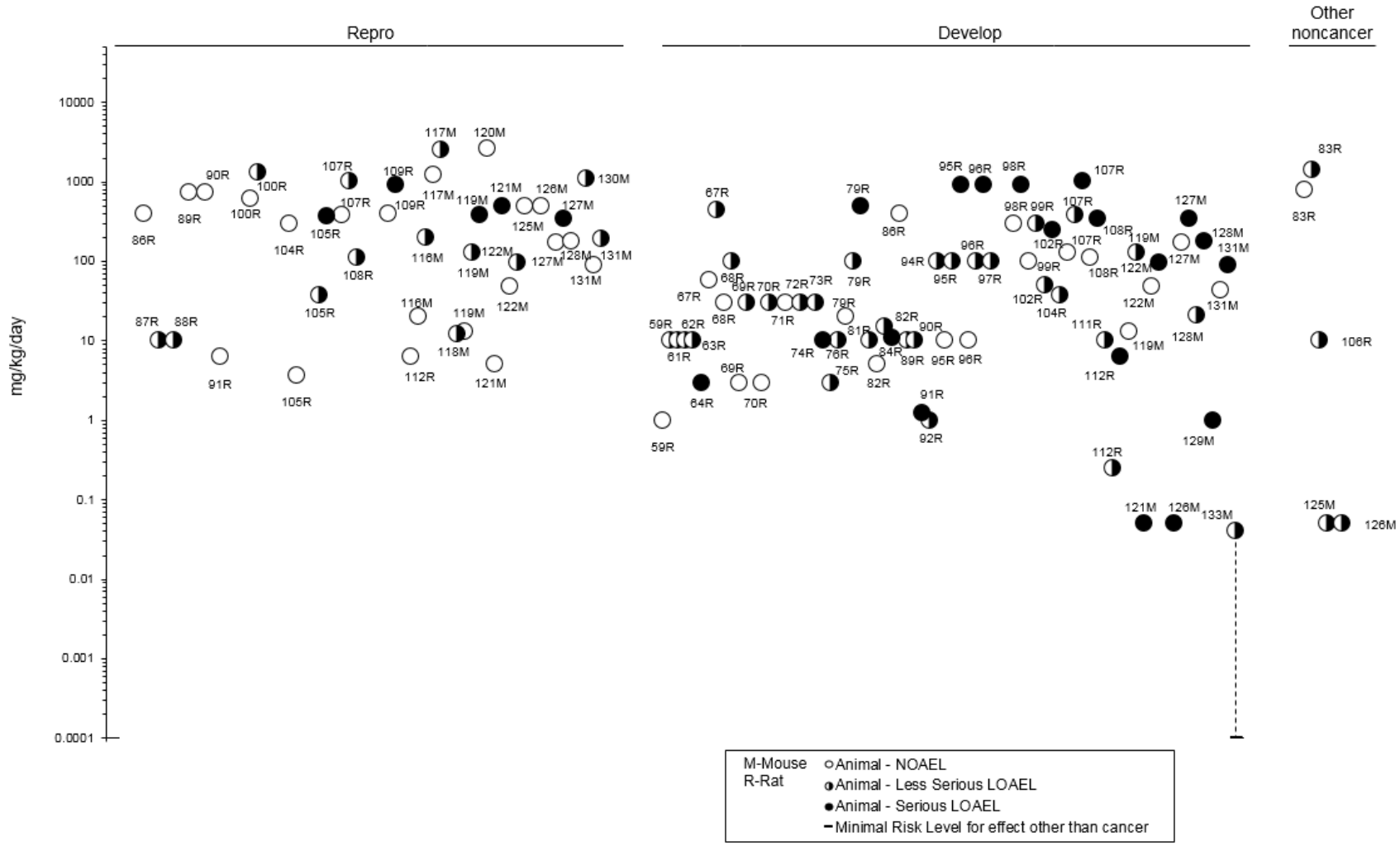


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Chronic (≥365 days)

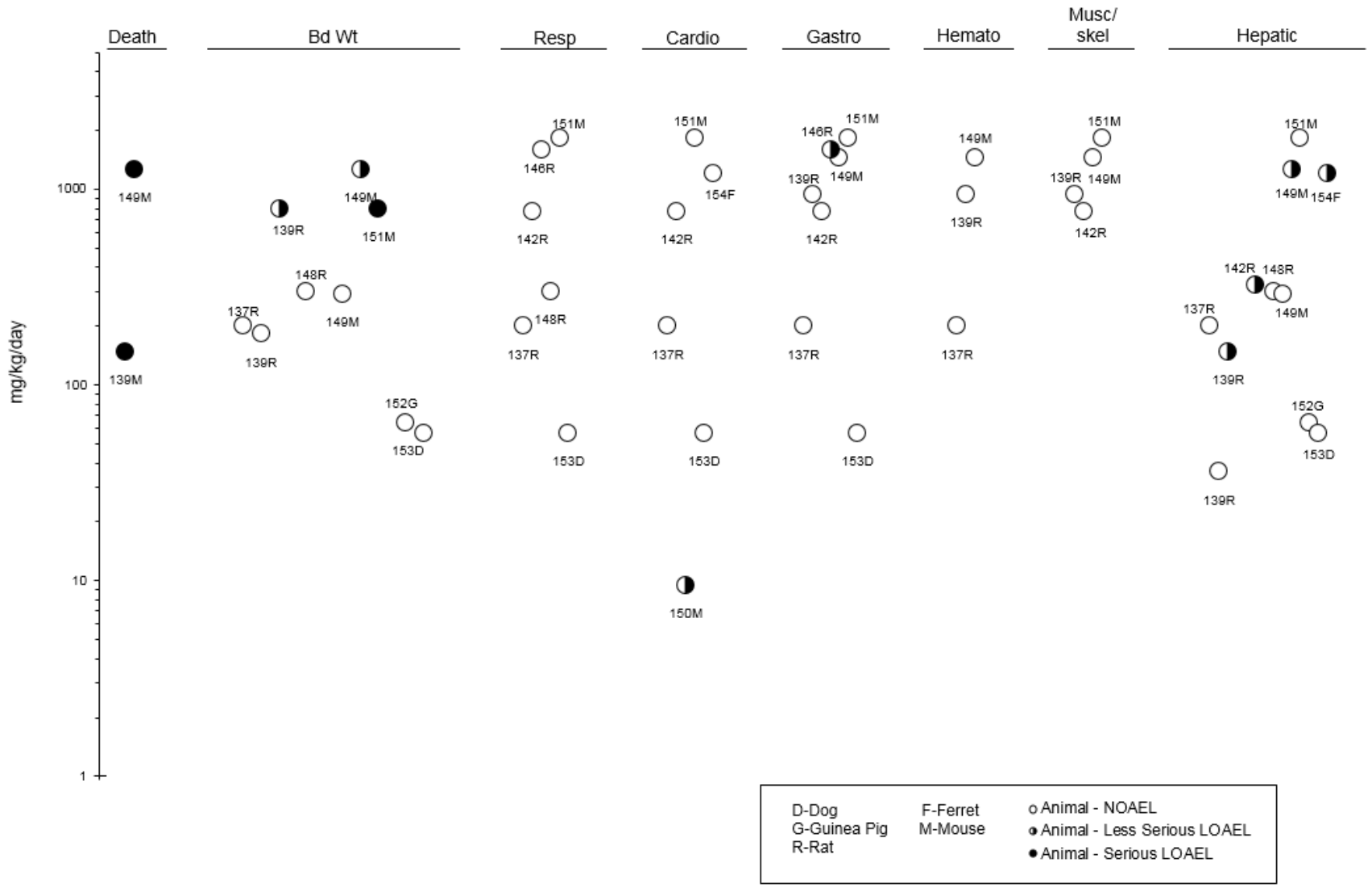


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Chronic (≥365 days)

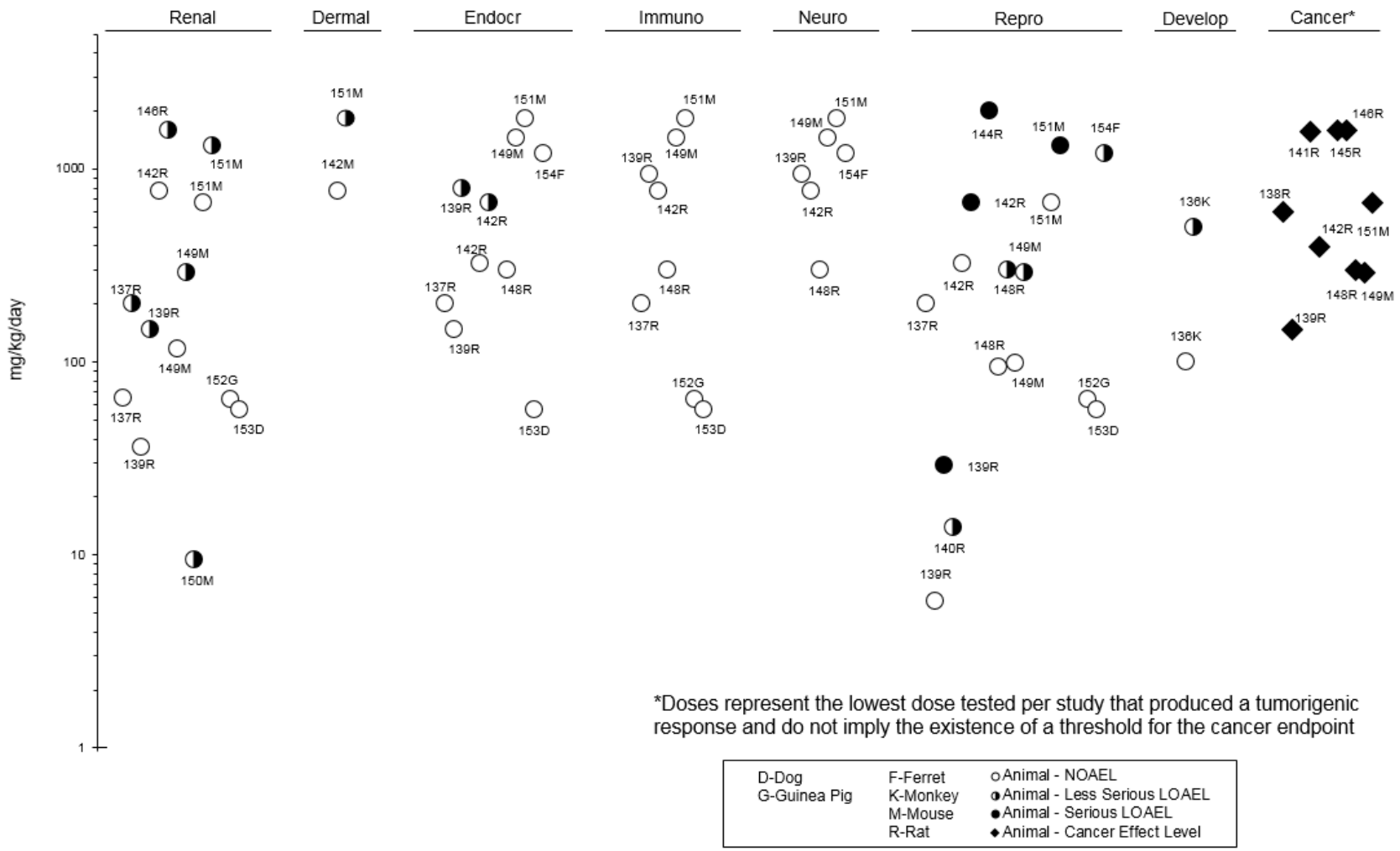


Table 2-3. Levels of Significant Exposure to DEHP – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Human 23 NS	7 days	Undiluted	CS	Dermal	Undiluted			
Shaffer et al. 1945								
Rabbit (NS) 6 NS	Once	≤19,800 mg/kg	CS, LE	Death			19,800	2/6 died
				Dermal	19,800			
Shaffer et al. 1945								

CS = clinical signs; DEHP = di(2-ethylhexyl)phthalate; LE = lethality; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

No studies were located regarding lethality in humans after inhalation exposure to DEHP. Studies in animals suggest that DEHP has low toxicity when inhaled. No deaths occurred in rats exposed to concentrations up to 21 ppm for 6 hours/day for 10 days (Merkle et al. 1988) or hamsters exposed to 0.0001 ppm for their lifetime (Schmezer et al. 1988). At a concentration of 0.0001 ppm, DEHP is present as a vapor, while at 21 ppm, it is an ultra fine aerosol. On the other hand, DEHP was found to be lethal to rats after 2–4 hours of exposure to a mist prepared by passing air through a heated sample of DEHP (Shaffer et al. 1945). However, the concentration of DEHP in the mist was not measured.

A single oral exposure to doses up to 10 g DEHP was not lethal to humans (Shaffer et al. 1945), and no case of death in humans after oral exposure to DEHP was identified in the available literature, suggesting that DEHP may not be acutely lethal to humans. This is supported by studies in rats and rabbits that indicate that single dose oral LD_{50} values are quite high (30,600–33,900 mg/kg) (Shaffer et al. 1945). To receive an equivalent dose, an adult human weighing 70 kg would have to consume about 4–5 pounds of DEHP. Some species seem to be more sensitive than others, potentially due to differences in toxicokinetics, as discussed in Section 3.1.6 (Animal-to-Human Extrapolations). In adult animals, exposure to 2,000 mg/kg/day (only dose tested) for up to 7 days resulted in mortalities in rabbits, but not in guinea pigs, mice, or rats (Parmar et al. 1988). After 2–4 weeks of exposure, deaths were observed at doses ≥2,000 mg/kg/day in rabbits, rats, and guinea pigs and 6,922 mg/kg/day in mice (Dalgaard et al. 2000; Myers 1992a; Parmar et al. 1987, 1988). Treatment of lactating female rats (postpartum days 1–7) with 5,000 mg DEHP/kg by gavage resulted in 25% mortality within 1 week of treatment (Cimini et al. 1994).

Deaths occurred at lower doses in longer-duration animal studies. In 2-generation studies, increased mortality was observed in F1 rats at doses of approximately 1,040–1,088 mg/kg/day; however, mortality rate was not increased above controls at doses ≤380 mg/kg/day (Schilling et al. 1999, 2001). In a 24-week dietary study, 100% mortality was observed after 16 weeks in mice exposed to doses of approximately 2,400 mg/kg/day in the diet (Ward et al. 1998); at the time of death, mean body weights were approximately 50% that of controls. In 2-year studies, survival was reduced in male F344 rats (12% less than controls) and male B6C3F1 mice (45% less than controls) that ingested 147 and 1,266 mg DEHP/kg/day in the diet, respectively (David et al. 1999, 2000a, 2000b). The most frequent cause of death in the chronic studies was mononuclear cell leukemia in the rats and liver tumors in the mice.

Certain populations, such as the young, may have increased susceptibility to DEHP-related mortality; however, the reason(s) why are not clear. Five doses of 2,000 mg DEHP/kg caused a 96% mortality in rats ≤21 days old, but there were no deaths in rats ≥42 days old (Dostal et al. 1987). Increased mortality (60%) was also observed in sexually immature rats and mice exposed to dietary doses of ≥11,000 mg/kg/day for 14 days (NTP 1982).

When rabbits were exposed to single dermal applications at doses up to 19,800 mg/kg DEHP using a modification of the U.S. Food and Drug Administration (FDA) cuff test, two of six rabbits in the highest dose group died. The dermal LD_{50} value calculated from these data was 24,750 mg/kg (Shaffer et al. 1945).

2.3 BODY WEIGHT

Overview. Many epidemiological studies, primarily cross-sectional in design, have examined associations between DEHP exposure (measured as urinary metabolites) and anthropometric measurements relating to body weight, such as BMI, waist circumference, and risk of obesity or being overweight. A systematic review of phthalate exposure (including DEHP) and obesity outcomes conducted by Goodman et al. (2014) evaluated studies published through June, 2013. Numerous inhalation and oral animal studies have evaluated body weight following exposure to DEHP for various durations. Potential mechanisms of obesity have been evaluated in a review by Kim and Park (2014). Studies evaluating weight after developmental exposure (e.g., birth weight) are discussed in Section 2.17 (Developmental).

Epidemiology Studies. The systematic review conducted by Goodman et al. (2014) concluded that the available data (through June, 2013) evaluating obesity outcomes and phthalate exposure did not indicate a consistent association between DEHP and BMI, waist circumference, or fat distribution.

Studies published after Goodman et al. (2014) that met inclusion criteria (Appendix B) are shown in Table 2-4; these include a cohort study (Teitelbaum et al. 2012) where exposure was measured approximately 1 year prior to anthropometric measurements; a cohort study (Bellavia et al. 2017) where exposure was measured in pregnant women during the first trimester and body weights were measured at first and second trimester visits; and nine cross-sectional or case-control studies that measured exposure and outcome at the same time. Six additional cohort studies evaluating potential associations between growth or obesity in children and prenatal exposure (maternal urinary metabolites) are discussed in Section 2.17 (Developmental), as this study design evaluates potential effects of exposure during early

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Cohort studies					
Bellavia et al. 2017 Cohort (United States [Boston])	347 pregnant women with full-term births recruited from a prospective pregnancy cohort at Brigham and Women's Hospital (LIFECODES cohort), mean age 32 years; maternal urine samples collected at 1st trimester visit (median 9.9 weeks), anthropometric measurements made at 1st trimester visit (median 9.9 weeks) and 2nd trimester visit (median 17.3 weeks) to determine early gestational weight gain (GWG).	Linear quantile regression adjusted for maternal age, race/ethnicity, education, smoking, alcohol, baseline BMI (at 1st trimester visit), specific gravity (SG)	Change in GWG per log-unit increase in SG-adjusted urinary metabolite concentration (50th percentile of GWG distribution)		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	0.4 (0.2–0.8) µmol/L (GM [IQR])	Q1: Reference Q2: 0.23 (-0.53, 0.98) Q3: -0.98 (-1.74, -0.21) Q4: -0.42 (-1.22, 0.39)
Teitelbaum et al. 2012, Cohort (United States [New York])	379 Hispanic and Black children (299 girls, 80 boys; age 6–8 years) recruited at the Mount Sinai Medical Center Pediatric Clinic, local community health centers, and local schools during 2004–2008 for a prospective cohort study (Growing Up Healthy Study). Children's urine samples collected at baseline; anthropometric measurements made 1 year later (mean age 8.42 years at followup).	Linear regression adjusted for urinary creatinine, age, sex, sedentary hours, metabolic equivalent hours, Hispanic ethnicity, caloric intake, season in which urine sample was collected, and parental education	BMI change per natural log-unit increase in urinary metabolite concentration		
			ΣDEHP	Girls: 235.5 µg/g Cr (median); Boys: 251.2 µg/g Cr (median)	β -0.03 (-0.44, 0.39)
			MEHP	Girls: 6.5 µg/g Cr; Boys: 6.3 µg/g Cr	β -0.03 (-0.38, 0.31)
			MEHHP	Girls: 72.0 µg/g Cr; Boys: 75.7 µg/g Cr	β 0.02 (-0.36, 0.41)
			MEOHP	Girls: 44.8 µg/g Cr; Boys: 50.4 µg/g Cr	β -0.04 (-0.43, 0.36)
			MECPP	Girls: 114.2 µg/g Cr; Boys:114.6 µg/g Cr	β -0.05 (-0.49, 0.38)
			Analysis of BMI Z-score did not alter results.		

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			Change in waist circumference per natural log-unit increase in urinary metabolite concentration		
			ΣDEHP	Girls: 235.5 µg/g Cr (median) Boys: 251.2 µg/g Cr (median)	β 0.00 (-1.11, 1.12)
			MEHP	Girls: 6.5 µg/g Cr Boys: 6.3 µg/g Cr	β 0.06 (-0.85, 0.98)
			MEHHP	Girls: 72.0 µg/g Cr Boys: 75.7 µg/g Cr	β 0.15 (-0.88, 1.19)
			MEOHP	Girls: 44.8 µg/g Cr Boys: 50.4 µg/g Cr	β -0.01 (-1.07, 1.05)
			MECPP	Girls: 114.2 µg/g Cr Boys:114.6 µg/g Cr	β -0.12 (-1.28, 1.05)
Cross-sectional and case-control studies					
Bellavia et al. 2017 Cross-sectional (United States [Boston])	347 pregnant women with full-term births recruited from a prospective pregnancy cohort at Brigham and Women's Hospital that delivered between 2006 and 2008 (LIFECODES cohort), mean age 32 years; maternal urine samples and anthropometric measurements collected at 1st trimester visit (median 9.9 weeks).	Linear quantile regression adjusted for maternal age, race/ethnicity, education, smoking, SG, and alcohol	Change in mean BMI per log-unit increase in SG-adjusted urinary metabolite concentration (entire cohort)		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	0.4 (0.2–0.8) µmol/L (GM [IQR])	Q1: Reference Q2: 1.93 (0.34, 3.52) Q3: 1.2 (-0.41, 2.8) Q4: 1.5 (-0.17, 3.18)
			Change in 25th percentile BMI per log-unit increase in SG-adjusted urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	0.4 (0.2–0.8) µmol/L (GM [IQR])	Q1: Reference Q2: 1.4 (0.12, 2.68) Q3: 1.23 (-0.06, 2.52) Q4: 2.32 (0.97, 3.67)

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			Change in 75th percentile BMI per log-unit increase in SG-adjusted urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	0.4 (0.2–0.8) µmol/L (GM [IQR])	Q1: Reference Q2: 3.29 (1.09, 5.49) Q3: 2.68 (0.45, 4.9) Q4: 1.68 (-0.64, 4.01)
			No significant shift in BMI was observed at any exposure level for the 50th percentile of BMI.		
James-Todd et al. 2016a Cross-sectional (United States [Boston])	350 pregnant women with full-term births. All else the same as Bellavia et al. (2017).	Linear regression adjusted for maternal age, race/ethnicity, education, smoking, SG, and alcohol	Change in baseline BMI per log-unit increase in SG-adjusted urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Q1: 0.12 µmol/L (median) Q2: 0.24 Q3: 0.53 Q4: 2.09	Q1: 26.2 (24.0, 28.3) Q2: 27.3 (25.1, 29.5) Q3: 27.5 (25.2, 29.7) Q4: 27.2 (25.0, 29.4)
James-Todd et al. 2016b, Case-control (United States)	965 cases of metabolic syndrome (464 men, 501 women) and 1,754 subjects without metabolic syndrome (924 men, 830 women), aged 20–80 years; participants in NHANES 2001–2010. Urine samples collected same day as anthropometric measurements.	Logistic regression adjusted for urinary creatinine, age, sex, race/ethnicity, total caloric intake, education, physical activity, smoking, and poverty	OR for central obesity (waist circumference ≥102 cm in men or ≥88 cm in women) comparing highest quartile of urinary concentration with lowest		
			ΣDEHP (MEHP, MEHHP, MEOHP)	With metabolic syndrome: 0.13 (0.12, 0.15) (GM [95% CI]) Without metabolic syndrome: 0.12 (0.10, 0.13)	OR 1.66 (1.16, 2.36)*

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Lin et al. 2016, Cross-sectional (Taiwan)	243 male and 550 female students (mean age 21.28 years), including 303 with and 486 without elevated blood pressure in childhood, from the YOTA study (recruited 1992–2000 from schools). Urine samples collected same day as anthropometric measurements.	Linear regression adjusted for age, gender, and smoking status	Association between BMI and log-transformed Cr-adjusted urinary metabolite concentration		
			MEHP	1.7–38.99 µg/g Cr	β 0.202* (NR)
			MEHHP	15.86–43.16 µg/g Cr	β 0.048 (NR)
			MEOHP	10.18–26.56 µg/g Cr	β -0.191 (NR)
Hou et al. 2015a, 2015b, Cross-sectional (Taiwan)	270 children and adolescents recruited from primary schools in Taipei, Taiwan (6.5–15 years), and 38 complainants involved in lawsuit regarding plasticizer-tainted foods (identified as part of Risk Assessment of Phthalate Incident in Taiwan program); ages 6.5–8 years. Urine samples collected same day as anthropometric measurements.	Linear and logistic regression adjusted for age, gender, and urinary creatinine	OR for increased BMI in highest quartile of urinary metabolite concentration compared with lowest		
			ΣDEHP	100.74–237.19	OR 1.48 (0.66, 3.3)
			MEHP	10.04–87.08	OR 0.78 (0.32, 1.9)
			MEHHP	23.49–60.30	OR 3.04 (1.25, 7.40)*
			MEOHP	16.43–41.00	OR 1.99 (0.79, 4.97)
			MECPP	31.70–77.63	OR 2.00 (0.82, 4.88)
			OR for increased waist-to-hip (circumference) ratio in highest quartile compared with lowest		
			ΣDEHP	100.74–237.19	OR 1.64 (0.82, 3.28)
			MEHP	10.04–87.08	OR 0.87 (0.42, 1.80)
			MEHHP	23.49–60.30	OR 2.44 (1.19, 5.01)*
			MEOHP	16.43–41.00	OR 2.90 (1.40, 6.03)*
			MECPP	31.70–77.63	OR 2.45 (1.19, 5.06)*

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			Change in waist circumference per unit increase in metabolite in the highest quartile compared to lowest		
			ΣDEHP	100.74–237.19	β 2.31 (-0.50, 5.12)
			MEHP	10.04–87.08	β -1.36 (-4.32, 1.60)
			MEHHP	23.49–60.30	β 4.18 (1.34, 7.03)*
			MEOHP	16.43–41.00	β 2.79 (-0.09, 5.68)
			MECPP	31.70–77.63	β 2.28 (-0.62, 5.17)
Yaghjyan et al. 2015a, 2015b, Cross-sectional (United States)	6,005 women ≥18 years of age (not pregnant and not diabetic); participants in NHANES 1999–2004. Urine samples collected same day as anthropometric measurements.	Ordered logistic regression adjusted for age, race, education, poverty, total calories, total fat, physical activity, menopausal status/hormone use, alcohol consumption, and smoking	OR for increased BMI per interquartile increase in Cr-adjusted urinary metabolite levels		
			ΣDEHP	19.59–58.66 µg/g Cr	OR 0.93 (0.84, 1.03)
			MEHP	1.49–5.95 µg/g Cr	OR 1.12 (1.03, 1.23)*
			MEHHP	9.86–31.09 µg/g Cr	OR 0.90 (0.80, 1.00)
			MEOHP	6.83–19.84 µg/g Cr	OR 0.90 (0.80, 1.01)
			MECPP	17.16–49.78 µg/g Cr	OR 0.81 (0.66, 1.00)
			OR for increased WC per interquartile increase in Cr-adjusted urinary metabolite levels		
			ΣDEHP	19.59–58.66 µg/g Cr	OR 0.90 (0.81, 1.00)
			MEHP	1.49–5.95 µg/g Cr	OR 1.05 (0.96, 1.15)
			MEHHP	9.86–31.09 µg/g Cr	OR 0.88 (0.79, 1.00)
			MEOHP	6.83–19.84 µg/g Cr	OR 0.89 (0.78, 1.01)
			MECPP	17.16–49.78 µg/g Cr	OR 0.80 (0.64, 0.99)*

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Buser et al. 2014, Cross-sectional (United States)	Children and adolescents (6–19 years) and non-pregnant, non-lactating adults (>19 years) from NHANES 2007–2008; subject number not reported. Urine samples collected same day as anthropometric measurements.	Logistic regression adjusted for age, race/ethnicity, calorie intake, serum cotinine, and urinary creatinine in all analyses, as well as income level (ages 6–19 only) and education level, recreational activity, smoking status, alcohol intake, and diabetes (adults only)	OR for obesity (BMI ≥30) in adults ≥20 years comparing highest quartile of urinary metabolite concentration with lowest quartile		
			ΣDEHP	0.18 (0.01) µmol/mL (GM [SE])	OR 1.62 (1.11, 2.37)*
			MEHP	2.01 (0.10)	OR 0.84 (0.55, 1.29)
			MEHHP	15.86 (0.85)	OR 1.51 (1.07, 2.14)*
			MEOHP	9.16 (0.47)	OR 1.44 (1.02, 2.05)*
			MECPP	24.30 (1.20)	OR 1.85 (1.29, 2.64)*
			OR for overweight (BMI 25–29.9) in adults ≥20 years comparing highest quartile of urinary metabolite concentration with lowest quartile		
			ΣDEHP	0.18 (0.01) µmol/mL (GM [SE])	OR 1.22 (0.89, 1.67)
			MEHP	2.01 (0.10)	OR 1.02 (0.78, 1.34)
			MEHHP	15.86 (0.85)	OR 1.15 (0.87, 1.53)
			MEOHP	9.16 (0.47)	OR 1.28 (0.98, 1.69)
			MECPP	24.30 (1.20)	OR 1.26 (0.87, 1.84)
			OR for obesity (BMI z-score ≥95th percentile) in children and adolescents (6–19) comparing highest quartile of urinary metabolite concentration with lowest quartile		
			ΣDEHP	0.24 (0.01) µmol/mL (GM [SE])	OR 1.09 (0.48, 5.49)
			MEHP	2.18 (0.11)	OR 0.84 (0.39, 1.80)
			MEHHP	21.03 (1.25)	OR 1.08 (0.51, 2.29)
			MEOHP	12.92 (0.72)	OR 1.07 (0.45, 2.58)
			MECPP	34.79 (1.66)	OR 0.96 (0.41, 2.24)

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			OR for overweight (BMI z-score between the 85th and 95th percentile) in children and adolescents (6–19 years old) comparing highest quartile of urinary metabolite concentration with lowest quartile		
			ΣDEHP	0.24 (0.01) µmol/mL (GM [SE])	OR 1.02 (0.44, 2.39)
			MEHP	2.18 (0.11)	OR 0.84 (0.41, 1.72)
			MEHHP	21.03 (1.25)	OR 1.11 (0.50, 2.50)
			MEOHP	12.92 (0.72)	OR 1.35 (0.59, 3.08)
			MECPP	34.79 (1.66)	OR 1.11 (0.54, 2.30)
Song et al. 2014, Cohort (United States [NHANES])	977 non-diabetic nurses from the Nurses' Health Study (NHS; age 30–55 years) and NHSII (age 25–42) recruited during 1996–2002 and followed for 10 years.		Association between BMI or weight gain and urinary metabolite concentration.		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	115–870 nmol/L	Effect estimates not reported; no significant association between metabolite levels and BMI or body weight gain.
Zhang et al. 2014, Cross-sectional (China)	493 children (247 boys, 246 girls, ages 8–13 years) recruited from suburban district in Shanghai between October and November 2011 (for the Puberty Timing and Health Effects in Chinese Children study). Urine samples collected same day as anthropometric measurements.	Logistic regression adjusted for socio-economic level, physical activity, dietary nutrient intake, puberty onset, and phthalate metabolite concentrations.	OR for obesity (weight >90th percentile) comparing highest and lowest quartiles of log-transformed urinary metabolite concentrations in girls		
			ΣDEHP	Girls 8–10 years: 5.2–497.7 Girls 11–13 years: 1.3–864.4 (min–max)	OR 0.078 (0.008, 0.791)*
			MEHP	Girls 8–10 years: <LOD–92.2 Girls 11–13 years: <LOD–117.1 (min–max)	OR 0.128 (0.013, 1.242)
			MEHHP	Girls 8–10 years: 3.2–290.0 Girls 11–13 years: 0.8–508.4 (min–max)	OR 0.084 (0.008, 0.91)*
			MEOHP	Girls 8–10 years: 1.2–115.5 Girls 11–13 years: <LOD–238.8 (min–max)	OR 0.092 (0.009, 0.958)*

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			OR for overweight (weight >80th and <90th percentiles) comparing highest and lowest quartiles of log-transformed urinary metabolite concentrations in girls		
			ΣDEHP	Girls 8–10 years: 5.2–497.7 Girls 11–13 years: 1.3–864.4 (min–max)	OR 0.811 (0.273, 2.405)
			MEHP	Girls 8–10 years: <LOD–92.2 Girls 11–13 years: <LOD–117.1 (min–max)	OR 0.664 (0.230, 1.913)
			MEHHP	Girls 8–10 years: 3.2–290.0 Girls 11–13 years: 0.8–508.4 (min–max)	OR 1.047 (0.339, 3.232)
			MEOHP	Girls 8–10 years: 1.2–115.5 Girls 11–13 years: <LOD–238.8 (min–max)	OR 0.092 (0.305, 2.829)
			Results for boys were not reported.		
Dirtu et al. 2013, Case-control (Belgium)	152 obese individuals recruited at the entry of a 12-month weight-loss program between November 2009 and February 2012 (46 men, 106 women; aged 18–84 years) and 43 non-obese, age- and sex-matched controls (12 men, 30 women; aged 19–59 years). Urine samples collected and anthropometric measurements made at baseline.	Linear regression adjusted for age and gender	Association between WC and urinary metabolite concentration in non-obese controls		
			ΣDEHP	Controls: 27–53	β -0.24
			MEHP	Controls: 2–5	β -0.10
			MEHHP	Controls: 9–19	β -0.20
			MEOHP	Controls: 3–9	β -0.29*
			MECPP	Controls: 12–20	β -0.26*
			Association between waist circumference at baseline and urinary metabolite concentration in obese cases		
			ΣDEHP	Cases: 30–61	β 0.01
			MEHP	Cases: 2–5	β -0.05
			MEHHP	Cases: 10–25	β 0.01
			MEOHP	Cases: 4–11	β -0.04
			MECPP	Cases: 12–22	β 0.04

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Wang et al. 2013, Cross-sectional (China)	259 students (ages 8–15 years) randomly selected from three primary and three middle schools in the Changning District of Shanghai City in 2011–2012; 124 normal weight, 53 overweight, and 82 obese subjects. Urine samples may have been collected after anthropometric measurements.	Linear regression adjusted for age, sex, and sum of other phthalates	Association between BMI and ln-transformed urinary metabolite concentrations		
			ΣDEHP	117.3 (GM)	β 0.015 (-0.026, 0.056)
			MEHP	21.3	β 0.048 (0.007, 0.089)*
			MEHHP	16.1	β 0.001 (-0.035, 0.037)
			MEOHP	22.9	β -0.001 (-0.037, 0.036)
			MECPP	28.8	β -0.006 (-0.042, 0.029)
			Association between waist circumference and ln-transformed urinary metabolite concentrations		
			ΣDEHP	117.3 (GM)	β 0.012 (-0.021, 0.044)
			MEHP	21.3	β 0.038 (0.006, 0.071)*
			MEHHP	16.1	β -0.002 (-0.03, 0.027)
			MEOHP	22.9	β 0.001 (-0.028, 0.03)
			MECPP	28.8	β -0.007 (-0.035, 0.022)
Hatch et al. 2008, Cross-sectional (United States [NHANES])	2,118 females and 2,251 males (age 6–80) from the general population; NHANES 1999–2002.	Linear regression adjusted for age, creatinine, height, race/ethnicity, socioeconomic status, percent of daily calories from total fat, daily servings of dairy, fruits, and vegetables, and television/video/ computer use	Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: females age 6–11 years		
			MEHP	5.4 (2.8) µg/g Cr (GM [SD])	BMI β 0.90 (-2.51, 0.71) WC β -2.51 (-6.52, 1.49)
			MEHHP	39.6 (2.5) µg/g Cr	BMI β 0.54 (-1.50, 2.57) WC β 1.83 (-3.48, 7.13)
			MEOHP	27.5 (2.4) µg/g Cr	BMI β -0.17 (-2.60, 2.26) WC β 0.45 (-5.56, 6.46)
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: females age 12–19 years		
			MEHP	3.8 (2.9) µg/g Cr (GM [SD])	BMI β -2.18 (-4.99, 0.63) WC β -1.51 (-2.81, -0.21)*

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			MEHHP	21.1 (2.6) µg/g Cr	BMI β 0.74 (-1.18, 2.65) WC β 1.81 (-3.19, 6.83)
			MEOHP	15.0 (2.4) µg/g Cr	BMI β 0.89 (-1.40, 3.18) WC β 1.79 (-4.10, 7.68)
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: females age 20–59 years		
			MEHP	4.0 (2.9) µg/g Cr (GM [SD])	BMI β -1.68 (-3.57, 0.21) WC β -2.17 (-5.99, 1.65)
			MEHHP	18.3 (2.8) µg/g Cr	BMI β 1.08 (-0.75, 2.92) WC β 3.13 (-0.73, 6.99)
			MEOHP	12.5 (2.7) µg/g Cr	BMI β 0.38 (-1.90, 2.66) WC β 1.52 (-2.98, 6.02)
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: females age 60–80 years		
			MEHP	3.3 (2.9) µg/g Cr (GM [SD])	BMI β -2.07 (-3.42, -0.73)* WC β -4.15 (-7.48, -0.81)*
			MEHHP	18.4 (2.7) µg/g Cr	BMI β -0.96 (-4.04, 2.11) WC β -2.82 (-8.89, 3.25)
			MEOHP	12.4 (2.6) µg/g Cr	BMI β 0.94 (-2.98, 4.85) WC β 2.46 (-7.41, 12.32)
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: males age 6–11 years		
			MEHP	5.5 (3.1) µg/g Cr (GM [SD])	BMI β -0.22 (-1.32, 0.89) WC β 0.55 (-3.31, 4.4)
			MEHHP	39.1 (2.4) µg/g Cr	BMI β 0.42 (-1.09, 1.92) WC β 1.27 (-2.43, 4.96)
			MEOHP	26.6 (2.4) µg/g Cr	BMI β 0.14 (-1.21, 1.48) WC β 0.6 (-2.68, 3.88)

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: males age 12–19 years		
			MEHP	2.7 (3.0) µg/g Cr (GM [SD])	BMI β -0.50 (-1.95, 0.94) WC β -1.39 (-5.15, 2.37)
			MEHHP	18.2 (2.8) µg/g Cr	BMI β 1.00 (-0.69, 2.69) WC β 2.15 (-1.77, 6.08)
			MEOHP	12.2 (2.8) µg/g Cr	BMI β 0.27 (-1.4, 1.94) WC β 0.68 (-2.67, 4.02)
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: males age 20–59 years		
			MEHP	3.3 (3.2) µg/g Cr (GM [SD])	BMI β 0.44 (-0.62, 1.52) WC β 0.91 (-1.43, 3.24)
			MEHHP	16.6 (3.0) µg/g Cr	BMI β 1.74 (-0.28, 3.76) WC β 4.60 (-0.03, 9.24)
			MEOHP	10.6 (2.8) µg/g Cr	BMI β 2.14 (-0.13, 4.41) WC β 5.81 (0.69, 10.94)
			Difference in BMI or WC between highest and lowest quartiles of urinary phthalate metabolite concentrations: males age 60–80 years		
			MEHP	2.5 (2.9) µg/g Cr (GM [SD])	BMI β -1.16 (-2.60, 0.28) WC β -2.42 (-5.76, 0.93)
			MEHHP	13.2 (2.9) µg/g Cr	BMI β 0.41 (-2.47, 3.28) WC β 0.68 (-7.42, 8.78)
			MEOHP	9.2 (2.7) µg/g Cr	BMI β 0.69 (-2.05, 3.44) WC β 2.31 (-4.97, 9.59)

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Stahlhut et al. 2007, Cross-sectional (United States [NHANES])	1,451 adult males >18 years who were not taking insulin, oral hypoglycemic agents, or sex hormone agonists/ antagonists; participants in NHANES 1999–2002. Urine samples collected same day as anthropometric measurements.	Linear regression adjusted for age, age, race/ ethnicity, total fat and calorie intake, physical activity level, smoking exposure, urinary creatinine, GFR, ALT, and GGT	Association between waist circumference and log-transformed urinary metabolite concentration		
			MEHP	11±1.3 µg/g Cr (mean±SE)	β 0.53 (NR)
			MEHHP	65.8±7.9 µg/g Cr	β 1.65* (NR)
			MEOHP	38.7±4.5 µg/g Cr	β 1.79* (NR)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; ALT = alanine transaminase transferase; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; GM = geometric mean; IQR = interquartile range; LOD = limit of detection; max = maximum; MECPP = 2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethyl-hexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; SD = standard deviation; SE = standard error; SG = specific gravity; WC = waist circumference; YOTA = Young Taiwanese Cohort

development. Teitelbaum et al. (2012) observed no association between DEHP metabolite levels in the urine of 7-year-old children and BMI or waist circumference in the children at age 8 years.

Bellavia et al. (2017) observed an inverse U-shaped relationship between first trimester urinary ∑DEHP metabolite levels and early gestational weight gain (between first and second trimesters) in a cohort of pregnant women with full-term births in a prospective analysis. In a cross-sectional analysis of the same cohort, urinary ∑DEHP metabolite levels were associated with higher first trimester BMI (Bellavia et al. 2017). In other cross-sectional and case-control studies, associations were reported for increased BMI in adults (Lin et al. 2016; Yaghjyan et al. 2015a, 2015b) and children (Hou et al. 2015a, 2015b; Wang et al. 2013), waist circumference in children (Hou et al. 2015a, 2015b; Wang et al. 2013), and increased odds of central obesity (waist circumference ≥102 cm in men or ≥88 cm in women) and obesity (BMI ≥30) in adults (Buser et al. 2014; James-Todd et al. 2016b). Three studies reported lower obesity with higher DEHP metabolite levels. Yaghjyan et al. (2015a, 2015b) reported decreased odds of increased waist circumference in adult women; Zhang et al. (2014) observed lower odds of obesity (weight >90th percentile) in children aged 8–13 years; and Dirtu et al. (2013) reported negative associations between waist circumference and DEHP metabolite levels.

The epidemiological data on DEHP metabolite levels and obesity parameters may be confounded by covariation among body weight, caloric intake, dietary composition (e.g., processed versus unprocessed foods), urinary creatinine levels, and DEHP exposure. As discussed in Section 5.6, diet is the primary source of exposure to DEHP. Individuals with higher body weight may experience higher caloric intake, leading to higher DEHP exposure. This relationship could lead to correlations between urinary metabolite levels and BMI or waist circumference that stem from higher caloric (and DEHP) intake rather than an effect of DEHP on these endpoints. By considering caloric intake as a covariate, confounding can be minimized; studies that considered caloric intake include Teitelbaum et al. (2012), James-Todd et al. (2016b), Yaghjyan et al. (2015a, 2015b), and Buser et al. (2014).

The use of urinary creatinine levels to correct for dilution of metabolite levels may also confound the data pertaining to BMI and waist circumference. Creatinine is a breakdown of muscle metabolism, and its levels in urine depend upon factors such as muscle mass, gender, age, and diet (among other factors; Johns et al. 2015). Because urinary creatinine levels are correlated to BMI and muscle mass independently of phthalate exposure (Johns et al. 2015), studies that used creatinine-corrected metabolite levels to assess associations with BMI or similar metrics (Lin et al. 2016; Yaghjyan et al. 2015a, 2015b) or reported results after adjustment for urinary creatinine (Buser et al. 2014; Hou et al. 2015a, 2015b;

James-Todd et al. 2016b; Teitelbaum et al. 2012) may yield spurious results for BMI or waist circumference. Studies that did not account for dilution by creatinine or specific gravity correction, or by consideration of one of these as a covariate in modeling (Dirtu et al. 2013; Zhang et al. 2014), may also be biased due to the lack of consideration of dilution. In their systematic review, Goodman et al. (2014) noted that positive associations between phthalates and obesity or overweight measures were most often seen in studies that did not account for urinary dilution of metabolite levels.

Animal Studies. In adult rats, no body weight effects were observed following nose-only exposure to concentrations up to 63 ppm for 4 weeks (5 days/week, 6 hours/day) (Klimisch et al. 1991, 1992). In mice, no body weight effects were observed in females intermittently exposed to concentrations up to 0.81 ppm for 14 weeks (20 minutes/day; 5 days/week for the first 2 weeks, 1 day/week for the next 12 weeks) (Larsen et al. 2007).

Numerous studies have documented reductions in body weight gain in rodents following oral exposure to high doses. However, dietary studies are complicated by evidence of decreased palatability at high doses, resulting in decreased food consumption. Due to this, gavage and dietary studies are discussed separately below. Body weight effects reported at dietary doses associated with decreased food consumption of a similar magnitude are not considered LOAELs in Table 2-2; however, since the relative contribution of decreased food intake cannot be fully determined, these values are also not listed as NOAELs. Body weight effects reported from dietary studies in the absence of food consumption data are also not reported as LOAELs in Table 2-2 since the potential impact of palatability cannot be assessed. However, all findings are discussed below.

Gavage studies in rodents. No exposure-related changes in body weight have been reported in nonpregnant, adult rodents following gavage exposure to acute doses ≤2,000 mg/kg/day (Guo et al. 2013; Lee and Koo 2007; Li et al. 2012a; Moser et al. 2003; Stroheker et al. 2005; Zacharewski et al. 1998) or intermediate-duration doses ≤1,000 mg (Akingbemi et al. 2001; Dalgaard et al. 2000; Hannon et al. 2014; Li et al. 2012a; Piepenbrink et al. 2005). The only intermediate-duration study that tested gavage doses >1,000 mg/kg/day reported a 9–32% decrease in body weight in male Wistar rats exposed to 5,000–10,000 mg/kg/day for 4 weeks (Dalgaard et al. 2000). No chronic-duration gavage studies in rodents were identified.

In pregnant animals, Sprague-Dawley or Long-Evans rats exposed to ≥625 mg/kg/day via gavage from gestation day (GD) 14 to 18, body weight gain decreases >30% were observed; actual body weight data

were not reported (Hannas et al. 2011). Another Sprague-Dawley rat study reported body weight loss in dams exposed to 750 mg/kg/day via gavage from GD 12 to postnatal day (PND) 0 (Chen et al. 2010). However, no changes in maternal body weight were observed in 12 additional rodent studies evaluating exposure during gestation/lactation at gavage doses ≤1,000 mg/kg/day (Table 2-2).

Dietary studies in rodents. Acute dietary studies do not report body weight effects at doses ≤1,250 mg/kg/day in rodents (Astill et al. 1986; Kitaoka et al. 2013; Muhlenkamp and Gill 1998; Sasaki et al. 2003). A 17% decrease was reported in mice following dietary exposure to 3,850 mg/kg/day for 7 days (Muhlenkamp and Gill, 1998); however, food consumption was not measured.

In intermediate-duration dietary studies in rats, decreases in body weight or body weight gain >10% in the absence of food consumption changes were reported at doses ranging from 737 to 1,724 mg/kg/day (Agarwal et al. 1986; Gray et al. 1977; Mitchell et al. 1985; Myers 1992b). Body weight changes at dietary doses ranging from 1,114 to 2,496 mg/kg/day were associated with significant reductions in food intake, suggesting potential palatability issues at high doses that may influence body weight due to decreased food consumption (Barber et al. 1987; CMA 1984; Exxon Chemical Americas 1990; Gray et al. 1977; Myers 1992b). However, a paired-feeding study in male rats at 1,440 mg/kg/day indicated that weight loss observed following intermediate-duration exposure could not be completely accounted for based on decreased food intake (Gray et al. 1977). In studies without food consumption data, body weight effects in rats were observed at doses ≥2,100 mg/kg/day, but not ≤1,300 mg/kg/day (Agarwal et al. 1986; Mitchell et al. 1985; NTP 1982; Short et al. 1987).

In intermediate-duration dietary studies in mice, decreases in body weight or body weight gain >10% in the absence of food consumption changes were reported at doses ranging from 1,100 to 7,899 mg/kg/day (Myers 1992b; Toyosawa et al. 2011). Decreased food consumption (18–20%) was only reported in male mice during the first 2 weeks of a 4-week study following exposure to 6,922 mg/kg/day (Myers 1992b). However, this dose was still considered a LOAEL for body weight effects due to the large magnitude of effect (35% decrease in body weight). In studies without food consumption data, body weight effects in mice were observed at doses ≥1,300 mg/kg/day, but not ≤1,200 mg/kg/day (NTP 1982; Sasaki et al. 2003).

In a chronic dietary study in F344 rats, a 15% decrease in body weight in the absence of reduced food intake was observed following exposure to 789 mg/kg/day for 104 weeks (David et al. 2000a). However, other 1- to 2-year studies in F344 rats reported both reduced body weights and reduced food intake levels

at dietary doses ≥322 mg/kg/day (Kluwe et al. 1982a; Marsman et al. 1988; NTP 1982). In chronic rat studies without food consumption data, body weight effects in rats were generally observed at doses >300 mg/kg/day (Carpenter et al. 1953; Rao et al. 1990; Tamura et al. 1990; Voss et al. 2005). However, one study in Sprague-Dawley rats reported an approximate 10 and 20% decrease in body weight after 6 months of exposure to 140 and 1,400 mg/kg/day, respectively, with terminal body weight decreases of approximately 8 and 27%, respectively, after 102 weeks (Ganning et al. 1991). In mice, chronic exposure to dietary doses ≥799 mg/kg/day, but not ≤672 mg/kg/day, resulted in decreased body weight in the absence of altered food consumption (David et al. 2000b; Kluwe et al. 1982a; NTP 1982). No exposure-related body weight effects were observed in guinea pigs exposed to doses up to 64 mg/kg/day for 1 year (Carpenter et al. 1953).

In a multigeneration study in Sprague-Dawley rats, exposure-related decreases in body weight were observed in F0 and F1 parental animals at dietary doses of 447–659 mg/kg/day without evidence of decreased food consumption (Blystone et al. 2010; NTP 2005). In other 2-generation studies in Wistar rats, exposure-related decreases in body weight and food consumption were observed in F0 and F1 parental animals at dietary doses of 1,040–1,088 mg/kg/day; no body weight or food consumption effects were observed at ≤380 mg/kg/day (Schilling et al. 1999, 2001). No maternal body weight effects were observed in a gestational/lactational study in Wistar rats at dietary doses up to 405 mg/kg/day (Andrade et al. 2006c; Grande et al. 2006). In gestational studies in mice, maternal body weight effects were observed in the absence of decreased food intake at doses ≥191 mg/kg/day, but not ≤170 mg/kg/day (Price et al. 1988b; Shiota and Nishimura 1982; Shiota et al. 1980; Tyl et al. 1988). No changes in parental body weight were observed in a continuous breeding study in mice at dietary doses up to 390 mg/kg/day (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984) or a 1-generation study in mice at dietary doses up to 180.77 mg/kg/day (Tanaka 2002). However, a 1-generation study by Schmidt et al. (2012) reported an approximate 20% increase in body weight and food consumption in parental mice exposed to dietary levels of 0.05–500 mg/kg/day for 8 weeks.

Other mammalian species. Body weight effects were only noted in ferrets, with a 31% decrease in body weight after exposure to 1,200 mg/kg/day for 14 months (Lake et al. 1976). However, food consumption was not measured in the study by Lake et al. (1976). No body weight effects were noted in monkeys exposed to 2,500 mg/kg/day via gavage for 13 weeks (Kurata et al. 1998). No exposure-related body weight effects were noted in dogs exposed to 56.6 mg/kg/day via capsule for 1 year (Carpenter et al. 1953).

Mechanisms of Obesity. Kim and Park (2014) suggest several mechanisms for DEHP-induced obesity, including activation of peroxisome proliferator activated receptors (PPARs), disruption of thyroid function (which can lead to altered regulation of energy balance and metabolic function), and epigenetic modulation resulting from a suboptimal fetal environment. Support for these mechanisms based on available experimental data included: (1) increased fat accumulation in DEHP-exposed mice expressing human PPARα; (2) promotion of differentiation and lipid accumulation in 3T3-L1 cells (embryonic mouse fibroblasts that differentiate to adipocyte-like cells) by mono(2-ethylhexyl)phthalate (MEHP), a PPARγ agonist; and (3) decreased plasma T4 levels and iodide uptake in rodent thyroid follicular cells exposed to DEHP (which is suggestive of impaired thyroid function that could lead to decreased metabolic function and subsequent weight gain).

Summary. Available human epidemiological studies suggest a potential association between DEHP exposure and obesity in adults. However, most of these studies have numerous limitations arising from cross-sectional design and lack of consistent control for potential confounders. The vast majority of animal studies evaluating body weight focus on body weight decreases following exposure to high levels of DEHP. Many high-dose dietary studies reported decreased food intake, indicating that decreased palatability at high doses may contribute to observed body weight effects. However, a paired-feeding study showed that decreased body weight was not entirely attributable to decreased food intake. One study reported elevated body weight with low dietary exposure (Schmidt et al.2012); additional endpoints from this study related to metabolic syndrome (increased adipose tissue and serum leptin) are further discussed in Section 2.18 (Other Noncancer).

2.4 RESPIRATORY

Overview. There are few data pertaining to the potential respiratory effects of human exposure to DEHP. Only one animal study evaluated respiratory function following inhalation exposure to DEHP. Several animal studies evaluated lung weight and/or histology following oral or inhalation exposure. Only one study evaluated nasal histology.

Epidemiology Studies. In a panel study with repeated urine samples and spirometry tests in 418 Korean adults >60 years old, increased DEHP metabolite (mono-2-ethyl-5-hydroxyhexylphthalate [MEHHP] and mono-(2-ethyl-5-oxohexyl)phthalate [MEOHP]) levels in urine were associated with poorer pulmonary function test scores (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] and forced expiratory flow at 25–75% of FVC [$FEF_{25–75}$]; Park et al. 2013). In this study (Park et al. 2013), the

authors observed altered associations when the data were stratified by genetic polymorphisms in catalase (CAT), superoxide dismutase (SOD2), and myeloperoxidase (MPO), suggesting that gene-environment interactions may alter the effect of DEHP exposure on lung function. A negative association between pulmonary function and DEHP exposure also occurred in a cross-sectional study of 3,157 subjects (ages 6–49 years) in Canada, in which an increase in the sum of DEHP metabolites (MEHP, MEHHP, MEOHP) in the urine was associated with impaired lung function (FEV_1, FVC, and FEV_1/FVC), primarily in males and subjects 17–49 years of age (Cakmak et al. 2014). However, no association between lung function measures and MEHP in urine (mean 2.0 ng/mL in women and 3.3 ng/mL in males) was observed in 240 adult participants in NHANES III, 1988–1994 (Hoppin et al. 2004). Kolena et al. (2014) observed *improved* pulmonary function (FEV_1/FVC) with higher urinary MEHP levels (mean 15 ng/mL) in a study of 30 community service workers (mean age 46 years) with exposure to DEHP along with other air pollutants for an average of 7.9 years (men) and 5.6 years (women) during waste processing or loading; other DEHP metabolites were not evaluated. Interpretation of this study is limited by small sample size.

Unusual lung effects, resembling hyaline membrane disease caused by insufficient surfactant production, were observed 4 weeks after birth in three children who were exposed to DEHP in respirator tubes during mechanical ventilation as preterm infants (Roth et al. 1988). These infants initially showed improvements after birth prior to progressive alterations in the lungs, which were not attributable to typical lung damage associated with artificial ventilation (e.g., oxygen toxicity, barotrauma, or bronchopulmonary dysplasia). Although interpretation of these findings is complicated by the preexisting compromised health status of the preterm infants, information provided by the authors indicated that DEHP was released from the walls of the PVC respiratory tubes used by the infants, supporting the potential for exposure.

Animal Studies. Rapid shallow breathing (decreased tidal volume and increased respiratory rate) was observed during lung function analysis of female mice following a 60-minute exposure to DEHP at 19 ppm (Larsen et al. 2007). No alterations in lung function were observed at 2 ppm, and no other respiratory system endpoints were evaluated. No changes in lung weight were observed in female weanling rats exposed to DEHP at concentrations up to 1.6 ppm for 6 hours/day, 5 days/week for 9 weeks (Ma et al. 2006). At 63 ppm, but not ≤3 ppm, increased lung weights accompanied by thickening of the alveolar septa and proliferation of foam cells were observed in male rats exposed for 6 hours/day, 5 days/week for 4 weeks (Klimisch et al. 1991, 1992). These effects were reversible within an 8-week post-exposure period, and were not observed at any time point in similarly-exposed females.

Additionally, no histopathological lesions were observed in the lungs of male or female rats following exposure (Klimisch et al. 1991, 1992).

One study reported an increased incidence (compared with controls) of eosinophilic bodies in nasal cavities of mice exposed to DEHP at dietary doses of 1,100 mg/kg/day for 26 weeks (no other doses tested) (Toyosawa et al. 2001). No other available studies reviewed nasal effects following oral exposure.

No adverse effects on the trachea or lung were reported in any of the oral animal studies reviewed. In intermediate-duration studies, no changes in lung weights and/or lung or trachea histology were observed in monkeys at doses up to 2,500 (Kurata et al. 1998), rats at doses up to 3,000 mg/kg/day (Gray et al. 1977; Myers 1992b; NTP 1982; Poon et al. 1997), or mice at doses up to 7,899 mg/kg/day (Myers 1992a, NTP 1982; Toyosawa et al. 2001). In chronic-duration studies, no changes in lung weights or histology were observed in dogs at 56.6 mg/kg/day (Carpenter et al. 1953), rats at doses up to 1,600 mg/kg/day (Carpenter et al. 1953; Kluwe et al. 1982a; NTP 1982; Rao et al. 1990; Voss et al. 2005), or mice at doses up to 1,821 mg/kg/day (Kluwe et al. 1982a; NTP 1982). Pulmonary function was not assessed in any of these studies.

In a developmental study, altered lung structure has been reported in PND 1 and 21 offspring of rats exposed to DEHP at gavage doses of 750 mg/kg/day from GD 12 to PND 0 or from GD 12 to PND 21, respectively (Chen et al. 2010). Lung alterations included increased thickness of alveolar septa and less airspace in the lung, which was attributed to a significant increase in the proportion of interstitial lung tissue. However, no clinical signs of respiratory distress were observed in pups. No structural changes were observed in the lungs at maternal doses ≤100 mg/kg/day (Chen et al. 2010). No changes in lung weights were observed in sexually immature monkeys exposed to 500 mg/kg/day for 14 days (Pugh et al. 2000).

A series of studies reported elevated immune responses in the lungs of mice sensitized to OVA following both inhalation and oral exposure to DEHP (Guo et al. 2012; Han et al. 2014; Larsen et al. 2007; Yang et al. 2008). These studies are discussed in Section 2.14 (Immunological).

Summary. Available human and animal data do not suggest that the respiratory system is a sensitive target of DEHP toxicity; however, data on respiratory function and potential nasal effects are limited.

2.5 CARDIOVASCULAR

Overview. Available epidemiological studies evaluating cardiovascular effects (that met selection criteria) include cross-sectional and case-control studies of blood pressure. Studies examining serum levels of triglycerides and cholesterol are discussed in Section 2.9 (Hepatic). A limited number of animal studies evaluated cardiovascular effects, including blood pressure, heart weight, and heart histology.

Epidemiology Studies. The potential association between DEHP exposure and high blood pressure was evaluated in one cohort study in pregnant women, and five cross-sectional studies in the general population (Table 2-5). Four of the five cross-sectional studies (James-Todd et al. 2016b; Shiue and Hristova 2014; Trasande and Attina 2015; Trasande et al. 2013b) used NHANES data and reported associations between DEHP urinary metabolite levels and increased blood pressure. These cross-sectional studies are limited by inability to establish temporality between exposure and effect, as well as the use of single urine measurements to assess exposure. In the pregnancy cohort, no associations were observed between maternal blood pressure or pregnancy-induced hypertensive disorders and DEHP metabolite concentration in maternal urine (Werner et al. 2015).

Animal Studies. No changes in heart weight or histology were observed in rats following nose-only exposure to DEHP concentrations up to 63 ppm for 4 weeks (5 days/week, 6 hours/day) (Klimisch et al. 1992). No other studies were located regarding cardiovascular effects in animals after inhalation exposure to DEHP.

Kamijo et al. (2007) reported elevated systolic blood pressure (compared with controls) in mice exposed to approximately 9.5 or 48.5 mg/kg/day of DEHP in feed for 6–22 months; however, these effects are likely secondary to the observed renal dysfunction in this study, as discussed in Section 2.10 (Renal). Elevated blood pressure associated with impaired kidney function was also observed in adult offspring of maternal rats exposed to DEHP from GD 0 to PND 21 at 0.25 or 6.25 mg/kg/day; systolic pressure was elevated in low dose males on day 21, systolic pressure was elevated in both sexes at both doses at 33 weeks, and diastolic pressure was elevated in both sexes at the low dose at 33 weeks (Wei et al. 2012). In contrast, a mild (but statistically significant) 4% decrease in systolic blood pressure was observed in adult offspring of rats exposed to 300 mg/kg/day from GD 14 to PND 0; neither kidney function nor kidney histology were evaluated in adult offspring in this study (Martinez-Arguelles et al. 2013).

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
James-Todd et al. 2016b, Cross-sectional (United States [NHANES])	965 cases of metabolic syndrome (464 men and 501 women) and 1,754 subjects without metabolic syndrome (924 men and 830 women), aged 20–80 years; participants in NHANES 2001–2010. Urine samples collected same day as blood pressure measurements.	Logistic regression adjusted for urinary creatinine, age, sex, race/ethnicity, total caloric intake, education, physical activity, smoking, and poverty	Prevalence OR for high blood pressure comparing highest quartile of urinary concentration with lowest (cases and controls grouped)		
			ΣDEHP (MEHP, MEHHP, MEOHP)	With metabolic syndrome: 0.13 (0.12, 0.15) (GM [95% CI]) Without metabolic syndrome: 0.12 (0.10, 0.13)	All: OR 1.56 (1.14, 2.12)* Men: OR 1.85 (1.12, 3.05)* Women: OR 1.24 (0.82, 1.88)
Lin et al. 2016, Cross-sectional (Taiwan)	794 adult students (243 men and 550 women; mean age 21.28 years), including 303 with and 486 without elevated blood pressure in childhood, from the YOTA study (recruited 1992–2000 from schools). Urine sample collected same day as blood pressure measurements.	Linear regression adjusted for age, gender, and smoking status	Association between systolic blood pressure (mm Hg) and log-transformed Cr-adjusted urinary metabolite concentration		
			MEHP	1.7–38.99 µg/g Cr	β 0.225 (NR)
			MEHHP	15.86–43.16 µg/g Cr	β 0.144 (NR)
			MEOHP	10.18–26.56 µg/g Cr	β 0.136 (NR)

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Trasande and Attina 2015, Cross-sectional (United States [NHANES])	1,329 children (688 boys and 641 girls) aged 8–19 years, participants in NHANES 2009–2012. Urine sample collected same day as blood pressure measurement.	Linear or logistic regression adjusted for sex, caloric intake, physical activity, poverty-income ratio, serum cotinine, urinary creatinine, BMI category, race/ethnicity, and age category, and subsample weighting	OR for blood pressure >90th percentile for age/height z-score/sex per log-unit increase in urinary metabolite concentration		
			ΣDEHP	0.077–0.313 µM	OR 1.31 (0.90, 1.91)
			MEHP	NR	OR 1.09 (0.79, 1.50)
			MEHHP	NR	OR 1.27 (0.89, 1.81)
			MEOHP	NR	OR 1.18 (0.83, 1.66)
			MECPP	NR	OR 1.47 (0.95, 2.27)
			Association between blood pressure z-score and log-transformed urinary metabolite concentration		
			ΣDEHP	0.077–0.313 µM	Systolic: β 0.10 (0.03, 0.18)* Diastolic: β 0.09 (0.04, 0.17)*
			MEHP	NR	Systolic: β 0.06 (-0.03, 0.12) Diastolic: β 0.04 (-0.02, 0.10)
			MEHHP	NR	Systolic: β 0.09 (0.02, 0.16)* Diastolic: β 0.09 (0.01, 0.16)*
			MEOHP	NR	Systolic: β 0.08 (0.01, 0.16)* Diastolic: β 0.09 (0.002, 0.16)*
			MECPP	NR	Systolic: β 0.11 (0.03, 0.19)* Diastolic: β 0.07 (-0.01, 0.16)

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Werner et al. 2015, Cohort	369 pregnant women aged ≥18 years; participants in the Health Outcomes and Measures of the Environment Study recruited between 2003 and 2006. Urine samples were collected at 16 and 26 weeks (on average) of gestation. Blood pressure data included two readings in early gestation (<20 weeks) and the two highest blood pressures after 20 weeks. Physician diagnoses of pregnancy-induced hypertensive diseases were recorded, including maternal hypertension (systolic ≥140 mm Hg and diastolic ≥90 mm Hg), preeclampsia, HELLP syndrome, or eclampsia.	Linear regression adjusted for maternal race, maternal age at delivery, household income, education, marital status, serum cotinine concentration, weeks of gestation at blood pressure measurement, parity, BMI at 16 weeks of gestation and previous use of blood pressure medications	Change in blood pressure at <20 weeks per 10-fold increase in log-transformed creatinine-adjusted urinary metabolite concentration at 16 weeks		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	53–159 µg/g Cr (average concentration from 16 and 26 weeks of gestation)	Diastolic β -0.4 (-1.6. 0.8) Systolic β -0.2 (-2.0, 1.6)
			Change in blood pressure at ≥20 weeks per 10-fold increase in creatinine-adjusted urinary metabolite concentration at 16 or 26 weeks		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	53–159 µg/g Cr (average concentration from 16 and 26 weeks of gestation)	Diastolic 16 weeks: β -0.8 (-2.2, 0.5) 26 weeks: β 0.3 (-1.3, 1.9) Average: β -0.6 (-2.4, 1.3) Systolic 16 weeks: β -1.0 (-3.0, 1.0) 26 weeks: β -0.8 (-3.1, 1.6) Average: β -1.6 (-4.3, 1.2)
			RR for pregnancy-induced hypertensive disorder per 10-fold increase in creatinine-adjusted urinary metabolite concentration at 16 or 26 weeks		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	53–159 µg/g Cr (average concentration from 16 and 26 weeks of gestation)	16 weeks: RR 0.85 (0.46, 1.58) 26 weeks: RR 1.42 (0.64, 3.13) Average: RR 1.09 (0.45, 2.66)

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Shiue and Hristova 2014, Cross-sectional (United States [NHANES])	20,293 adults (10,081 male and 10,212 female) aged ≥20 years, participants in NHANES 2009–2012. Urine sample collected same day as blood pressure measurement.	Logistic regression adjusted for urine creatinine, age at examination, sex, ethnicity, BMI, and subsample weighting	OR for high blood pressure (systolic ≥140 mm Hg and diastolic ≥90 mm Hg) with change (not specified) in log-transformed urinary metabolite concentration		
			MEHP	Normal blood pressure: 4.15±16.49 High blood pressure: 3.36±6.62	OR 1.03 (0.82–1.30)
			MEHHP	Normal blood pressure: 27.75±155.35 High blood pressure: 25.03±50.74	OR 1.21 (1.01–1.46)*
			MEOHP	Normal blood pressure: 16.45±97.03 High blood pressure: 15.22±25.48	OR 1.21 (1.01–1.45)*
			MECPP	Normal blood pressure: 40.10±249.63 High blood pressure: 38.52±64.13	OR 1.29 (1.04–1.59)*
			Shiue (2014a, 2014b) evaluated associations between blood pressure and urinary metabolite levels in subsets of this population (2009–2010 and 2011–2012 NHANES participants, respectively). In these studies, associations were seen with the same urinary metabolites.		

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Trasande et al. 2013b Cross-Sectional (United States [NHANES])	2,463 children (1,276 boys and 1,187 girls) aged 8–19 years; participants in 2003–2008 NHANES. Urine sample collected same day as blood pressure measurement.	Linear or logistic regression adjusted for urinary creatinine, BMI category, race/ethnicity, age category, caregiver education, poverty-income ratio, sex, serum cotinine, caloric intake, and television watching	OR for blood pressure >90th percentile for age/height z-score/sex per log-unit increase in urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	0.166–0.704 M	OR 0.94 (0.82, 1.08)
			Association between blood pressure z-score and log-transformed urinary metabolite concentration		
			ΣDEHP(M MEHP, MEHHP, MEOHP, MECPP)	0.166–0.704 M	Systolic: β 0.04 (0.001, 0.08)* Diastolic: β -0.005 (-0.04, 0.03)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; HELLP = hemolysis, elevated liver enzymes, low platelet count; IQR = interquartile range; MECPP = 2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; YOTA = Young Taiwanese Cohort

In other oral studies reviewed, no changes in heart weight or histology were observed; however, cardiovascular function was not assessed in any of these studies. No changes in heart weight were observed in sexually immature monkeys exposed to 500 mg/kg/day for 14 days (Pugh et al. 2000). In intermediate-duration studies, no changes in heart weight and/or histology were observed in monkeys at doses up to 2,500 mg/kg/day (Kurata et al. 1998), rats at doses up to 10,000 mg/kg/day (Dalgaard et al. 2000; Gray et al. 1977; Hazelton Washington 1992b; NTP 1982; Poon et al. 1997; Shaffer et al. 1945), or mice at doses up to 7,899 mg/kg/day (Myers 1992a; NTP 1982; Toyosawa et al. 2001). In chronic-duration studies, no changes in heart weight or histology were observed in dogs at 56.6 mg/kg/day (Carpenter et al. 1953), ferrets at 1,200 mg/kg/day (Lake et al. 1976), rats at doses up to 1,600 mg/kg/day (Carpenter et al. 1953; Kluwe et al. 1982a; NTP 1982), or mice at doses up to 1,821 mg/kg/day (Kluwe et al. 1982a; NTP 1982).

A potential effect on human heart muscle contractility was identified in *in vitro* studies. MEHP displayed a dose-dependent negative inotropic effect that weakened human atrial trabecular contractions at concentrations of 15–200 µg/mL, with an IC_{50} of 85 µg/mL (Barry et al. 1990). This suggests the possibility that high levels of serum MEHP could have a cardiotoxic effect in humans. However, rapid metabolism of MEHP would act to minimize the probability that MEHP concentrations would reach the concentration associated with the negative inotropic effect. The authors suggested that infants with multisystem failures would be the group at greatest risk to a cardiotoxic effect of MEHP. Yet, there was no indication of cardiovascular effects in 18 infants who had increased plasma levels of DEHP (8.3±5.7 µg/mL, mean highest concentration) from exposure during ECMO therapy for 3–10 days (DEHP had leached from plastic tubing) (Karle et al. 1997). Cardiac performance was evaluated by using echocardiograms to estimate output from heart rate, systolic blood pressure, left ventricular shortening fraction, and stroke volume measurements.

Summary. Mixed results were obtained in human studies for the association between DEHP exposure and elevated blood pressure. Evidence from animal studies suggests that altered blood pressure is secondary to renal toxicity following exposure to DEHP. Available animal data do not indicate that the cardiovascular system is a sensitive target of DEHP toxicity.

2.6 GASTROINTESTINAL

Human Studies. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to DEHP.

Acute exposures to large oral doses of DEHP can cause gastrointestinal distress. When two adult male volunteers ingested a single oral dose of 5 or 10 g DEHP (70 and 140 mg/kg based on 70-kg body mass), the individual consuming the larger dose complained of mild abdominal pain and diarrhea (Shaffer et al. 1945). No other effects of exposure were noted.

Animal Studies. No studies were located regarding gastrointestinal effects in animals after inhalation exposure to DEHP.

In oral studies, pseudoductular lesions and altered acinar cell foci were observed in the pancreas of rats administered dietary DEHP at 3,000 mg/kg/day for 108 weeks (only dose tested) (Rao et al. 1990). These lesions are expected to affect digestive system functions of the pancreas, as opposed to endocrine function. No other chronic-duration studies reported histopathological lesions in the gastrointestinal system for dogs given 56.6 mg/kg/day (Carpenter et al. 1953), rats at doses up to 939 mg/kg/day (Carpenter et al. 1953; David et al. 2000a; Kluwe et al. 1982a; NTP 1982), or mice at doses up to 1,821 mg/kg/day (David et al. 2000b; Kluwe et al. 1982a; NTP 1982). Similarly, no histopathological lesions in the gastrointestinal system were observed following intermediate-duration exposure to doses up to 2,500 mg/kg/day in monkeys (Kurata et al. 1998), 3,000 mg/kg/day in rats (Gray et al. 1977; Hazelton Washington 1992b; NTP 1982; Poon et al. 1997), or 7,899 mg/kg/day in mice (Hazelton Washington 1992a; NTP 1982; Toyosawa et al. 2001).

Summary. The dataset is too limited to evaluate potential gastrointestinal effects from DEHP exposure.

2.7 HEMATOLOGICAL

Epidemiological Studies. Wang et al. (2015) reported no differences in hemoglobin levels between 352 DEHP-exposed Chinese workers in three PVC factories (factory average exposures ranging from 233 to 707 μg/m^3 DEHP) and 104 unexposed workers (average exposure, 0.26 μg/m^3 DEHP). No other studies examining hematological effects in humans after exposure to DEHP were located.

Animal Studies. No changes were observed in a comprehensive hematological evaluation in rats following nose-only exposure to DEHP concentrations up to 63 ppm for 4 weeks (5 days/week, 6 hours/day) (Klimisch et al. 1992). No other studies were located regarding hematological effects in animals after inhalation exposure to DEHP.

In nonhuman primates, no hematological changes were reported following oral DEHP exposure. Exposure to DEHP for 14–28 consecutive days did not cause hematological changes in sexually immature or mature Cynomolgus monkeys at doses of 500 or 1,000 mg/kg/day, respectively (Pugh et al. 2000; Satake et al. 2010) or marmoset monkeys at 2,000 mg/kg/day (ICI Americas Inc. 1982; Rhodes et al. 1986). Similarly, no adverse hematological effects were reported in marmoset monkeys following exposure to DEHP at doses up to 2,500 mg/kg/day via gavage for 13 weeks (Kurata et al. 1998).

Altered hematological parameters have been inconsistently reported in rodents following oral exposure to DEHP. Slight but significant decreases in red blood cell counts and serum hemoglobin were seen in male Sprague-Dawley rats exposed to dietary DEHP at approximately 375.2 mg/kg/day; doses ≤37.6 mg DEHP/kg/day were without hematological effect (Poon et al. 1997). In another 13-week dietary study in F344 rats, significant reductions in red blood cell count, hemoglobin, and hematocrit, and an increase in platelets, were observed in males at ≥850.1 mg/kg/day and significant reductions in hemoglobin, hematocrit, myeloid: erythroid ratio, and segmented neutrophils were observed in females at 1,857.6 mg/kg/day; no biologically significant hematological changes were observed at ≤261.2 mg/kg/day (Myers 1992b). Additionally, in a 17-week dietary study in Sprague-Dawley rats, significantly reduced hemoglobin levels were observed in males and significantly reduced packed cell volume was observed in both males and females at ≥737 mg/kg/day, but not ≤152 mg/kg/day (Gray et al. 1977). However, exposure of male albino rats to doses of 200–1,900 mg/kg/day DEHP in the diet for 90 days had no effect upon red blood cell counts, hemoglobin levels, or differential white cell counts (Shaffer et al. 1945). In mice, significantly reduced hemoglobin and hematocrit were observed in males and females exposed to dietary DEHP at doses ≥1,209 and 2,888 mg/kg/day, respectively, for 28 days; no hematological changes were observed at dietary doses ≤270 mg/kg/day (Myers 1992a). No changes have been observed in comprehensive hematological evaluations in chronic-duration studies at dietary doses up to 939 mg/kg/day in rats or 1,458 mg/kg/day in mice (Carpenter et al. 1953; David et al. 2000a, 2000b).

Summary. Data are sparse, but it does not appear that the primate hematological system is sensitive to DEHP exposure. Inconsistent hematological effects are reported in rodents exposed to DEHP.

2.8 MUSCULOSKELETAL

Human Studies. No studies were located regarding musculoskeletal effects in humans after exposure to DEHP.

Animal Studies. No changes were observed in the histology of the gastrocnemius muscles of rats following nose-only exposure to DEHP concentrations up to 63 ppm for 4 weeks (5 days/week, 6 hours/day) (Klimisch et al. 1992). No other studies were located regarding musculoskeletal effects in animals after inhalation exposure to DEHP.

No adverse effects on the musculoskeletal system were reported in an intermediate-duration study in marmoset monkeys at doses up to 2,500 mg/kg/day (Kurata et al. 1998). No adverse effects were reported in acute-, intermediate-, or chronic-duration oral studies in rats at doses up to 1,100, 3,000, or 939 mg/kg/day, respectively (Astill et al. 1986; David et al. 2000a; Gray et al. 1977; Kluwe et al. 1982a, 1982b, 1985; Myers 1992b; NTP 1982; Poon et al. 1997); or in intermediate- or chronic-duration studies in mice at doses up to 2,600 or 1,821 mg/kg/day, respectively (David et al. 2000b; Kluwe et al. 1982a, 1982b, 1985; NTP 1982; Toyosawa et al. 2001).

Summary. No epidemiological data exist for DEHP exposure and the musculoskeletal endpoint. An adult monkey and multiple rodent studies indicate that the musculoskeletal system is not adversely affected from DEHP exposure.

2.9 HEPATIC

Overview. Human data on hepatic effects of DEHP are extremely limited. Numerous oral and inhalation animal studies have evaluated hepatic effects following exposure to DEHP, including serum chemistry, biochemistry in liver tissue, liver weight, and liver histology. Several secondary sources have reviewed potential mechanisms of DEHP hepatotoxicity.

Epidemiology Studies. Wang et al. (2015) observed increases in facility-averaged serum alanine transaminase (ALT) (2.4–3-fold higher) and gamma-glutamyl transferase (GGT) (1.4–1.6-fold higher) in 352 Chinese workers exposed to DEHP at three different PVC manufacturing facilities (facility average exposures ranging between 233 and 707 µg/m^3 DEHP in the 3 factories) when compared with levels in 104 unexposed workers (average exposure, 0.26 µg/m^3 DEHP). Plasma cholinesterase activity was reduced by >30% in post-exposure samples of some workers at these facilities (25, 10, and 7 workers from small-, medium-, and large-sized facilities, respectively). This enzyme is synthesized by the liver; therefore, a reduction in plasma cholinesterase activity may be indicative of liver dysfunction (Meng et al. 2013). A correlation was observed between reduced plasma cholinesterase activity and DEHP residues in

plasma (Wang et al. 2015). Serum levels of total bilirubin, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total protein did not differ among the groups. Serum liver enzymes (ALT and AST) were not increased in 52 Taiwanese children exposed to DEHP in contaminated foods (dose estimates ranged up to 0.1874 mg/kg/day; Wu et al. 2013); however, the duration of exposure was not known.

Epidemiological studies that examined serum cholesterol and triglycerides and used urinary metabolite levels to assess exposure are shown in Table 2-6. All five of these studies were cross-sectional in design. A positive association between hypertriglyceridemia and DEHP exposure was reported in a study of NHANES participants with and without metabolic syndrome (data from cases and non-cases were combined for regression analysis; James-Todd et al. 2016b), but other studies examining triglyceride levels observed no association (Lin et al. 2016; Trasande and Attina 2015, Trasande et al. 2013b; Yaghjyan et al. 2015a, 2015b). Similarly, Lin et al. (2016) reported a negative relationship between MEHP in urine and high-density lipoprotein (HDL) cholesterol levels in 793 young adults in Taiwan, but no association was seen with other metabolites (MEHHP or MEOHP) or in other studies of this endpoint (James-Todd et al. 2016b; Trasande and Attina 2015, Trasande et al. 2013b; Yaghjyan et al. 2015a, 2015b). None of the available studies indicated that DEHP urinary metabolite levels were associated with alterations in LDL or total cholesterol levels (Table 2-6).

Animal Studies—Histopathology and Morphology. In the only inhalation study that evaluated liver histology, no exposure-related hepatic lesions were observed in rats following intermittent exposure to concentrations up to 63 ppm for 4 weeks (Klimisch et al. 1991, 1992).

In oral studies in nonhuman primates, no histopathological changes were observed in monkeys exposed to doses up to 2,500 mg/kg/day for up to 13 weeks (ICI Americas Inc. 1982; Kurata et al. 1998; Rhodes et al. 1986; Satake et al. 2010; Short et al. 1987).

Other than observations of hepatocellular hypertrophy (described below with liver weight data), 17 acute oral studies in rodents (Table 2-2) did not find exposure-related changes during microscopic examination of the liver following exposure to DEHP at doses up to 1,500 mg/kg/day or intermediate doses up to 10,000 mg/kg/day. Additionally, no histopathological changes were observed in hamsters exposed to doses up to 1,000 mg/kg/day for 14 days (Lake et al. 1984).

Table 2-6. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
James-Todd et al. 2016b, Case-control (United States)	965 cases of metabolic syndrome (464 men, 501 women) and 1,754 subjects without metabolic syndrome (924 men, 830 women), aged 20–80 years; participants in NHANES 2001–2010. Urine and blood samples collected same day.	Logistic regression adjusted for urinary creatinine, age, sex, race/ethnicity, total caloric intake, education, physical activity, smoking, and poverty	Prevalence OR for abnormal serum lipid and cholesterol levels comparing highest quartile of urinary concentration with lowest.		
			ΣDEHP (MEHP, MEHHP, MEOHP)	With metabolic syndrome: 0.13 (0.12, 0.15) (GM [95% CI]) Without metabolic syndrome: 0.12 (0.10, 0.13)	Hypertriglyceridemia OR 1.55 (1.12, 2.14)* Low HDL cholesterol OR 1.05 (0.74, 1.49)
Lin et al. 2016, Cross-sectional (Taiwan)	243 male and 550 female students (mean age 21.28 years), including 303 with and 486 without elevated blood pressure in childhood, from the YOTA study (recruited 1992–2000 from schools). Urine and blood samples collected same day.	Linear regression adjusted for age, gender, and smoking status	Association between serum lipid and cholesterol levels and log-transformed Cr-adjusted urinary metabolite concentration		
			MEHP	1.7–38.99 µg/g Cr	Log-triglycerides β 0.000 (NR) HDL cholesterol β -0.325* (NR) LDL cholesterol β 0.455 (NR)
			MEHHP	15.86–43.16 µg/g Cr	Log-triglycerides β -0.0004 (NR) HDL cholesterol β 0.344 (NR) LDL cholesterol β -0.537 (NR)
			MEOHP	10.18–26.56 µg/g Cr	Log-triglycerides β -0.011 (NR) HDL cholesterol β 0.262 (NR) LDL cholesterol β -1.129 (NR)

Table 2-6. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Trasande and Attina 2015, Cross-Sectional (United States [NHANES])	1,329 children (688 boys and 641 girls) aged 6–19 years, participants in NHANES 2009–2012. Urine and blood samples collected same day.		OR for abnormal serum lipid or cholesterol levels per log-unit increase in urinary metabolite concentration		
			ΣDEHP (not specified)	0.077–0.313 µM	Triglycerides ≥100 mg/dL OR 0.91 (0.69, 1.19) HDL <40 mg/dL OR 0.89 (0.58, 1.36)
Yaghjyan et al. 2015a, 2015b, Cross-sectional (United States)	6,005 women ≥18 years of age (not pregnant and not diabetic); participants in NHANES 1999–2004. Urine and blood samples collected same day.	Ordered logistic regression adjusted for age, race, education, poverty, total calories, BMI, total fat, physical activity, menopausal status/hormone use, alcohol consumption, and smoking	OR for higher quartile of serum lipid or total or LDL cholesterol level (or lower HDL cholesterol) per quartile increase in Cr-adjusted urinary metabolite levels		
			ΣDEHP	19.59–58.66 µg/g Cr	Triglycerides OR 0.94 (0.81, 1.09) Total cholesterol OR 1.00 (0.90, 1.11) HDL cholesterol OR 1.05 (0.95, 1.15) LDL cholesterol OR 1.08 (0.92, 1.26)
			MEHP	1.49–5.95 µg/g Cr	Triglycerides OR 0.91 (0.78, 1.05) Total cholesterol OR 1.00 (0.90, 1.11) HDL cholesterol OR 1.02 (0.91, 1.13) LDL cholesterol OR 0.98 (0.85, 1.14)
			MEHHP	9.86–31.09 µg/g Cr	Triglycerides OR 0.94 (0.81, 1.09) Total cholesterol OR 1.01 (0.90, 1.14) HDL cholesterol

Table 2-6. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
					OR 1.05 (0.96, 1.15) LDL cholesterol OR 1.10 (0.94, 1.29)
			MEOHP	6.83–19.84 µg/g Cr	Triglycerides OR 0.99 (0.84, 1.16) Total cholesterol OR 0.98 (0.88, 1.10) HDL cholesterol OR 1.03 (0.94, 1.12) LDL cholesterol OR 1.12 (0.96, 1.31)
			MECPP	17.16–49.78 µg/g Cr	Triglycerides OR 1.15 (0.88, 1.50) Total cholesterol OR 0.95 (0.80, 1.13) HDL cholesterol OR 1.06 (0.93, 1.21) LDL cholesterol OR 1.14 (0.95, 1.36)

Table 2-6. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Trasande et al. 2013b, Cross-sectional (United States [NHANES])	1,276 male and 1,187 females aged 6–19 years; participants in 2003–2008 NHANES. Urine and blood samples collected same day.	Logistic regression adjusted for urinary creatinine, BMI category, race/ethnicity, age category, caregiver education, poverty-income ratio, sex, serum cotinine, caloric intake, and television watching	OR for abnormal serum lipid or cholesterol levels per log-unit increase in urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	0.166–0.704 mol/L	Triglycerides ≥100 mg/dL OR 1.05 (0.90, 1.22) HDL <40 mg/dL OR 0.94 (0.82, 1.08)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein; MECPP = 2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; YOTA = Young Taiwanese Cohort

A few intermediate-duration studies have reported exposure-related hepatic lesions other than hepatocellular hypertrophy in rats and mice following oral DEHP exposure. Centrilobular necrosis and inflammation were observed in F344 female rats after exposure to 1,500 mg/kg/day for 14 days, but not at doses ≤500 mg/kg/day (Berman et al. 1995). Another study in F344 rats reported marked individual cell necrosis with a ductal cell reaction in one lobe of the liver in 1/5 males following dietary exposure to 105 mg/kg/day for 21 days; however, these lesions were not observed in males exposed to higher doses (667–2,101 mg/kg/day) or females at doses up to 1,892 mg/kg/day (CMA 1984). Because this finding was limited to a single animal at a low dose only, it is likely a spontaneous effect. In a 28-day study in male F344 rats, an increased incidence of hepatocyte cytoplasmic eosinophilia was observed at 2,496 mg/kg/day, but not ≤1,093 mg/kg/day (Exxon Chemical Americas 1990). Increased incidence of hepatocellular eosinophilia was also observed in adult F1 rats in a 2-generation study in Wistar rats at DEHP doses ≥340 mg/kg/day, but not 113 mg/kg/day (Schilling et al. 2001). Additional lesions at 1,088 mg/kg/day in F1 adults included focal bile duct proliferation and altered hepatic foci. However, these hepatic lesions were not observed in another 2-generation study in Wistar rats at dietary doses up to approximately 1,040 mg/kg/day (Schilling et al. 1999). In mice, moderate focal coagulative necrosis was observed in the livers of B6C3F1 mice after exposure to dietary doses ≥1,209 mg/kg/day for 13 weeks, but not dietary doses of approximately 245–270 mg/kg/day (Myers 1992a).

In chronic studies in F344 rats, observed hepatic lesions other than hepatocellular hypertrophy included spongiosis hepatis (cystic degeneration) in males at ≥147 mg/kg/day, increased incidence of clear cell foci in males at ≥320 mg/kg/day, and increased cytoplasmic eosinophilia, Kupffer cells, and hepatocyte pigmentation in males and females at 789 and 939 mg/kg/day, respectively (David et al. 2000a; Kluwe et al. 1982a, NTP 1982). David et al. (1999, 2000b) also reported increased cytoplasmic eosinophilia and hepatocyte pigmentation in male and female B6C3F1 mice exposed to 1,266 or 1,458 mg/kg/day, respectively, but not at doses up to 354.2 mg/kg/day. However, no histopathological changes in the liver were observed in another 2-year study in mice at doses up to 1,821 mg/kg/day (Kluwe et al. 1982a; NTP 1982). Other chronic studies in rats did not report hepatic lesions at doses up to 300 mg/kg/day (Carpenter et al. 1953; Voss et al. 2005). In other species, exposure-related hepatic lesions were not observed in guinea pigs at doses up to 64 mg/kg/day or dogs exposed to 56.6 mg/kg/day for 1 year (Carpenter et al. 1953).

Morphological examinations have shown enlarged liver cells and lipofuscin deposits in rats exposed to DEHP, indicating that peroxidation of cellular lipids had occurred (Lake et al. 1987; Mitchell et al. 1985; Price et al. 1987). On a microscopic level, there was a definite increase in hepatic peroxisomes in the

centrilobular and periportal areas of the liver and there was often an increase in the number of mitochondria (Hodgson 1987; Nair and Kurup 1987a). Lipid filled lysosomes were observed in some cases (Mitchell et al. 1985). Each of these changes contributed to cellular hypertrophy. Many of the morphological changes described above were seen in the male rats at doses ≥50 mg/kg/day but did not appear in the females until doses ≥200 mg/kg/day (Mitchell et al. 1985), indicating that male rats are somewhat more susceptible than females.

Two studies (Arcadi et al. 1998; Maranghi et al. 2010) indicated histopathological changes in developing animals; these studies are discussed in Section 2.17 (Developmental).

Animal Studies—Clinical Chemistry. In the only inhalation study that evaluated hepatic serum enzymes, no exposure-related changes were observed in rats following intermittent exposure to concentrations up to 63 ppm for 4 weeks (Klimisch et al. 1991, 1992).

In monkeys, no changes in hepatic serum enzyme levels were observed at doses up to 2,500 mg/kg/day for up to 13 weeks (ICI Americas Inc. 1982; Kurata et al. 1998; Rhodes et al. 1986). Similarly, no biologically relevant changes in hepatic serum enzyme levels have been reported in rats following acute- or intermediate-duration oral exposure up to 1,858 mg/kg/day (Astill et al. 1986; Myers 1992b; Poon et al. 1997) or chronic-duration oral exposure up to 939 mg/kg/day (David et al. 2000a). In mice, no changes in hepatic serum enzyme levels were observed following intermediate-duration oral exposure up to 7,899 mg/kg/day (Myers 1992a) or chronic-duration exposure up to 1,458 mg/kg/day (David et al. 2000b).

Decreases in circulating cholesterol and triglyceride levels were seen in rats exposed to DEHP at doses >100 mg/kg/day (Astill et al. 1986; Barber et al. 1987; CMA 1984; Poon et al. 1997; Reddy et al. 1976). DEHP also inhibited cholesterol synthesis in the liver from male rats and rabbits (Bell 1982). In a subsequent study, Bell and Buthala (1983) demonstrated that the inhibition of cholesterol synthesis in the liver was due to a reduction in the activity of microsomal acylCoA:cholesterol acyltransferase, an enzyme responsible for the esterification of cholesterol. The lowered serum cholesterol concentration may also be due to the inhibition of cholesterol synthesis and stimulation of the conversion of cholesterol to bile acids in the liver (Nair and Kurup 1986).

Animal Studies—Elevated Liver Weight and Hypertrophy, Peroxisomal Proliferation, Enzyme Induction. These endpoints are associated with hepatomegaly in animals and may reflect adaptation of

the liver to xenobiotic exposure; therefore, they may not be relevant to human health. The European Society of Toxicologic Pathology (ESTP) convened an expert panel to define what constitutes an adverse hepatic effect and whether hepatic effects induced by nuclear receptors such as PPARα, constitutive androstane receptor (CAR), or pregnane X receptor (PXR) are rodent-specific adaptive reactions; the findings of the panel are summarized by Hall et al. (2012). According to these criteria, increased liver weight *without* histological evidence of hepatobiliary damage (degeneration, fibrosis, necrosis, cholestasis) is not considered adverse or relevant for human risk assessment unless at least two of the following three parameters are observed: (1) at least 2–3 times increase in ALT levels; (2) biologically significant change in other biomarkers of hepatobiliary damage (ALP, AST, GGT, etc.); or (3) biologically significant change in another clinical pathology marker indicating liver dysfunction (albumin, bilirubin, bile acids, coagulation factors, cholesterol, triglycerides, etc.). ATSDR has adopted the criteria from Hall et al. (2012) for determining the adversity of the liver effects reported in the rodent following exposure to DEHP since the proposed mechanism of liver toxicity for DEHP is PPAR-mediated (Kushman et al. 2013; Rusyn and Corton 2012); DEHP has also been shown to activate PxR and CAR (Rusyn and Corton 2012) (see ***Mechanisms of Hepatic Toxicity*** at the end of this section). Therefore, these effects are only discussed briefly below, and were not considered adverse effects unless hepatocellular degenerative or necrotic changes or evidence of biliary or other liver cell damage were also present. If parameters other than liver weight, hypertrophy, enzyme induction, and/or peroxisome proliferation were evaluated, the lowest doses associated with the liver weight increases and hepatocellular hypertrophy are noted in the LSE tables even though the dose levels are considered NOAELs. Studies that evaluated parameters associated with hepatomegaly only (and not clinical chemistry and/or histopathology) were not included in Tables 2-1 and 2-2 because they were considered inadequate to assess hepatic toxicity; however, these studies are discussed briefly below.

No evidence of elevated liver weight, hypertrophy, peroxisomal proliferation, or enzyme induction was observed in nonhuman primates following oral exposure to DEHP. No evidence of liver enlargement was observed in monkeys exposed to doses up to 2,500 mg/kg/day for up to 13 weeks (ICI Americas Inc. 1982; Kurata et al. 1998; Rhodes et al. 1986; Satake et al. 2010; Short et al. 1987). Additionally, there was no evidence of peroxisomal proliferation or enzyme induction in monkeys exposed to doses up to 2,500 mg/kg/day for up to 13 weeks (ICI Americas Inc. 1982; Kurata et al. 1998; Rhodes et al. 1986; Short et al. 1987).

In contrast to nonhuman primate findings, oral exposures to DEHP characteristically result in a marked increase in liver weight and hepatocyte hypertrophy in rats and mice. The lowest reported doses

associated with these effects in adult, non-pregnant rats and mice were 50–60 and 180 mg/kg/day, respectively (Blystone et al. 2010; Mitchell et al. 1985; NTP 2005; Sasaki et al. 2003). One gestational/lactation exposure study reported increased maternal liver weight at 5 mg/kg/day (Pocar et al. 2012). Thirty additional studies in rats or mice also reported increased liver weight and/or hepatocellular hypertrophy at higher doses (Table 2-2).

In other mammalian species, hypertrophy and/or elevated liver weights have been observed in hamsters exposed to ≥100 mg/kg/day for 14 days (Lake et al. 1984), guinea pigs exposed to 64 mg/kg/day for 1 year (Carpenter et al. 1953), and ferrets exposed to 1,200 mg/kg/day for 14 months (Lake et al. 1976). No evidence of liver enlargement was observed in dogs exposed to 56.6 mg/kg/day for 1 year (Carpenter et al. 1953).

Enlarged livers may be attributable to rapid cell division (hyperplasia), along with cellular hypertrophy, as hepatic hyperplasia appears to be the initial physiological response to DEHP exposure in rats (Busser and Lutz 1987; Smith-Oliver and Butterworth 1987). When rats were exposed to single doses ≥150 mg DEHP/kg, there was an increase in cell division within 24 hours (Berman et al. 1995; Busser and Lutz 1987; Smith-Oliver and Butterworth 1987). During the early stages of a chronic study, repeated oral doses ≥50 mg/kg/day increased mitotic activity when given to rats for 3 consecutive days (Mitchell et al. 1985). The increase in mitosis occurred only in the early stages of treatment and did not persist beyond the first week of exposure in studies with 3–12-month durations (Marsman et al. 1988; Mitchell et al. 1985; Smith-Oliver and Butterworth 1987).

Exposure to DEHP in rats and mice was consistently associated with peroxisomal proliferation. In the only inhalation study that evaluated this endpoint, no exposure-related evidence of peroxisomal proliferation was observed in rats following intermittent exposure to concentrations up to 63 ppm for 4 weeks (Klimisch et al. 1991, 1992). In acute oral rat studies, induction of peroxisomal enzymes and peroxisomal proliferation were observed at doses ≥530 and ≥1,000 mg/kg/day, respectively (Astill et al. 1986; David et al. 1999; Ganning et al. 1989; Hasmall et al. 2000; Lake et al. 1984; Poon et al. 1997; Shin et al. 1999).

Following intermediate-duration oral exposure, evidence of peroxisomal enzyme induction was apparent in rats at doses ≥50 mg/kg/day (Astill et al. 1986; Barber et al. 1987; Cattley et al. 1987; CMA 1984; Exxon Chemical Americas 1990; Ganning et al. 1991; Lake et al. 1984, 1987; Marsman et al. 1988; Mitchell et al. 1985; Rao et al. 1987; Short et al. 1987; Tamura et al. 1990). In mice, peroxisomal enzyme

induction was significantly elevated at ≥1,881 mg/kg/day following exposure for 1–13 weeks and ≥292.3 mg/kg/day following exposure for 104 weeks (David et al. 1999); no other studies evaluated peroxisomal enzymes in mice. Observed changes in peroxisomal enzymes included induction of enzymes responsible for fatty acid catabolism (palmitoyl-CoA oxidase, enoyl-CoA hydratase, carnitine acyltransferase, and α-glycerophosphate dehydrogenase) in rats and mice after exposure to DEHP by factors as great as 1,500%. Findings for induction of peroxisomal catalase in rats are mixed, with some dietary studies reporting decreased catalase activity (Ganning et al. 1989; Rao et al. 1987), increased catalase activity (Conway et al. 1989; Ganning et al. 1991; Perera et al. 1986; Tamura et al. 1990), or no change in activity (Elliott and Elcombe 1987; Perera et al. 1986). The findings did not show a clear pattern with respect to strain, sex, or exposure duration, and may be mediated by factors unrelated to DEHP exposure.

Findings for peroxisomal proliferation in other mammalian species are limited. In hamsters, slight peroxisomal proliferation was observed following a 14-day exposure to 1,000 mg/kg/day; however, no changes were observed in peroxisomal enzymes (Lake et al. 1984). Peroxisomal proliferation was not observed in guinea pigs exposed to 950 mg/kg/day for 4 days (Hasmall et al. 2000). Catalase was decreased in ferrets exposed to 1,200 mg/kg/day for 14 months (Lake et al. 1976).

The mixed-function oxidase (MFO) system appears to be affected by DEHP in rodents (Ganning et al. 1991; Short et al. 1987). Significant induction of fatty acid omega hydroxylase and P-450 4A1 messenger ribonucleic acid (mRNA) were reported following DEHP administration to rats (Sharma et al. 1988, 1989). Increases in hepatic levels of cytochrome P-450, NADPH cytochrome c reductase, lauryl-11- and 12-hydroxylase, ethoxycoumarin-O-deethylase, ethylmorphine-N-demethylase, and/or aniline hydroxylase were induced by DEHP exposure of rats to doses ≥50 mg/kg/day (Barber et al. 1987; CMA 1984; Ganning et al. 1991; Lake et al. 1984; Mitchell et al. 1985; Short et al. 1987) and in ferrets exposed to 1,200 mg/kg/day for 14 months (Lake et al. 1976). No exposure-related changes were observed in the MFO system in dogs exposed to 56.6 mg/kg/day for 1 year (Carpenter et al. 1943).

Mechanisms of Hepatic Toxicity. Kushman et al. (2013) identified nine mechanistic events for DEHP and its metabolites in the liver based on a survey of several highly cited and diverse reviews (Caldwell 2012; Guyton et al. 2009; Klaunig et al. 2003; McKee 2000; Melnick 2001; Peters et al. 2005; Roberts et al. 2007; Rusyn and Corton 2012; Rusyn et al. 2006). The key mechanistic events include: (1) PPAR activation (most likely α); (2) peroxisome proliferation; (3) cell proliferation; (4) activation of other nuclear receptors; (5) Kupffer cell activation; (6) suppression of hepatocellular apoptosis; (7) oxidative

stress; (8) inhibition of gap-junctional intracellular communication (GJIC); and (9) genotoxicity. The role of specific key events in rodent liver cancer is in Section 2.19 (Mechanisms of Liver Cancer).

PPAR activation in the liver of mice and rats by DEHP and metabolites is well established (Rusyn and Corton 2012). MEHP activates mouse and human PPARα, PPARδ, and PPARγ. PPARα is expressed at higher levels in mouse and rat liver compared to human liver. In the liver, PPARα plays a role in fatty acid uptake and transport, ketogenesis, and lipogenesis. The hallmarks of PPARα activation include: (1) an increase in the number and size of peroxisomes (i.e., peroxisome proliferation); (2) increased expression, protein, or activity of acyl Co-A oxidase or CYP4A (i.e., ω-lauric acid hydroxylase); and (3) increased levels of carnitine acyl Co-A transferase. These effects are generally observed in rats and mice, but were not seen in studies of nonhuman primates (i.e., marmosets and Cynomolgus monkeys). PPARα is also responsible for the burst of hepatocyte proliferation that is seen with peroxisome proliferating compounds, including DEHP, in rodents (i.e., proliferation is not observed in PPARα-null mice).

Induction of peroxisomal and microsomal enzymes mediated by PPARα contributes to an increase in the formation of reactive oxygen species (ROS; measure of oxidative stress) in the rodent liver. Glutathione peroxidase and superoxide dismutase are important elements in the cellular defenses against free radical oxygen; however, reduction in these enzymes has been reported following acute-, intermediate-, and chronic-duration oral exposure in rats (Conway et al. 1989; Elliott and Elcombe 1987; Perera et al. 1986; Tamura et al. 1990) and chronic-duration oral exposure in ferrets (Lake et al. 1976). Depletion of these enzymes may not be detected due to changes in carbohydrate metabolism, indicating increased hepatic glucose utilization (Gerbracht et al. 1990; Lake et al. 1976; Mitchell et al. 1985). These metabolic findings support increased demand for hepatic glucose utilization, which would produce the reducing equivalents necessary for the activity of glutathione peroxidase. Additional evidence of oxidative stress includes increased levels of lipid ubiquinone (Turuneen and Dallner 1998) and cellular ubiquinone (Nair and Kurup 1987b) in rats following intermediate-duration oral exposure to DEHP.

DEHP and its metabolites have been shown to activate other nuclear receptors in human cells including the estrogen receptor, human pregnane X-receptor and the constitutive androstane receptor (CAR); however, the role of activation of these receptors in liver toxicity has not been fully elucidated (Rusyn and Corton 2012). Activation of Kupffer cells in the rat liver following exposure to DEHP resulted in the production of ROS as measured by spin trapping and electron spin resonance techniques. Kupffer cell activation may also result in release of inflammatory cytokines and mitogenic growth factors in the liver

(Roberts et al. 2007; Rusyn and Corton 2012), and suppression of apoptosis and increased DNA synthesis were also observed in the liver of rats and mice exposed to DEHP and MEHP (Rusyn and Corton 2012).

The effect of DEHP on liver metabolism might be mediated by changes in the structure of the cell membranes. Both membrane proteins and lipids are altered with DEHP exposure (Bartles et al. 1990; Edlund et al. 1987; Ganning et al. 1987; Gupta et al. 1988). Following 15 days of dietary exposure to 1,000 mg/kg/day DEHP, the concentration of membrane protein CE-9 was increased in rats. This protein appears to be related to transport of the biochemical signal that stimulates peroxisome proliferation. Other membrane protein concentrations were decreased with DEHP exposure in rats, including epidermal growth factor receptor, asialoglycoprotein receptor, dipeptidylpeptidase-IV, HA-312, and HA-4 (Bartles et al. 1990; Gupta et al. 1988). There were increases in the concentrations of the membrane lipids, dolichol and dolichol phosphate, upon the introduction of DEHP into the diet of rats (Edlund et al. 1987; Ganning et al. 1987). Dolichol phosphate participates in the synthesis of membrane glycoproteins. Accordingly, glycoprotein membrane receptor sites could be affected by DEHP through this mechanism, leading to altered movement of materials across membranes and signaling changes in cell metabolism.

Hepatic damage may also be mitigated in part due to the reaction of hydrogen peroxide with cellular lipids. Slight, but significant, increases in malondialdehyde and conjugated dienes (markers for the reaction of peroxides with fatty acids) were seen in rat hepatic cells following 28 days of exposure to 2,000 mg/kg/day DEHP (Elliott and Elcombe 1987). In a separate study, there was no increase in oxidized lipids, as indicated by malondialdehyde concentrations, in exposed rat livers following 79 weeks of dietary exposure to 1,500 mg/kg/day DEHP (Tamura et al. 1990). Lipofuscin deposits, a long-term marker for lipid reactions with peroxides, were identified in the livers of rats exposed to between 500 and 2,000 mg/kg/day DEHP for their lifetime (Price et al. 1987). Inhibition of GJIC in rodent liver was also correlated with PPARα-mediated peroxisome proliferation (McKee et al. 2000).

Summary. Human data on hepatic effects of DEHP are extremely limited, but suggest that occupational exposure levels may be associated with increased serum liver enzyme levels and decreased plasma cholinesterase activity. In cross-sectional studies of general population exposures, urinary metabolite levels were generally not associated with changes in triglyceride or cholesterol levels; there were no studies of other hepatic endpoints in humans exposed to DEHP in the environment or in consumer products. In rodents, high DEHP doses resulted in degenerative and necrotic hepatic changes. Dogs and monkeys are less likely to experience changes in the liver after exposure. At lower exposure levels, the predominant noncancer effects observed in laboratory animals exposed to DEHP included elevated liver

weight, hypertrophy, peroxisome proliferation, and/or enzyme induction. As discussed above, the adversity and human relevance of these findings are unclear.

2.10 RENAL

Overview. A limited number of epidemiological studies evaluated renal clinical chemistry and/or urinalysis parameters in DEHP-exposed populations. Data in animals following inhalation exposure are limited, but several oral animal studies evaluated kidney function, weight, and histology.

Epidemiology Studies. In a study of 352 Chinese workers exposed to DEHP at three different PVC manufacturing facilities (average exposures ranging between 233 and 707 μg/m^3 DEHP in the three factories), serum urea and creatinine levels did not differ from those in 104 unexposed workers (Wang et al. 2015). Among 52 Taiwanese children exposed to foods contaminated with DEHP (duration of time unknown), serum blood urea nitrogen (BUN) and creatinine levels did not differ from those in unexposed children, and there were no differences in urinalysis findings (protein, occult blood, or erythrocyte or leukocyte counts; Wu et al. 2013). A cross-sectional study (Trasande et al. 2014) using 2009–2010 NHANES data on 667 children reported an association between higher levels of DEHP metabolites in urine and increasing urinary albumin/creatinine ratio (ACR; ~3-fold increase in DEHP metabolites was associated with 0.55 mg/g increase in ACR). Elevated ACR indicates elevated protein levels in the urine and is a biomarker for kidney disease. However, the odds of micro- or macroalbuminuria (ACR ≥30 mg/g) were not increased in children with higher levels of DEHP metabolites in urine (odds ratio [OR] per log unit increase in DEHP exposure 1.11, 95% confidence interval [CI] 0.78–1.57; Trasande et al. 2014). Tsai et al. (2016) reported higher urinary ACR (1.43±1.0 mg/mmol in group with exposure estimated to be >0.05 mg/kg/day, compared with 0.47±0.33 mg/mmol in unexposed group; p=0.006; p for trend with dose <0.0001) among Taiwanese children who had consumed DEHP-contaminated foods, as well as a higher prevalence of microalbuminuria (12.9%, 9/70 children) in those children with the highest intake of such foods, compared with unexposed children (0%, n=18 children). No other studies were located regarding renal effects in humans after inhalation or oral exposure to DEHP.

Animal Studies. Following inhalation exposure to DEHP, no changes in renal serum chemistry, kidney weight, or kidney histology were observed in rats exposed nose-only to concentrations up to 63 ppm for 4 weeks (5 days/week, 6 hours/day) (Klimisch et al. 1992).

In orally exposed nonhuman primates, no changes in clinical chemistry measures of renal function, urinalysis parameters, or kidney weight or histology were observed in marmoset monkeys exposed to 2,000 mg/kg/day for 14 days (ICI Americas Inc. 1982; Rhodes et al. 1986). Similarly, no exposure-related changes were observed in clinical chemistry or kidney weight or histology in monkeys exposed to doses up to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998; Satake et al. 2010).

Histopathological changes in the kidney have been observed in multigeneration and chronic-duration oral studies in rats. In a 3-generation study in Sprague-Dawley rats, increased incidences of kidney lesions (medullary mineralization and tubular dilation) were observed in F1 and F2 parental males and F2 parental females at doses ≥447 mg/kg/day, but not ≤57 mg/kg/day (Blystone et al. 2010; NTP 2005). Similarly, in 2-generation studies in Wistar rats, renal tubule dilation and renal pelvis calcification were observed in F1 adults at 1,088 mg/kg/day, but not ≤1,040 mg/kg/day (Schilling et al. 1999, 2001). Consistent with the observation that renal effects occur at higher doses, no kidney lesions were observed in a combination chronic/2-generation study in Sherman rats exposed to doses up to 200 mg/kg/day (Carpenter et al. 1953). At chronic-duration dietary exposures ≥789 mg/kg/day, increased severity of normally occurring renal tubule pigmentation and chronic progressive nephropathy was observed in both sexes (David et al. 2000a); no exposure-related changes in kidney histology were observed at doses ≤774 mg/kg/day (David et al. 2000a; Kluwe et al. 1982a; NTP 1982). Rao et al. (1990) reported lipofuscin pigments in the tubular epithelium of rats exposed to 1,900 mg/kg/day for 108 weeks. The lesions in rats are consistent with spontaneous nephropathy commonly observed in aged rats, and suggest that treatment with DEHP might accelerate the onset of the lesion in younger rats. In shorter-duration studies, no histopathological changes were observed in most rat studies at doses up to 10,000 mg/kg/day for up to 4 weeks, up to 3,000 mg/kg/day for up to 13 weeks, or up to 1,440 mg/kg/day for 17 weeks (Astill et al. 1986; Barber et al. 1987; CMA 1984; Dalgaard et al. 2000; Gray et al. 1977; NTP 1982; Poon et al. 1997; Shaffer et al. 1945). However, one study reported increased cellular pigmentation in the proximal tubule epithelium of male and female rats at 1,724 and 1,857.6 mg/kg/day, respectively, after dietary exposure for 13 weeks (Myers 1992b).

Histopathological changes in the kidney have also been reported in intermediate- and chronic-duration studies in mice. Acute renal inflammation, characterized by tubular necrosis, tubular dilation, tubular regeneration, and occasional neutrophilic infiltrates, was observed in male and female mice after exposure to dietary doses of 6,922 and ≥2,888 mg/kg/day, respectively, for 28 days (Myers 1992a). These lesions were not observed in male or female mice exposed to doses up to 2,600 mg/kg/day for 4–13 weeks (Myers 1992a; NTP 1982). Tubular regeneration was also observed in male and female mice exposed to

1,100 mg/kg/day (only dose tested) for 28 weeks; hydronephrosis was also observed in exposed females (Toyosawa et al. 2001). In chronic studies, doses ≥9.5 mg/kg/day resulted in mild glomerulonephritis and cell proliferation in the kidneys of male SV/129 mice (Kamijo et al. 2007). In B6C3F1 mice, chronic progressive nephropathy was observed in both sexes following exposure to doses ≥292.2 mg/kg/day for 104 weeks (David et al. 2000b). However, another 2-year study in B6C3F1 mice only observed an increased incidence of chronic inflammation of the kidney in males at 1,325 mg/kg/day, with incidences comparable to controls at 672 mg/kg/day in males and at doses up to 1,821 mg/kg/day in females (Kluwe et al. 1982a; NTP 1982).

There is limited evidence for impaired renal function in intermediate-duration studies. Following dietary exposure for 13 weeks, serum BUN levels were slightly, but significantly, elevated by 24–47% in male and female F344 rats at ≥261.2 and ≥850.1 mg/kg/day, respectively (Myers 1992b). Additionally, in a 17-week dietary study, both renal concentrating and diluting ability were reduced at week 17 in female rats exposed to 1,414 mg/kg/day, suggesting mild renal functional impairment (23% increase in urine volume in the concentrations test; 47% decrease in urine volume in the dilution test) (Gray et al. 1977). However, no changes in urinalysis and/or clinical chemistry parameters were observed in rats exposed to doses up to 1,440 mg/kg/day for 13–17 weeks (Gray et al. 1977; Poon et al. 1997) or doses up to 939 mg/kg/day for 2 years (David et al. 2000a). In a chronic study in SV/129 mice, doses ≥9.5 mg/kg/day resulted in increased protein in the urine (Kamijo et al. 2007); however, no changes in urinalysis parameters were observed in B6C3F1 mice exposed to doses up to 1,458 mg/kg/day for 2 years (David et al. 2000b). No exposure-related changes were observed in clinical chemistry measures in mice following intermediate-duration (28 days) exposure to doses up to 7,899 mg/kg/day (Myers 1992a) or chronic-duration (2 years) exposure to doses up to 1,458 mg/kg/day (David et al. 2000b; Kamijo et al. 2007).

Absolute and/or relative kidney weight increases of >10% were observed in several intermediate- and chronic-duration rat studies at doses ≥113 mg/kg/day (Blystone et al. 2010; Carpenter et al. 1953; David et al. 2000a; Gray et al. 1977; Myers 1992b; NTP 2005; Poon et al. 1997; Schilling et al. 2001) and in acute-duration studies following exposure to 1,000 mg/kg/day (Dostal et al. 1987; Hellwig et al. 1997). However, kidney weight changes did not occur in other rat studies at acute-duration doses of 500–1,100 mg/kg/day (Astill et al. 1986; Lee and Koo 2007) or intermediate-duration doses up to 2,101 mg/kg/day (Barber et al. 1987; Grande et al. 2006; Schilling et al. 1999). In mouse studies, relative kidney weight was increased in female mice exposed to 1,100 mg/kg/day for 26 weeks (Toyosawa et al. 2001); however, no kidney weight changes occurred in mice exposed to intermediate-duration doses up to

7,899 mg/kg/day or chronic doses up to 48.5 mg/kg/day (Kamijo et al. 2007; Myers 1992a). In studies reporting kidney weight changes, decreased body weights were often observed, and only rarely were renal weight changes associated with histopathological changes (Blystone et al. 2010; NTP 2005; Schilling et al. 2001; Toyosawa et al. 2001) or impaired function (Gray et al. 1977; Myers 1992b).

The relevance of the kidney effects observed in the dietary studies in rats and mice is unclear. Some of the findings (David et al. 2000a, 2000b) suggest exacerbation of typically observed age-, species-, and/or sex-related lesions following DEHP exposure in the absence of impaired kidney function. However, impaired kidney function and kidney lesions were also reported in young rats following developmental exposure to doses ≥0.25 mg/kg/day in some studies (Arcadi et al. 1998; Wei et al. 2012), indicating that the developing kidney may be sensitive to DEHP exposure; see Section 2.17 (Developmental) for more details. Unlike hepatic findings, renal lesions observed in mice do not appear to be primarily associated with PPARα activation, because both wild-type and PPARα knockout (-/-) mice develop kidney lesions after intermediate-duration dietary exposure (Kamijo et al. 2007; Ward et al. 1998). In fact, Kamijo et al. (2007) proposed that PPARα activation protects against DEHP-induced renal toxicity because PPARα knockout (-/-) mice showed increased sensitivity to renal toxicity compared with wild-type mice following chronic-duration dietary exposure to DEHP, including increased urinary protein, serum BUN and creatinine, and indices of glomerular lesions (cell proliferation and mesangial expansion indices).

In other mammalian species, no adverse renal effects were seen in guinea pigs or dogs exposed to doses up to 64 or 56.6 mg/kg/day, respectively, for 1 year (Carpenter et al. 1953).

Summary. Human data regarding renal effects following DEHP exposure are extremely limited and inconsistent. There is some evidence that the kidney is a sensitive target of DEHP toxicity in animals following oral exposure. However, most of the available studies observed kidney damage in animals only at high doses.

2.11 DERMAL

Human Studies. No studies of dermal effects in humans exposed to DEHP by inhalation or oral exposure were located. In an early patch test study, no evidence of dermal irritation or skin sensitization was reported after undiluted DEHP (dose not specified) was applied to 23 volunteers on the skin of the back and under occluded conditions for 7 days, followed by a challenge application 10 days later (Shaffer et al. 1945).

Animal Studies. No studies were located regarding dermal effects in animals following inhalation exposure to DEHP.

No histopathological changes in the skin were observed following intermediate-duration oral exposure to DEHP in marmoset monkeys exposed to doses up to 2,500 mg/kg/day (Kurata et al. 1998), rats exposed to doses up to 419.3 mg/kg/day (Poon et al. 1997), or mice exposed to 1,100 mg/kg/day (Toyosawa et al. 2001). In 2-year dietary studies, no histopathological skin lesions were observed in rats or mice at DEHP doses up to 774 or 1,821 mg/kg/day, respectively (Kluwe et al. 1982a; NTP 1982).

Single doses of up to 19,800 mg/kg DEHP were applied to rabbit skin using a modified FDA cuff test procedure. There was no evidence of dermal irritation caused by DEHP during the 14-day observation period (Shaffer et al. 1945).

2.12 OCULAR

Human Studies. No studies were located regarding ocular effects in humans after exposure to DEHP.

Animal Studies. No studies were located regarding ocular effects in animals following inhalation exposure to DEHP.

No ocular effects were noted during an ophthalmological examination of rats following a 13-week exposure to DEHP in the diet at doses up to 1,857.6 mg/kg/day (Myers 1992b). No other studies performed ophthalmological examination following oral DEHP exposure.

In other studies, no histopathological changes in the eyes were observed in marmoset monkeys exposed to doses up to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998), rats exposed to doses up to 419.3 mg/kg/day (Poon et al. 1997), or mice exposed to 1,100 mg/kg/day for 26 weeks (Toyosawa et al. 2001).

There was no necrosis of rabbit cornea after ocular exposure to a single dose of 0.5 mL (495 mg) DEHP, but a slight transient congestion of the eyelids was observed (Shaffer et al. 1945). These data indicate that neat DEHP has a low potential for ocular irritation in rabbits.

2.13 ENDOCRINE

Overview. Various endocrine organs have been evaluated after exposure to DEHP. This section focuses on the pancreas, adrenal gland, pituitary gland, and thyroid/parathyroid glands. While reproductive organs also have endocrine function, these organs (testes, ovaries) and the hormones that they produce are discussed in Section 2.16 (Reproductive). Human epidemiological data have evaluated potential associations between DEHP exposure and thyroid hormone levels. Data regarding potential endocrine effects in animals following DEHP exposure were available from one inhalation study and numerous oral studies.

Epidemiology Studies—Thyroid Dysfunction. Effects of DEHP exposure on thyroid function (serum levels of triiodothyronine [T3], thyroxine [T4], and thyroid stimulating hormone [TSH]) have been evaluated in 10 epidemiological studies in which DEHP exposure was evaluated using urinary metabolite biomarkers (Table 2-7).

Five studies examining thyroid hormone levels in pregnant women did not provided consistent findings. In the largest of these (n=2,521 women; Yao et al. 2016), increased MEHP and MEHHP levels in first trimester urine were associated with decreased free and total T4 and increased TSH levels in maternal serum; no association was observed between total T3 levels and MEHP or MEHPP levels, and MEOHP levels were not associated with any thyroid hormone levels. However, in another study of 439 pregnant women, increased MEHP levels in maternal urine were associated with increased total T4 and decreased TSH levels in maternal serum during gestation weeks 26 and 35, but not at early gestational time points (Johns et al. 2016). In a small study of pregnant women in Puerto Rico, increased DEHP metabolite levels in urine collected between 24 and 28 weeks of gestation were associated with lower free T4, while there was no association when urine samples collected during weeks 16–20 of gestation were analyzed, or in a longitudinal analysis of the data (Johns et al. 2015). In contrast, no association between MEHP levels in urine collected during gestation week 28 and free or total T4 was observed in a small study of 76 Taiwanese women undergoing amniocentesis (Huang et al. 2007). In a follow-up study of a different group of 98 Taiwanese women undergoing amniocentesis, increased MEOHP levels in the urine were associated with decreased TSH levels and increased MECPP levels were associated with decreased total T3 levels when data were combined across three time-points (one per trimester); none of the metabolites were associated with free or total T4 levels (Huang et al. 2018).

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
Pregnant women					
Huang et al. 2018, Cohort/ cross-sectional (Taiwan, China)	98 pregnant women referred for amniocentesis (2013–2014); mean age 35.0 years. Maternal blood and urine samples collected during each trimester (median 18, 26, and 39 weeks of gestation); cord blood collected at delivery.	Linear mixed models repeated measures analysis adjusted for maternal age at enrollment, gestational age at sample collection, urinary creatinine, and serum TBG levels For cord blood analysis, models were adjusted for maternal age at enrollment, urinary creatinine, and maternal thyroid level	Change in ln-transformed maternal serum thyroid hormone per ln-unit increase in ln-transformed urinary metabolite		
			ΣDEHP	Visit 1: 21.64 (16.44, 28.25) ng/mL; Visit 2: 30.68 (24.51, 38.39) ng/mL; Visit 3: 39.34 (31.60, 48.97) ng/mL (GM [95%CI])	TSH: -0.074 (-0.161, 0.013) TT3: -0.022 (-0.046, 0.003) TT4: 0.003 (-0.015, 0.021) FT4: 0.007 (-0.017, 0.030)
			MEHP	Visit 1: 2.43 (1.67, 3.52) ng/mL; Visit 2: 3.45 (2.43, 4.91) ng/mL; Visit 3: 2.49 (1.60, 3.87) ng/mL	TSH: -0.006 (-0.059, 0.047) TT3: -0.0001 (-0.016, 0.015) TT4: -0.002 (-0.013, 0.009) FT4: 0.006 (-0.008, 0.020)
			MEHHP	Visit 1: 2.67 (1.75, 4.08) ng/mL; Visit 2: 5.33 (3.63, 7.82) ng/mL; Visit 3: 9.69 (7.27, 12.91) ng/mL	TSH: -0.018 (-0.072, 0.037) TT3: -0.013 (-0.028, 0.002) TT4: -0.005 (-0.016, 0.007) FT4: -0.008 (-0.023, 0.006)
			MEOHP	Visit 1: 3.41 (2.45, 4.75) ng/mL; Visit 2: 5.36 (4.06, 7.08) ng/mL; Visit 3: 8.38 (6.68, 10.52) ng/mL	TSH: -0.083 (-0.157, -0.009)* TT3: -0.012 (-0.033, 0.010) TT4: 0.001 (-0.015, 0.016) FT4: -0.011 (-0.031, 0.010)
			MECCP	Visit 1: 6.15 (4.37, 8.65) ng/mL; Visit 2: 9.89 (7.95, 12.30) ng/mL; Visit 3: 12.46 (10.03, 15.50) ng/mL	TSH: -0.051 (-0.124, 0.021) TT3: -0.027 (-0.047, -0.006)* TT4: 0.004 (-0.011, 0.019) FT4: -0.008 (-0.027, 0.011)
			No significant association was seen in analyses of maternal serum hormone levels stratified by visit, or in analyses of the relationship between maternal urinary metabolite levels and cord serum hormone levels.		

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
Johns et al. 2016, Case-control (United States [Massachu-setts])	439 pregnant women (116 cases of preterm birth and 323 term birth controls); nested case-control study of women from LifeCodes prospective birth cohort. Urine and blood samples collected at each of four visits at median gestation weeks 9.71, 17.9, 26, and 35.1.	Linear mixed model adjusted for urinary SG, gestational age at time of sample collection, maternal age at enrollment, BMI at time of sample collection, and health insurance provider	Percent change in serum thyroid hormone per interquartile increase in urinary metabolite		
			ΣDEHP	Visit 1: 0.39 (3.16) µmol/L; Visit 2: 0.38 (3.01); Visit 3: 0.32 (3.04); Visit 4: 0.42 (3.18) (GM [GSD]); SG-adj)	TT3: 0.82 (-0.77, 2.41) FT4: 4.09 (-1.12, 9.29) TT4: 0.87 (-0.17, 1.91) TSH: -4.33 (-9.23, 0.84)
			MEHP	Visit 1: 10.6 (3.52); Visit 2: 10.9 (3.39); Visit 3: 9.46 (3.28); Visit 4: 9.83 (3.52)	TT3: 0.28 (-1.29, 1.85) FT4: 4.15 (-0.87, 9.16) TT4: 1.29 (0.26, 2.32)* TSH: -5.31 (-10.1, -0.23)*
			MEHHP	Visit 1: 34.7 (3.37); Visit 2: 34.8 (3.10); Visit 3: 27.2 (3.21); Visit 4: 9.83 (3.33)	TT3: 0.97 (-0.55, 2.5) FT4: 2.67 (-2.27, 7.62) TT4: 0.66 (-0.34, 1.66) TSH: -3.95 (-8.67, 1.01)
			MEOHP	Visit 1: 18.6 (3.28); Visit 2: 18.3 (3.03); Visit 3: 15.6 (3.19); Visit 4: 20.9 (3.22)	TT3: 1.08 (-0.41, 2.58) FT4: 3.89 (-0.99, 8.77) TT4: 0.86 (-0.13, 1.84) TSH: -3.74 (-8.38, 1.15)
			MECPP	Visit 1: 44.4 (3.35); Visit 2: 42.6 (3.25); Visit 3: 36.8 (3.31); Visit 4: 49.3 (3.35)	TT3: 0.86 (-0.83, 2.54) FT4: 4.89 (-0.52, 10.3) TT4: 0.86 (-0.25, 1.97) TSH: -3.98 (-9.17, 1.51)
			Repeated measures analysis with cases and controls combined.		

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
Yao et al. 2016, Cohort/ Cross-sectional (China)	2,521 pregnant women, mean age 26years, members of Ma'anshan Birth cohort, recruited at 1st prenatal visit (<14 weeks of gestation) at the Maternal and Child Health Center in Ma'anshan city. Maternal serum and urine samples collected at 1st prenatal visit (mean 10 weeks of gestation); cord serum collected at delivery.	Linear regression models adjusted for maternal age, prepregnancy BMI, parity, race, education level, residence in the previous 6 months, cigarette smoking, alcohol consumption, and gestational week at blood withdrawal Cord serum models additionally adjusted for infant sex, gestation age at delivery, and delivery mode	Mean change in maternal serum thyroid hormone per 1-SD increase in ln-transformed urinary metabolite		
			MEHP	NR	lnTSH: 0.101 (0.055, 0.147)* TT4: -0.163 (-0.261, -0.065)* FT4: -0.013 (-0.020, -0.006)* TT3: -0.453 (-1.771, 0.864)
			MEHHP	NR	lnTSH: 0.132 (0.086, 0.177)* TT4: -0.173 (-0.270, -0.075)* FT4: -0.011 (-0.017, -0.004)* TT3: 0.993 (-0.321, 2.306)
			MEOHP	NR	lnTSH: 0.051 (0.005, 0.097) TT4: -0.033 (-0.0131, 0.065) FT4: -0.002 (-0.009, 0.004) TT3: 0.509 (-0.806, 1.824)
			No significant association was seen in analyses of the relationship between maternal urinary metabolite levels and cord serum hormone levels.		
Johns et al. 2015, Cohort/ cross-sectional (Puerto Rico)	106 pregnant women aged 18–40 years, members of PROTECT birth cohort, recruited at 14 weeks of gestation from prenatal clinics and hospitals. Urine and serum samples collected at	Linear regression models adjusted for age at enrollment, prepregnancy BMI, and urinary SG	Percent change in serum thyroid hormone per interquartile increase in urinary metabolite		
			ΣDEHP	NR	FT3: 0.05 (-4.49, 4.49) FT4: -8.02 (-15.3, -0.8)* TSH: 2.79 (-10.8, 18.6)
			MEHP	Visit 1: 1.61–6.36; Visit 3: 1.69–6.73 (SG-adj)	NR
			MEHHP	Visit 1: 6.14–19.9; Visit 3: 7.28–16.9	NR
			MEOHP	Visit 1: 5.57–16.5; Visit 3: 6.22–14.8	NR

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
	1st and 3rd prenatal visits (16–20 and 24–28 weeks of gestation).		MECPP	Visit 1: 12.7–31.4; Visit 3: 13.4–29.3	NR
			Cross-sectional analysis (same day serum and urine samples) using visit 3 data only; no significant association seen with visit 1 data only or in longitudinal analysis.		
Huang et al. 2007, Cross-sectional (Taiwan, China)	76 pregnant women referred for amniocentesis (2005–2006) due to abnormal α-fetoprotein or free β-hCG or advanced age; mean age 33.6 years; mean week of gestation=27.9. Urine and blood samples collected on same day at referral.	Multiple linear regression adjusted for age, BMI, gestational age, and other phthalate monoesters	Change in serum thyroid hormone per log-unit increase in urinary metabolite		
			MEHP	31.4–121.0 µg/g Cr	FT4: -0.015 (NR) TT4: = -0.007 (NR)
			One outlier excluded due to hypothyroidism.		
Other populations					
Kuo et al. 2015, Cohort (Taiwan)	148 mother-child pairs recruited from hospital between 2009 and 2010. Single maternal urine sample collected during 3rd trimester; cord blood collected at delivery.	Multiple linear regression adjusted for age, infant gender, prepregnancy BMI, weight gain, gestational age, parity, educational level, cigarette smoking, alcohol intake, maternal serum TSH, and other urinary phthalate monoesters	Association between log-transformed cord blood TSH and maternal urinary metabolite level		
			MEHP	8.19–19.34 µg/g Cr	TSH: -1.342 (NR)
			MEHHP	14.84–33.81 µg/g Cr	TSH: -2.375 (NR)
			MEOHP	14.68–31.59 µg/g Cr	TSH: 2.676 (NR)

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
Dirtu et al. 2013, Case-control (Belgium)	152 obese individuals recruited at the entry of a 12-month weight-loss program between November 2009 and February 2012 (46 men, 106 women; aged 18–84 years) and 43 non-obese, age- and sex-matched controls (12 men, 30 women; aged 19–59 years). Urine and blood samples collected at baseline (obese and control) and during weight-loss treatment of obese individuals.	Linear regression adjusted for age and gender	Association between serum thyroid hormone level and urinary phthalate metabolite concentration in non-obese controls (male and female)		
			ΣDEHP	Controls: 27–53	FT4: 0.12 TSH: 0.38*
			MEHP	Controls: 2–5	FT4: 0.08 TSH: 0.27
			MEHHP	Controls: 9–19	FT4: 0.12 TSH: 0.31
			MEOHP	Controls: 3–9	FT4: 0.10 TSH: 0.40*
			MECPP	Controls: 12–20	FT4: 0.10 TSH: 0.38*
			Association between serum thyroid hormone level and urinary phthalate metabolite concentration (at baseline) in obese cases		
			ΣDEHP	Cases: 30–61	FT4: -0.02 TSH: 0.04
			MEHP	Cases: 2–5	FT4: 0.00 TSH: -0.05
			MEHHP	Cases: 10–25	FT4: 0.00 TSH: 0.01
			MEOHP	Cases: 4–11	FT4: -0.03 TSH: 0.04
			MECPP	Cases: 12–22	FT4: -0.07 TSH: 0.03
			95% CI values were not reported; p>0.1 for all. Gender-specific results also did not show any significant associations for DEHP metabolites.		

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
Meeker et al. 2011, Cross-sectional (United States)	1,346 adults (≥20 years of age) and 329 adolescents (ages 12–19) from 2007–2008 NHANES participants. Urine and blood samples collected on same day.	Multivariable linear regression adjusted for age, race, BMI, ln-serum cotinine, ln-urinary creatinine, and ln-urinary iodine	Change in serum thyroid hormone level per ln-unit increase in urinary metabolite in adolescents		
			MEHP	<LOD–4.5 µg/g Cr	FT3: 0.0081 (0.00035, 0.016) TT3: 4.00 (1.97, 6.03)* FT4: -0.0060 (-0.025, 0.013) TT4: 0.11 (-0.1, 0.33) TSH: -0.004 (-0.055, 0.046)
			MEHHP	10.3–45.32 µg/g Cr	FT3: 0.0084 (-0.0026, 0.019) TT3: 3.85 (1.44, 6.27)* FT4: 0.0003 (-0.017, 0.018) TT4: 0.089 (-0.11, 0.29) TSH: 0.045 (-0.026, 0.12)
			MEOHP	5.79–24.74 µg/g Cr	FT3: 0.0082 (-0.0036, 0.020) TT3: 4.24 (1.72, 6.75)* FT4: -0.0007 (-0.018, 0.017) TT4: 0.094 (-0.099, 0.29) TSH: 0.048 (-0.028, 0.12)
			MECPP	16.7–64.8 µg/g Cr	FT3: 0.011 (-0.00096, 0.023) TT3: 4.70 (1.97, 7.43)* FT4: 0.0033 (-0.018, 0.024) TT4: 0.15 (-0.046, 0.35) TSH: 0.048 (-0.029, 0.13)
			Change in thyroid hormone level per ln-unit increase in urinary metabolite in adults.		
			MEHP	<LOD–5.20 µg/g Cr	FT3: -0.00003 (-0.0085, 0.0085) TT3: -0.83 (-2.17, 0.051) FT4: -0.0054 (-0.020, 0.0091) TT4: -0.13 (-0.22, -0.045)* TSH: 0.028 (-0.0013, 0.057)

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
			MEHHP	9.84–37.0 µg/g Cr	FT3: -0.0021 (-0.0082, 0.0040) TT3: -1.49 (-2.72, -0.26)* FT4: -0.010 (-0.027, 0.0066) TT4: -0.21 (-0.32, -0.11)* TSH: 0.046 (0.012, 0.081)*
			MEOHP	5.43–20.5 µg/g Cr	FT3: -0.0024 (-0.0082, 0.0035) TT3: -1.36 (-2.54, -0.18)* FT4: -0.0088 (-0.026, 0.0081) TT4: -0.19 (-0.36, -0.086)* TSH: 0.047 (0.012, 0.082)*
			MECPP	15.4–50.8 µg/g Cr	FT3: 0.0004 (-0.0063, 0.0070) TT3: -1.37 (-2.89, 0.15) FT4: -0.011 (-0.027, 0.0057) TT4: -0.23 (-0.33, -0.13)* TSH: 0.041 (0.006, 0.077)*
			Analyses weighted for sampling strategy.		
Boas et al. 2010, Cross-sectional (Denmark)	758 children aged 4–9 years, members of birth cohort who agreed to provide spot urine and blood samples. Urine and blood samples collected during clinical examination.	Multivariate linear regression adjusted for sex and age	Change in serum thyroid hormone per log-unit increase in Cr-corrected urinary metabolite concentration		
			ΣDEHP	NR	FT3: 0.04 (-0.12, 0.21) TT3: 0.06 (-0.02, 0.14) FT4: 0.05 (-0.4, 0.49) TT4: 1.91 (-2.64, 6.46) TSH: 0.04 (-0.01, 0.08)
			MEHP	4.1–11 µg/g Cr (male); 4.1–12 µg/g Cr (female)	FT3: 0.04 (-0.09, 0.18) TT3: 0.02 (-0.05, 0.08) FT4: -0.06 (-0.42, 0.3) TT4: -0.65 (-4.37, 3.07) TSH: 0.03 (-0.01, 0.07)

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
			MEHHP	33–84 µg/g Cr (male); 36–81 µg/g Cr (female)	FT3: 0.05 (-0.11, 0.2) TT3: 0.05 (-0.02, 0.13) FT4: 0.15 (-0.25, 0.55) TT4: 2.52 (-1.6, 6.64) TSH: 0.03 (-0.01, 0.08)
			MEOHP	17–42 µg/g Cr (male); 18–41 µg/g Cr (female)	FT3: 0.04 (-0.12, 0.2) TT3: 0.05 (-0.02, 0.13) FT4: 0.05 (-0.38, 0.47) TT4: 1.86 (-2.53, 6.24) TSH: 0.04 (0.00, 0.09)
			MECPP	29–68 µg/g Cr (male); 33–75 µg/g Cr (female)	FT3: 0.01 (-0.15, 0.17) TT3: 0.05 (-0.03, 0.13) FT4: -0.08 (-0.52, 0.36) TT4: 0.77 (-3.75, 5.29) TSH: 0.03 (-0.02, 0.07)
			Cr-corrected analysis for all children (girls and boys combined); p>0.05 for all.		

Table 2-7. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference and study type	Population	Method of analysis	Urinary metabolite levels		Regression coefficient (β) (95% CI)[a]
Meeker et al. 2007, Cross-sectional (United States [Massachu-setts])	408 male partners of subfertile couples, ages 18–55 years old, evaluated at fertility clinic between January 2000 and May 2004. Urine and blood samples collected on same day.	Multivariate linear regression adjusted for age, BMI, current smoking, and time of day of blood sample. TSH concentrations log-transformed; FT3 and testosterone untransformed	Change in serum thyroid hormone per interquartile range increase in ln-transformed, SG-adjusted urinary metabolites		
			MEHP	3.16–21.3	FT4: -0.013 (-0.042, 0.017) TT3: -0.021 (-0.042, -0.001)* TSH: 0.97 (0.9, 1.04)
			MEHHP	23.4–113	FT4: 0.008 (-0.017, 0.033) TT3: -0.002 (-0.03, 0.025) TSH: 0.98 (0.88, 1.08)
			MEOHP	16.3–71.3	FT4: 0.013 (-0.01, 0.035) TT3: 0.003 (-0.024, 0.028) TSH: 0.97 (0.88, 1.06)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CI = confidence interval; DEHP = di(2-ethylhexyl)phthalate; FT3 = free triiodothyronine; FT4 = free thyroxine; GM = geometric mean; GSD = geometric standard deviation; hCG = human chorionic gonadotropin; LOD = limit of detection; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NHANES = National Health and Nutrition Examination Survey; NR = not reported; PROTECT = Puerto Rico Test Site for Exploring Contamination Threats; SG = specific gravity; SG-adj = specific gravity adjusted; TBG = thyroxine-binding globulin; TSH = thyroid-stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyroxine

In two studies, no associations were observed between maternal urinary DEHP metabolite levels and cord serum thyroid hormone levels (Huang et al. 2018; Yao et al. 2016). In cross-sectional studies of other populations, associations were seen between DEHP urinary metabolite levels and increased serum TSH in adults (Dirtu et al. 2013; Meeker et al. 2011) but not adolescents (Meeker et al. 2011) or in obese individuals (Dirtu et al. 2013); decreased total T3 and T4 in adults (Meeker et al. 2007, 2011); and increased total T3 in adolescents (Meeker et al. 2011). No associations between DEHP metabolites in urine and serum thyroid hormone levels were observed in a cross-sectional study of children 4–9 years old (Boas et al. 2010).

Animal Studies—Thyroid/Parathyroid Gland. Only one animal study was found in the literature that evaluated the function of the thyroid gland. In this study, there were no changes in serum thyroid hormones in PND 21 or 63 offspring born to Sprague-Dawley rat dams exposed to DEHP at doses up to 400 mg/kg/day from GD 6 to PND 20 (Kobayashi et al. 2006).

No changes in thyroid/parathyroid weight or histology were observed in any oral study reviewed. In rats, no exposure-related weight and/or histology effects were observed in acute- or intermediate-duration studies at doses up to 3,000 mg/kg/day (Astill et al. 1986; Gray et al. 1977; Myers 1992b; NTP 1982; Poon et al. 1997), chronic-duration studies at doses up to 939 mg/kg/day (David et al. 2000a; Kluwe et al. 1982a, 1985; NTP 1982), gestational/lactation exposure studies at doses up to 405 mg/kg/day (Grande et al. 2006), or 2- or 3-generation studies at doses up to 659 mg/kg/day (Blystone et al. 2010; NTP 2005; Voss et al. 2005). In mice, no exposure-related weight and/or histology effects were observed in intermediate-duration studies at doses up to 7,899 (Myers 1992a; NTP 1982; Toyosawa et al. 2001) or chronic-duration studies at doses up to 1,821 mg/kg/day (David et al. 2000a; Kluwe et al. 1982a; NTP 1982). In other species, no exposure-related weight and/or histology effects were observed in sexually immature Cynomolgus monkeys exposed to 500 mg/kg/day for 14 days (Pugh et al. 2000), marmoset monkeys following at doses up to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998), ferrets exposed to 1,200 mg/kg/day for 14 months (Lake et al. 1976), or dogs exposed to 56.6 mg/kg/day for 1 year (Carpenter et al. 1953).

Mechanism of Thyroid Disruption. Several mechanisms have been proposed for phthalate-induced disruption in thyroid homeostasis (Miodovnik et al. 2014). Transcriptional activity of the sodium-iodine symporter (NIS) was altered by some phthalates, resulting in reduced uptake of iodine into the thyroid. DEHP was shown to be a thyroid receptor antagonist, and inhibited the binding of T3 to the purified thyroid receptor.

Animal Studies—Pancreas. As discussed in Section 2.6 (Gastrointestinal), pseudoductular lesions and altered acinar cell foci were observed in the pancreas of rats administered dietary DEHP at 3,000 mg/kg/day for 108 weeks (only dose tested) (Rao et al. 1990). These lesions are expected to affect digestive system (exocrine) functions of the pancreas, as opposed to endocrine function. No other chronic-duration studies reported histopathological lesions in the pancreas in dogs at 56.6 mg/kg/day (Carpenter et al. 1953), rats at doses up to 939 mg/kg/day (Carpenter et al. 1953; David et al. 2000a; Kluwe et al. 1982a, 1985; NTP 1982), or mice at doses up to 1,821 mg/kg/day (David et al. 2000b; Kluwe et al. 1982a; NTP 1982). Similarly, no histopathological lesions in the pancreas were observed following intermediate-duration exposure to doses up to 2,500 mg/kg/day in monkeys (Kurata et al. 1998), 3,000 mg/kg/day in rats (Gray et al. 1977; Hazelton Washington 1992b; NTP 1982; Poon et al. 1997), or 7,899 mg/kg/day in mice (Hazelton Washington 1992a; NTP 1982; Toyosawa et al. 2001).

Animal Studies—Adrenal Gland. The function of the adrenal gland was evaluated in developmental studies and reported an approximate 50% reduction in serum aldosterone levels in male adult offspring of Sprague-Dawley rats exposed to DEHP at doses ≥100 mg/kg/day from GD 14 to PND 0 (Martinez Arguelles et al. 2011, 2013). In female offspring, serum aldosterone was significantly increased by approximately 2-fold at maternal doses of 300 mg/kg/day (Martinez Arguelles et al. 2011). These changes were not observed in PND 21 offspring. No changes in serum corticosterone were observed in either sex at either time point at maternal doses up to 750 mg/kg/day (Martinez Arguelles et al. 2011). While no changes were observed in serum angiotensin levels (which stimulate aldosterone production), significant reductions in angiotensin receptors *Agtr1a*, *Agtr1b*, and *Agtr2* were observed in the adrenal gland of adult male offspring of DEHP-exposed dams (not assessed in female offspring) (Martinez-Arguelles et al. 2011).

Histopathological changes in the adrenal gland were observed inconsistently in oral studies in adult F344 rat. In a 3-generation study of F344 rats, adrenal cortical vacuolation was observed in F0 male rats exposed to a dietary dose of approximately 659 mg/kg/day, but not at doses ≤447 mg/kg/day (Blystone et al. 2010; NTP 2005). This was not observed in F1 or F2 parental males or parental females from any generation (Blystone et al. 2010; NTP 2005). Increased vacuolation and width in the zona glomerulosa in the adrenal gland were also observed in male and female F344 rats exposed to dietary doses ≥1,724 mg/kg/day for 13 weeks; no histopathological changes were observed at doses ≤918.4 mg/kg/day (Myers 1992b). However, no changes in adrenal histology were reported in F344 rats following dietary

exposures up to 3,000 mg/kg/day for 12 weeks or 774 mg/kg/day for 2 years (Kluwe et al. 1982a, 1985; NTP 1982).

In other rat strains (Sprague-Dawley, Wistar, Sherman), no histopathological changes were observed in the adrenal glands in intermediate-duration studies at doses up to 10,000 mg/kg/day (Dalgaard et al. 2000; Poon et al. 1997), in chronic-duration studies at doses up to 300 mg/kg/day (Carpenter et al. 1953; Voss et al. 2005), or in a 2-generation study at doses up to 1,088 mg/kg/day (Schilling et al. 2001). Additionally, no changes in adrenal histology were observed in Wistar rats following intermittent nose-only inhalation concentrations up to 63 ppm for 4 weeks (Klimisch et al. 1992). In mice, no changes in adrenal gland histology were observed in intermediate-duration studies at doses up to 7,899 mg/kg/day (Myers 1992a; NTP 1982; Toyosawa et al. 2001) or chronic-duration studies at doses up to1,821 mg/kg/day for 2 years (Kluwe et al. 1982a; NTP 1982). In other mammalian species, no changes in adrenal gland histology were observed in marmoset monkeys following exposure to gavage doses up to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998), ferrets exposed to 1,200 mg/kg/day for 14 months (Lake et al. 1976), or dogs exposed to 56.6 mg/kg/day for 1 year (Carpenter et al. 1953)

Studies of adrenal gland weight following oral DEHP exposure during early life stages do not indicate a consistent organ weight effect attributable to exposure. Decreased adrenal weight was observed in adult offspring of Sprague-Dawley rats exposed to 750 mg/kg/day from GD 14 to PND 0, but not ≤300 mg/kg/day (Martinez-Arguelles et al. 2011). In a series of experiments in Sprague-Dawley and Long-Evans weanling male rats, adrenal gland weight was significantly decreased in Sprague-Dawley rats exposed to ≥100 mg/kg/day for 22 days immediately following weaning, but not following exposures to up to 900 mg/kg/day for 35, 42, or 76 days postweaning (Noriega et al. 2009). In Long-Evans rats, adrenal gland weight was significantly decreased at 900 mg/kg/day, but not ≤300 mg/kg/day, following exposure for 35 days post-weaning, but not following exposure for 42 or 76 days (22-day duration not examined in Long-Evans rats) (Noriega et al. 2009). The study authors did not propose a rationale for why adrenal gland weight effects disappeared with longer exposure duration, but it may represent a transient effect to initial exposure that recovers with time. Male offspring of Wistar rats exposed to DEHP at doses ≥10 mg/kg/day from GD 7 to PND 16 also showed decreased adrenal weight on PND 16 in one study, but not at doses up to 100 mg/kg/day in another using the same protocol (Christiansen et al. 2010).

In contrast, *increased* relative adrenal weights were observed in F0, F1, and F2 parental male rats exposed to an approximate dietary dose of 659 mg/kg/day, but not ≤447 mg/kg/day, during a 3-generation

reproductive study (Blystone et al. 2010; NTP 2005). Adrenal weight changes were not observed in parental females. No exposure-related changes in adrenal gland weight were reported in any other oral study in rats reviewed, including acute-duration studies with doses up to 5,000 mg/kg/day (Berman et al. 1995; Lee and Koo 2007), intermediate-duration studies with doses up to 10,000 mg/kg/day (Dalgaard et al. 2000; Gray et al. 1977), a lifetime exposure study with doses up to 300 mg/kg/day (Voss et al. 2005), a 2-generation study with doses up to 1,088 mg/kg/day (Schilling et al. 2001), or a developmental study with doses up to 300 mg/kg/day (Gray et al. 2009). Similarly, no change in adrenal weight was observed in a 4-week inhalation study in rats at nose-only concentrations up to 63 ppm (Klimisch et al. 1992). In sexually immature Cynomolgus monkeys, no exposure-related changes in adrenal weight were observed following gavage exposure to 500 mg/kg/day for 14 days (Pugh et al. 2000).

Gestational exposure to DEHP produced effects on the adrenals of adult offspring, including altered control of aldosterone and changes to cholesterol and lipid metabolism (Martinez-Arguelles and Papadopoulos 2015; Martinez-Arguelles et al. 2013). DEHP exposure *in utero* resulted in decreased adrenal aldosterone production and decreased mineralocorticoid receptor (MR) expression in adult Leydig cells (at PND 60, but not PND 21), leading to reduced testicular testosterone formation independent of a direct effect on the steroidogenic pathway. Cortisone levels were not affected, suggesting that DEHP induced alterations in fetal zona glomerulosa development. In isolated glomerulosa cells, DEHP increased many of the same genes upregulated by angiotensin II and potassium, including genes encoding potassium channels, at PND 60 but not PND 21 (Martinez Arguelles et al. 2013). The PPARα pathways appear to be critical for maintaining adequate aldosterone biosynthesis in the adult rat.

DEHP was shown to interfere with mitochondrial cholesterol transport in *ex vivo* zona glomerulosa cells obtained from PND 20 rats exposed to 500 mg/kg DEHP for 10 days. Global gene expression data showed down-regulation of the gene encoding hormone-sensitive lipase (*Lipe*) and a decrease in the levels of free cholesterol available for steroid biosynthesis at PND 60 (male rats exposed *in utero*) (Martinez-Arguelles and Papadopoulos 2015; Martinez-Arguelles et al. 2013).

Animal Studies—Pituitary Gland. No exposure-related changes in serum adrenocorticotropin levels were observed in male or female adult offspring of Sprague-Dawley rats exposed to DEHP at doses ≥100 mg/kg/day from GD 14 to PND 0 (Martinez Arguelles et al. 2011). No additional studies evaluating serum pituitary hormone levels were identified.

The incidence of vacuolation of basophils in the pars distalis in the pituitary gland was increased in male Sprague-Dawley rats after dietary exposure to DEHP at doses ≥737 mg/kg/day for 17 weeks; this effect was not observed in males exposed to 142 mg/kg/day or at 2- or 4-week interim sacrifices at doses up to 1,440 mg/kg/day (Gray et al. 1977). These cells are known as "castration cells" because they appear after gonadectomy due to decreased testosterone secretion by the testes, and are therefore considered a sensitive indicator of gonadal deficiency. Increased "castration cells" were also observed in male F344 rats in a 13-week study following dietary exposure to 1,724 mg/kg/day, but not ≤850.1 mg/kg/day (Myers 1992b) and in a 2-year study following dietary exposure to 789 mg/kg/day, but not ≤147 mg/kg/day (David et al. 2000a). See Section 2.16 (Reproductive) for more information regarding gonadal effects of DEHP exposure.

Hypertrophy of anterior pituitary cells (pars anterior) was observed in male F344 rats administered approximately 674 mg/kg/day for 2 years; no changes were observed at 322 mg/kg/day (Kluwe et al. 1982a, 1985; NTP 1982). No changes were observed in females at doses up to 774 mg/kg/day. Anterior pituitary cell hypertrophy was not observed in other chronic-duration F344 rat study at doses up to 939 mg/kg/day (David et al. 2000a), or shorter-duration studies in F344, Sprague-Dawley, or Wistar rats at doses up to 3,000 mg/kg/day (Blystone et al. 2010; Gray et al. 1977; Myers 1992b; NTP 1982, 2005; Poon et al. 1997; Schilling et al. 1999, 2001). In mice, no histopathological changes in the pituitary gland were observed following intermediate-duration exposure to doses up to 7,899 mg/kg/day (Myers 1992a; NTP 1982; Toyosawa et al. 2001) or chronic-duration exposure to doses up to 1,821 mg/kg/day (David et al. 2000a; Kluwe et al. 1982a; NTP 1982). In nonhuman primates, no histopathological changes in the pituitary gland were observed in marmoset monkeys following exposure to doses up to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998).

No exposure-related changes were observed in pituitary weights of Sprague-Dawley rats exposed to doses up to 1,440 mg/kg/day for 17 weeks (Gray et al. 1977), or F0 or F1 Wistar rats exposed to doses up to 1,088 mg/kg/day over 2 generations (Schilling et al. 1999, 2001), or marmoset monkeys exposed to doses up to 2,500 mg/kg/day for 13 weeks (Kurata et al. 1998).

Summary. Data from epidemiological studies suggest that there may be a possible association between DEHP exposure and altered thyroid hormone levels in humans, although the individual studies have additional limitations not described in detail here. There is no evidence of thyroid damage following DEHP exposure from the single available animal study that specifically evaluated thyroid function. In animals, there is some evidence for adverse effects in the adrenal and pituitary glands. Animal data

suggest that the developing animal may be particularly sensitive to DEHP-mediated effects in endocrine organs.

2.14 IMMUNOLOGICAL

Overview. Epidemiological data on immune system effects of DEHP include studies addressing potential associations between prenatal DEHP exposure and asthma, wheezing, elevated IgE, eczema, atopic dermatitis, and food allergy. Several animal studies evaluated the potential for DEHP exposure via inhalation or oral exposure to enhance allergic immune reactions. Additional animal studies evaluated immune organ weight and histology. Potential underlying mechanisms for the observed adjuvant effect have also been studied.

Epidemiology Studies. Epidemiological studies of immunological health outcomes (including allergy, asthma, serum IgE levels, etc.) selected for review are in Table 2-8. In studies that examined the risk for asthma symptoms or wheezing (Gascon et al. 2015a; Ku et al. 2015; Whyatt et al. 2014), Gascon et al. (2015a) reported increased risk of wheeze between birth and age 7 and risk of asthma at age 7 with doubling of maternal DEHP metabolite levels in urine. No association was seen in the other studies, possibly due to bias or analysis limited to a subset of DEHP metabolites (Ku et al. 2015; Whyatt et al. 2014).

Maternal levels of DEHP urinary metabolites were not associated with IgE in cord blood (Ashley-Martin et al. 2015). However, MEHP levels in both maternal urine (during pregnancy) and children's urine at 5 years of age were positively (β 0.50 and 0.36, respectively) associated with higher serum IgE in children 8 years of age (Ku et al. 2015). A cross-sectional study of children 3–5 years of age did not find an association between the children's DEHP metabolite levels and IgE sensitization (Bekö et al. 2015), although further confirmation of this result is needed. Interestingly, Wang et al. (2014) reported that only 2-year-old boys had urinary MEHP levels positively associated with serum IgE, although girls were also evaluated.

No association was observed between DEHP metabolites in maternal urine during pregnancy and cord blood levels of interleukin-33 (IL-33) or thymic stromal lymphopoietin (TSLP), inflammatory markers that, when elevated in cord blood, predict allergic disease later in life (Ashley-Martin et al. 2015). Prenatal DEHP exposure does not appear to be associated with atopic dermatitis or eczema in early childhood, based on the findings of three birth cohort studies in Poland, Spain, and New York (Gascon et

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Ashley-Martin et al. 2015, Cohort (Canada)	1,137 children, members of birth cohort (Maternal-Infant Research on Environmental Chemicals); pregnant women (14 weeks of gestation) recruited from 10 cities between 2008 and 2011. Single urine sample collected during first trimester. Cord blood samples collected at birth.	Bayesian hierarchical logistic regression adjusted for maternal age and SG	OR for elevated IgE ≥0.5 ku/L in cord blood with log-transformed maternal urinary metabolite concentration		
			ΣDEHP	NR	OR 1.0 (0.7–1.5)
			MEHP	IgE ≥0.5 ku/L: 2.6 (2.7) IgE <0.5 ku/L: 2.6 (2.5) (GM [GSD])	NR
			MEHHP	IgE ≥0.5 ku/L: 10.4 (2.7) IgE <0.5 ku/L: 10.6 (2.4)	NR
			MEOHP	IgE ≥0.5 ku/L: 7.4 (2.5) IgE <0.5 ku/L: 7.4 (2.3)	NR
			OR for elevated IL-33 and TSLP (both ≥80th percentile; pg/mL) in cord blood with log-transformed maternal urinary metabolite concentration		
			ΣDEHP	NR	OR 1.0 (0.7–1.3)
			MEHP	IL-33 and TSLP ≥80th percentile: 2.5 (2.6) IL-33 and TSLP <80th percentile: 2.7 (2.5) (GM [GSD])	NR
			MEHHP	IL-33 and TSLP ≥80th percentile: 9.4 (2.6) IL-33 and TSLP <80th percentile: 10.7 (2.5)	NR
			MEOHP	IL-33 and TSLP ≥80th percentile: 6.8 (2.5) IL-33 and TSLP <80th percentile: 7.5 (2.3)	NR

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Bekö et al. 2015, Case-control (Denmark)	200 cases, children 3–5 years old with at least two parentally-reported conditions (asthma, allergic rhinoconjunctivitis, or eczema), from the city of Odense or its suburbs, and 300 randomly selected controls. Blood and urine samples collected on the day of clinical examination.	Logistic regression adjusted for breast-feeding, allergic predisposition, sex, social class, renovation due to moisture damage and cat and dog allergens in the dust	OR for IgE sensitization with log-transformed urinary metabolite concentration		
			MEHP	Cases: IgE-: 3.7; IgE+: 4.01 (median) Controls: 5.18	NR (NS)
			MEHHP	Cases: IgE-: 31.7; IgE+: 33.2 Controls: 33.5	NR (NS)
			MEOHP	Cases: IgE-: 13.3; IgE+: 16.0 Controls: 17.5	NR (NS)
			MECPP	Cases: IgE-: 29.9; IgE+: 31.5 Controls: 36.6	Among asthma patients: OR 2.9 (1.12, 7.6)*
			ORs for IgE sensitization among controls and among cases with rhinoconjunctivitis and atopic dermatitis were not significant (not reported)		
Ku et al. 2015, Cohort (Taiwan)	171 children, members of birth cohort; pregnant women recruited during the 3rd trimester between December 2000 and November 2001. Single maternal urine sample collected at enrollment; children's urine samples collected at ages 2, 5, and 8. At 8 years of age, children were evaluated for asthma symptoms and blood sample collected for IgE measurement.	Logistic regression adjusted for parental allergies and family members' smoking status (wheezing, asthma) and linear regression, adjusted for sex and parental allergies	OR for wheezing or asthma comparing highest quintile (>80th percentile) of maternal urinary metabolite concentration with those <80th percentile		
			ΣDEHP (MEHP, MEHHP)	50.22 (42.22, 59.72) µg/g Cr (GM [95% CI])	Wheezing OR 3.12 (0.98–9.98) Asthma OR 0.81 (0.21–3.14)
			MEHP	16.90 (14.49, 19.72) µg/g Cr	NR
			Association between log-transformed serum IgE and log-transformed metabolite concentration in maternal urine		
			ΣDEHP (MEHP, MEHHP)	50.22 (42.22, 59.72) µg/g Cr (GM [95% CI])	Allergic children β 0.20 (NR) Non-allergic children β 0.12 (NR) All children β 0.03 (NR)

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			MEHP	16.90 (14.49, 19.72) µg/g Cr	Allergic children β 0.50* (NR) Non-allergic children β 0.24 (NR) All children β 0.38 (NR)
			Association between log-transformed serum IgE and log-transformed metabolite concentration in child's urine at 5 years of age		
			ΣDEHP (MEHP, MEHHP)	NR	Allergic children β 0.29 (NR) Non-allergic children β -0.14 (NR) All children β 0.14 (NR)
			MEHP	11.9 µg/g Cr (GM)	Allergic children β 0.36* (NR) Non-allergic children β -0.22 (NR) All children β 0.10 (NR)
			No significant association between serum IgE and metabolite concentration in child's urine at 2 years of age		

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Stelmach et al. 2015, Cohort (Poland)	147 children (82 boys, 65 girls), members of birth cohort (Polish Mother and Child Cohort); pregnant women recruited during first trimester from maternity units or clinics. Single maternal urine sample collected during 3rd trimester. Children's allergy symptoms determined at age 2 years by parental report supplemented by medical chart review.	Logistic regression adjusted for atopy in family, father's education, frequency of cleaning, and breastfeeding (atopic dermatitis) or pets at home during pregnancy and breastfeeding (food allergy)	OR for atopic dermatitis or food allergy with log-transformed maternal urinary metabolite concentration		
			ΣDEHP	1.73–37.75 µg/g Cr	Atopic dermatitis OR 0.36 (0.08, 1.51) Food allergy OR 0.97 (0.29, 3.30)
			MEHP	0.04–0.64 µg/g Cr	Atopic dermatitis OR 0.47 (0.13, 1.75) Food allergy OR 0.45 (0.13, 1.58)
			MEHHP	0.11–20.57 µg/g Cr	Atopic dermatitis OR 0.70 (0.29, 1.70) Food allergy OR 1.02 (0.45, 2.31)
			MEOHP	0.69–6.54 µg/g Cr	Atopic dermatitis OR 0.46 (0.14, 1.59) Food allergy OR 1.02 (0.34, 3.04)
			There were no significant associations between atopic dermatitis or food allergy and children's urinary metabolite concentrations		

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Gascon et al. 2015a, Cohort (Spain)	391 children (238 boys and 224 girls), members of birth cohort (INMA/ Environment and Childhood); pregnant women recruited during first trimester at public hospital or health center. Urine samples collected during 1st and 3rd trimesters and results averaged for analysis. Allergy outcomes in the prior 6 or 12 months determined by maternal questionnaire at 6 and 14 months and 4 and 7 years of age. Atopy determined as IgE ≥2 kU/L to common allergens measured in blood sample collected at age 4 years.	Logistic regression, adjusted for maternal education, number of siblings, maternal smoking during pregnancy, maternal history of asthma/allergy, and maternal BMI	RR for allergic and respiratory outcomes between birth and age 7, with doubling of log2-transformed maternal urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	69.5–147.9 µg/g Cr	Wheeze RR 1.25 (1.04–1.50)* Eczema RR 1.00 (0.83–1.20)
			RR for asthma at age 7 or atopy at age 4, with doubling of log2-transformed maternal urinary metabolite concentration		
			ΣDEHP	69.5–147.9 µg/g Cr	Asthma at age 7 RR 1.38 (1.05–1.82)* Atopy at age 4 RR 1.13 (0.60–2.11)
			MEHP	7.3–17.2 µg/g Cr	NR
			MEHHP	17.9–41.5 µg/g Cr	NR
			MEOHP	14.3–30.3 µg/g Cr	NR
			MECPP	27.2–59.8 µg/g Cr	NR
Wang et al. 2014, Cohort/ cross-sectional (Taiwan)	483 children (244 boys and 239 girls), members of birth cohort (Taiwan Birth Panel cohort); pregnant women recruited during 3rd trimester from selected hospitals. Single maternal urine sample collected during 3rd trimester; children's urine samples collected at ages 2 and 5 years. Atopic disorders determined by parental questionnaire at ages 2 and 5 years. Children's blood samples collected at ages 2 and 5 for serum IgE determination.	Linear regression adjusted for gestational age, maternal education, maternal history of atopy, and prenatal environmental tobacco smoke exposure (IgE), or logistic regression, adjusted for gender,	Association between log-transformed serum IgE at age 2 years and log-transformed child's urinary metabolite concentration at age 2 years		
			MEHP	16.01 (1.12) µg/g Cr (GM [SE])	All children: β 0.191* (NR) Boys: β 0.256* (NR) Girls: β 0.107 (NR)
			OR for atopic dermatitis comparing highest quartile of child's urinary metabolite concentration at age 2 years with lowest quartile		
			MEHP	16.01 (1.12) µg/g Cr (GM [SE])	Atopic dermatitis at age 2 years OR 1.31 (0.50, 3.45) Atopic dermatitis at age 5 years OR 1.76 (0.67, 4.64)

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)	Effect estimate (95% CI)[a]
		gestational age, maternal education, maternal history of atopy, and pre-natal ETS exposure		
Whyatt et al. 2014, Cohort (United States [New York])	300 children (137 boys and 163 girls), members of birth cohort (CCCEH); black or Dominican mothers recruited prior to 20th week of pregnancy, between 1998 and 2004. Single maternal urine sample collected during 3rd trimester (mean 34 weeks of gestation); children's urine samples collected at ages 3, 5, and 7 years. Asthma determined by questionnaire administered to parent when children were ages 5, 6, 7, 9, and 11 years of age	Poisson regression with robust standard error estimation using generalized estimating equations, adjusted for maternal asthma, household smoke exposure, maternal prenatal BPA exposure, maternal prenatal demoralization[b], maternal prenatal urinary SG, and child age	RR for asthma symptoms, compared with nonasthmatics, comparing highest tertile of ln-transformed maternal urinary metabolite concentration with lowest MEHHP 10.6–50.0	History of asthma symptoms RR 0.97 (0.74, 1.28) Diagnosis of current asthma RR 1.03 (0.89, 1.20) History of asthma but diagnosis of not current asthma RR 0.95 (0.82, 1.10)

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Bertelsen et al. 2013, Cross-sectional (Norway)	623 children, members of birth cohort (Environment and Childhood Asthma cohort); healthy infants born in Oslo were enrolled between January 1, 1992 and March 31, 1993. A subset of the cohort with lung function measurement at birth and/or participants in 2-year followup study were invited to 10-year followup; of those who agreed, 623 were selected, with preferential sampling of those with asthma (21% prevalence). Current asthma defined by history of asthma and symptoms, asthma medicine use, or clinical signs in the previous 12 months. Urine samples collected same day as clinical examination.	Logistic regression adjusted for urine SG, sex, parental asthma, and household income	OR for current asthma with log-transformed urinary metabolite concentration		
			ΣDEHP	0.58–1.18 µmol/L (SG-adj)	Highest versus lowest quartile: OR 1.6 (0.83, 3.2) Per log-IQR change: OR 0.99 (0.75, 1.3)
			MEHP	5.0–12.5	NR
			MEHHP	56.9- 116.4	NR
			MEOHP	36.1–75.3	NR
			MECPP	71.7–153.2	NR
Hoppin et al. 2013, Cross-Sectional (United States [NHANES])	2,325 children ≥6 years old; participants in NHANES 2005–2006 with complete data. Allergic symptoms determined by questionnaire; urine samples collected same day.	Logistic regression adjusted for age, race, gender, BMI, creatinine, and cotinine	OR for current allergic symptoms per log-unit increase in urinary metabolite concentration in children ages 6–17 years		
			ΣDEHP	54.15–230.02 (survey-weighted)	Current asthma OR 0.26 (0.14, 0.49) Current wheeze OR 0.58 (0.24, 1.42) Current hay fever OR 0.78 (0.18, 3.48) Current rhinitis OR 1.52 (0.86, 2.66)
			MEHP	<LOD–6.74	NR
			MEHHP	15.16–75.70	NR

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			MEOHP	10.95–46.08	NR
			MECPP	25.29–101.93	NR
			OR for current allergic symptoms per log-unit increase in urinary metabolite concentration in adults (≥18 years)		
			ΣDEHP	33.21–160.81 (survey-weighted)	Current asthma OR 1.16 (0.82, 1.64) Current wheeze OR 1.23 (0.86, 1.77) Current hay fever OR 1.09 (0.59, 2.01) Current rhinitis OR 1.09 (0.86, 1.38)
			MEHP	<LOD–6.19	NR
			MEHHP	9.59–50.46	NR
			MEOHP	6.10–13.48	NR
			MECPP	15.29–74.83	NR
Hsu et al. 2012, Cross-sectional (Taiwan)	101 children (63 boys, 38 girls), mean age 7 years; members of group recruited between 2005 and 2006 from randomly selected kindergartens and day care centers in Taiwan; from group, 59 cases with at least 2 parent-reported allergic disease or symptoms in prior 12 months and 42 controls selected; case status confirmed by clinical diagnosis. Urine samples collected during household visit for dust collection, within 1 year of clinical examination.	Logistic regression adjusted for child's gender, age, presence of fever, and if taken any medication in the recorded week; as well as parents' smoking status, allergic history and education levels, and the month the sampling took place	OR for allergic disease or symptom comparing highest quartile of urinary metabolite concentration with lowest		
			MEHP	5.7–20.0 µg/g Cr	Asthma OR 1.29 (0.13–12.89) Rhinitis OR 0.96 (0.25–3.71) Eczema OR 0.85 (0.20–3.55)
			MEHHP	25.4–85.3 µg/g Cr	NR
			MEOHP	23.4–79.6 µg/g Cr	NR

Table 2-8. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)	Effect estimate (95% CI)[a]
Just et al. 2012, Cohort (United States [New York])	244 children (119 boys and 125 girls), members of CCCEH) described above for Whyatt et al. (2014). Fractional exhaled NO concentrations (FeNO; a marker of airway inflammation) measured during followup visits when children were aged 4.9–9.1 years.	Generalized estimating equations with robust standard errors, adjusted for maternal urinary SG, age, sex, race/ethnicity, time of day of FeNO collection, and ambient NO, as well as seroatopy	Percent difference in fractional NO concentration with log-unit increase in maternal urinary metabolite concentration	
			MEHHP 42 (36, 49) (GM [95% CI])	0.0 (-6.4, 6.9)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.
[b]Demoralization is defined as “a psychological state characterized by helplessness, hopelessness, a sense of failure and the inability to cope” or a “giving up-given up” complex (Tecuta et al. 2015); maternal demoralization was assessed via questionnaire.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; BPA = bisphenol A; CCCEH = Columbia Center for Children’s Environmental Health; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; GSD = geometric standard deviation; IgE = immunoglobulin E; IL-33 = interleukin 33; INMA = Infancia y Medio Ambiente; IQR = interquartile range; LOD = limit of detection; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NHANES = National Health and Nutrition Examination Survey; NR = not reported; NS = not significant; OR = odds ratio; RR = risk ratio; SE = standard error; SG = specific gravity; SG-adj = specific gravity adjusted; TSLP = thymic stromal lymphopoietin

al. 2015a; Stelmach et al. 2015; Wang et al. 2014). In addition, although the data are more limited, no association was observed between maternal levels of urinary DEHP metabolites and food allergy in a small birth cohort study in Poland (n=147; Stelmach et al. 2015). Maternal urinary MEHHP levels during pregnancy were not associated with a change in fractional exhaled nitric oxide (a marker of airway inflammation) in children ~5–9 years old (Just et al. 2012); other metabolites of DEHP were not measured in this study.

Animal Studies—Immune Function. Several animal studies have reported adjuvant effects of low levels of DEHP exposure in mice sensitized to OVA. In these studies, OVA-sensitized mice were exposed to DEHP prior to an OVA challenge. Immune responses were measured in treated animals and compared with responses in OVA-sensitized controls. In an inhalation study, OVA-sensitized mice intermittently exposed to 0.81 ppm DEHP for 14 weeks showed elevated OVA-specific IgG1, eosinophils, neutrophils, and lymphocytes following a 3-day OVA challenge (Larsen et al. 2007). Immune responses were not elevated at exposure concentrations ≤0.11 ppm. Enhanced immune responses in OVA-sensitized mice were also observed following oral exposure to DEHP doses ≥0.03 mg/kg/day (lowest dose tested) for 28–52 days (Guo et al. 2012; Han et al. 2014; Yang et al. 2008). Immune changes following OVA challenge were increased, including OVA-specific serum IgE and IgG1, cytokine production, and follicular helper cell population. Additionally, these researchers observed increases in the severity of tissue cell infiltration, airway remodeling, and germinal center formation in splenic lymphoid nodules at ≥0.3 mg/kg/day. At DEHP doses ≥0.7 mg/kg/day, there were increased eosinophils in BAL fluid and airway responsiveness (Guo et al. 2012; Han et al. 2014; Yang et al. 2008). Increased airway hyperresponsiveness was also reported in both sensitized and non-sensitized animals exposed to ≥0.7 and 70 mg/kg/day, respectively, compared with appropriate controls (Yang et al. 2008). However, the magnitude of effect was greater in sensitized animals. In the study by Guo et al. (2012), no exposure-related findings were observed in non-sensitized animals. Neither Han et al. (2014) nor Larsen et al. 2007) evaluated non-sensitized animals.

Similar adjuvant responses were not observed in studies using other allergens. For example, intermittent oral exposure to DEHP at doses up to 19 mg/kg/day (1 day/week for 4 weeks) did not increase allergen-induced atopic dermatitis in mice exposed to the mite allergen (*Dermatophagoides pteronyssinus*), compared with allergen-only exposed controls (Sadakane et al. 2014). Similarly, delayed-type hypersensitivity (DTH) responses to keyhole limpet hemocyanin (KLH) were not increased in female rats following a 16-day exposure to DEHP at concentrations up to 300 mg/kg/day (Piepenbrink et al. 2005). In this study, rats were sensitized to KLH at 11 and 12 weeks post-exposure and evaluated for DTH

responses 13 weeks post-exposure. Piepenbrink et al. (2005) also evaluated DTH responses in juvenile and adult female offspring of rats exposed to DEHP at doses up to 300 mg/kg/day from GD 6 to 21. As seen in exposed adults, enhanced DTH responses were not observed following developmental exposure.

There is some evidence of altered immune endpoints measured *ex vivo* following DEHP exposure. In the inhalation study described above, mediastinal lymph nodes harvested from treated OVA-sensitized animals had significantly increased *ex vivo* secretion of the cytokines IL-5 and IL-10, compared with lymph nodes harvested from OVA controls (Larsen et al. 2007). However, evaluation of splenic immune function *ex vivo* has not shown exposure-related immune alterations following oral exposure to DEHP. No changes, compared with controls, were observed in mitogenesis in spleen cells harvested from mice exposed to DEHP at dietary doses up to 360 mg/kg/day for 10 or 20 days (Sasaki et al. 2003). Similarly, in the Piepenbrink et al. (2005) study described above, no exposure-related changes were observed in *ex vivo* cytokine production (interleukins [IL]-2, -4, -10, -12, or interferon [IFN]-γ) or production of signaling molecules TNF-α or nitric oxide by macrophages following in utero or adult exposure.

Animal Studies—Immune Organ Weight and Histology. One study reported thymic atrophy in mice exposed to ≥6,922 mg/kg/day for 28 days; no changes occurred at doses ≤2,579 mg/kg/day (Myers 1992a). No changes in thymic histology were observed in other mouse studies utilizing lower doses, including acute-duration studies at doses up to 360 mg/kg/day (Sasaki et al. 2003), intermediate-duration studies at doses up to 2,600 mg/kg/day (NTP 1982; Toyosawa et al. 2001), or chronic-duration studies at doses up to 1,821 mg/kg/day (Kluwe et al. 1982a, 1985, 1982b; NTP 1982). In rats, no changes in thymus histology were observed in acute studies at doses up to 5,000 mg/kg/day (Berman et al. 1995), intermediate-duration studies at doses up to 3,000 mg/kg/day (Gray et al. 1977; Myers 1992b; NTP 1982; Piepenbrink et al. 2005), chronic-duration studies at doses up to 774 mg/kg/day (Kluwe et al. 1982a, 1982b, 1985; NTP 1982), or a 2-generation study at doses up to 1,088 mg/kg/day (Schilling et al. 2001). Additionally, no exposure-related changes in thymic weights were observed in acute studies at doses up to 5,000 mg/kg/day (Berman et al. 1995), intermediate-duration studies at doses up to 1,857.6 mg/kg/day (Myers 1992b; Piepenbrink et al. 2005), a 2-generation study at doses up to 1,088 mg/kg/day (Schilling et al. 2001), or a gestational/lactation exposure study at doses up to 405 mg/kg/day (Grande et al. 2006).

No adverse effects were observed in other immune organs (spleen, lymph nodes, bone marrow) in any of the oral studies reviewed. In nonhuman primates, no changes in spleen weights were observed in sexually immature Cynomolgus monkeys exposed to 500 mg/kg/day for 14 days (Pugh et al. 2000). Carpenter et al. (1953) reported no changes in spleen histology in dogs at 56.6 mg/kg/day for 1 year. In rodents, no

changes in spleen, lymph node, and/or bone marrow histology or weights were observed in 30 studies at acute doses up to 5,000 mg/kg/day, intermediate-duration doses up to 10,000 mg/kg/day, or chronic-duration doses up to 1,821 mg/kg/day (Table 2-2). In addition, no changes in spleen histology were observed in a 4-week inhalation (nose-only) study in rats at concentrations up to 63 ppm (Klimisch et al. 1992).

Mechanisms of Altered Immune Function. The adjuvant effect of DEHP appears to be related to an imbalance in the humoral immune response mediated by cytokines released from hyperfunctioning T follicular helper cells (CD4+ Th cell subset) (Han et al. 2014). These cells synthesize excesses of IL-21 and IL-4, which result in increased secretion of allergy-related IgE and IgG1. Overexpressed transcription factors related to this process include Bcl-6 and c-Maf (Han et al. 2014). DEHP also enhanced the production and/or secretion of tumor necrosis factor-α (TNFα) by isolated macrophages or monocytes (Hansen et al. 2015). Direct activation of PPARs is not considered a likely mechanism for asthma, because PPARs primarily mediate anti-inflammatory effects in the lungs (Bolling et al. 2013).

Summary. Limited human data provide inconsistent findings, but some studies in sensitized animal suggest a potential association between DEHP exposure and enhanced immune system responses. One animal study reported thymic atrophy following high oral exposure; no additional studies evaluated this endpoint at comparable doses.

2.15 NEUROLOGICAL

Overview. Most of the epidemiological and animal data pertaining to neurological effects of DEHP are studies that have prenatal and/or early postnatal exposure; these studies are discussed in Section 2.17 (Developmental). Five cross-sectional studies have evaluated neurological effects in adults using NHANES data. A limited number of oral studies in animals evaluated neurological function in adult animals following exposure to DEHP. Brain weight and nervous tissue histology were evaluated in one inhalation study and several oral studies in animals exposed to DEHP.

Epidemiology Studies. Shiue (2015a) observed no associations between urinary levels of DEHP metabolites and self-reported hearing difficulty among 5,560 adult (20–69 years of age) NHANES (2011–2012) participants. The frequency of self-reported memory problems over the previous 7 days was not associated with DEHP metabolite levels in 1,792 elderly adults (60–80 years old) participating in NHANES 2011–2012 (Shiue 2015b).

No association between prevalence of self-reported depression and urinary DEHP metabolites was reported in studies of 3,342 adults >18 years old participating in NHANES surveys between 2005 and 2008 (Berk et al. 2014) or 2,030 elderly adults (≥60 years) participating in NHANES surveys between 2005 and 2012 (Kim et al. 2016b). However, Shiue (2015c), in an analysis of 5,560 adult (20–80 years of age) NHANES (2011–2012) participants, observed an association between risk of depression and increased concentrations of MECPP in urine (OR 1.22; 95% CI 1.00, 1.48), but not other DEHP metabolites. Furthermore, the association between prevalence of depression and MECPP levels was sustained in a model that simultaneously accounted for concurrent health conditions (such as cardiovascular, neurological, respiratory, and digestive conditions, as well as other diseases) that could also increase the risk of depression (Shiue 2015c). However, due to the cross-sectional nature of the available data, coupled with uncertainty in how well urinary metabolite levels predict long-term exposure to DEHP, these findings are considered preliminary.

Wang et al. (2015) reported clinical symptoms of neurotoxicity (i.e., headache, fatigue, dizziness, muscle weakness) in Chinese workers exposed to DEHP at three different PVC manufacturing facilities (average exposures ranging between 233 and 707 μg/m^3 DEHP in the three factories). As described in Section 2.9 (Hepatic), a correlation was observed between reduced plasma cholinesterase activity and DEHP residues in plasma. It is unclear whether the observed reduction in plasma cholinesterase activity is related to the reported clinical symptoms.

Animal Studies. No changes were observed in the histology of the brain, spinal cord, or sciatic nerve in rats following nose-only exposure to DEHP concentrations up to 63 ppm for 4 weeks (5 days/week, 6 hours/day) (Klimisch et al. 1992). Nervous system function was not assessed in this study, but no apparent clinical signs of toxicity were observed. No other studies regarding neurological effects in adult animals after inhalation exposure to DEHP were located.

A limited number of studies evaluated neurological function in adult animals after oral exposure to DEHP. A functional observational battery (FOB) and motor activity measurements were conducted in F344 rats before and after a single gavage dose of up to 5,000 mg DEHP/kg or daily gavage doses of up to 1,500 mg/kg/day for 10–14 days (Moser et al. 1995, 2003). The tests assessed autonomic, sensorimotor, and neuromuscular functions as well as excitability and activity. DEHP showed no neurobehavioral toxicity; however, a single administration of the 5,000 mg/kg dose produced signs of general debilitation (ptosis, piloerection, slight lacrimation, and hypothermia). Similarly, Dalgaard et al.

(2000) did not observe exposure-related changes in FOB tests in rats at doses up to 10,000 mg/kg/day for 4 weeks or 1,000 mg/kg/day for 9 weeks. In a 1-generation study in mice, no changes in exploratory behavior were observed in F0 animals after 3 weeks of exposure to doses up to 180.77 mg/kg/day (behavior assessed 1 week prior to mating) (Tanaka 2002). Clinical signs of neurotoxicity were reported in mice exposed to ≥6,922 mg/kg/day for 28 days, including hunched posture in most animals and hypoactivity in a few animals (Myers 1992a). Tremors were observed in one female mouse prior to death at 7,899 mg/kg/day.

No exposure-related changes in brain, spinal cord, or peripheral nerve histology or brain weights were observed in any of the oral studies reviewed; however, studies other than those mentioned above did not assess neurological function. In nonhuman primates, no changes in brain weight occurred in marmoset monkeys exposed to 2,000 mg/kg/day for 14 days (ICI Americas Inc. 1982; Rhodes et al. 1986). In rodents, no changes in nervous system histology and/or brain weight were observed in 21 studies after acute-duration exposure to 1,100 mg/kg/day, intermediate-duration exposure to doses up to 10,000 mg/kg/day, or chronic-duration exposure to doses up to 1,821 mg/kg/day (Table 2-2). Additionally, no changes in brain histology were observed in ferrets exposed to 1,200 mg/kg/day for 14 months (Lake et al. 1976).

Summary. Human epidemiological data regarding neurological effects are extremely limited. Based on available animal data, the adult neurological system is not a sensitive target of DEHP neurotoxicity.

2.16 REPRODUCTIVE

Overview. The potential effects of DEHP exposure on the male reproductive system have been evaluated in several human epidemiological studies, numerous rodent studies, and a limited number of studies in nonhuman primates. Potential effects on the female reproductive system have been evaluated in humans and animals as well, but to a lesser extent. A large number of reproductive studies have focused on the potential effects of DEHP on the developing reproductive system following prenatal, early postnatal, and/or pre-pubescent exposure. These data are in Section 2.17 (Developmental). Data regarding reproductive system toxicity following exposure to DEHP in adult humans and in sexually mature animals are below. For studies that exposed animals both prior to and through sexual maturation into adulthood (e.g., multigenerational studies), endpoints evaluated prior to sexual maturation are in Section 2.17 (Developmental), while endpoints evaluated in adult animals are below. Several studies evaluating potential mechanisms of reproductive toxicity are also discussed.

Epidemiology Studies—Male Reproductive Effects. Cross-sectional studies examining serum testosterone levels in men have indicated associations between decreasing total and/or free testosterone levels and increasing urinary MEHP levels (Chang et al. 2015; Joensen et al. 2012; Jurewicz et al. 2013; Meeker et al. 2009a; Mendiola et al. 2012; Pan et al. 2006; Wang et al. 2016); associations with other metabolites have not been seen (Table 2-9). The association was seen in studies of men recruited from the general population (Joensen et al. 2012) as well as among male partners of subfertile couples (Jurewicz et al. 2013; Meeker et al. 2009a; Wang et al. 2016) and in PVC workers with high exposure levels (MEHP urinary levels between 210 and 1,884 µg/g creatinine [interquartile range]; Pan et al. 2006). Among studies that did not observe any association with serum testosterone (Axelsson et al. 2015; Fong et al. 2015; Jönsson et al. 2005; Meeker and Ferguson 2014; Mendiola et al. 2011; Pan et al. 2015), two (Fong et al. 2015; Jönsson et al. 2005) did not report the timing of blood sample collection and did not consider time of sample collection in statistical analysis. Because serum testosterone levels vary over the course of the day, the lack of data on timing of sample collection (or consideration of timing in the statistical analysis) is an important limitation of these two studies. It is uncertain whether exposure levels differed among the positive and negative studies, because the studies did not report urinary metabolite levels consistently. The available data do not indicate whether reductions were of a magnitude to be considered adverse, or whether the reductions were associated with other adverse effects.

Associations between urinary DEHP metabolites and other reproductive hormone levels in serum were also observed in males in several of these cross-sectional studies. Reduced serum estradiol was associated with increased urinary MEHP in four studies (Meeker et al. 2009a; Mendiola et al. 2012; Pan et al. 2015; Wang et al. 2016), and increased sex hormone-binding globulin (SHBG) was associated with increased urinary levels of MEHP (Mendiola et al. 2011), MEOHP (Chang et al. 2015; Mendiola et al. 2012), and MEHHP (Mendiola et al. 2012). None of the studies observed a relationship with luteinizing hormone (LH) or inhibin B, and 11 of the 12 studies that evaluated serum FSH observed no association with DEHP metabolites in urine.

Only two of the cross-sectional studies examined serum levels of insulin-like factor 3 (INSL-3), a marker of Leydig cell function. Pan et al. (2015) observed an inverse association between INSL-3 and urinary MEHP, while Chang et al. (2015) saw no relationship with any DEHP metabolite.

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Coefficient (β) (95% CI) unless otherwise specified[a]
General population studies					
Axelsson et al. 2015, Cross-sectional (Sweden)	314 men, ages 17–20, residing within 60 km of Malmo, Sweden; participant and mother born and raised in Sweden; recruited between 2008 and 2010 from general population. Urine and blood samples collected at baseline visit.	Regression adjusted for BMI, own and parental smoking, and time of day	Mean difference in serum hormone level between highest and lowest quartiles of Cr-adjusted urinary metabolite concentration		
			MEHP	0.01–19 nmol/mmol Cr (min–max)	TT -2.7 (-11, 6.7) FT -0.9 (-8.8, 7.7) E2 4.8 (-4.2, 15) SHBG -1.3 (-4.7, 2.1) LH 6.3 (-4.7, 19) FSH 3.3 (-12, 22)
			MEHHP	0.5–340 nmol/mmol Cr	TT -0.9 (-9.7, 8.7) FT 1.1 (-6.9, 10) E2 2.3 (-6.5, 12) SHBG -1.5 (-4.9, 2.0) LH -4.8 (-15, 6.3) FSH -10 (-24, 5.9)
			MEOHP	0.2–200 nmol/mmol Cr	TT -1 (-9.7, 8.7) FT 0.4 (-7.7, 9.2) E2 0.8 (-7.9, 10) SHBG -1.0 (-4.4, 2.4) LH -7.2 (-17, 3.6) FSH -9.1 (-23, 7.1)
			MECPP	0.3–110 nmol/mmol Cr	TT 4.7 (-4.5, 15) FT 2.7 (-5.4, 12) E2 4.4 (-4.6, 14) SHBG 2.1 (-1.3, 5.6) LH -6.9 (-17, 4.0) FSH -8.9 (-23, 7.3)

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)			Coefficient (β) (95% CI) unless otherwise specified[a]
Meeker and Ferguson 2014, Cross-sectional (United States)	867 males including 160 ages 12–20, 267 ages 20–40, 221 ages 40–60, and 219 ages 60–80; participants in NHANES 2011–2012. Urine and blood samples collected same day.	Linear regression adjusted for urinary Cr, age, poverty-income ratio, BMI, race/ethnicity, and session of sample collections	Percent change in serum total testosterone (ng/dL) with IQR increase in Cr-adj urinary metabolite concentration			
			ΣDEHP	Ages 12–20	NR	-8.42 (-24.5, 11.0)
				Ages 20–<40		0.42 (-5.84, 7.09)
				Ages 40–<60		-7.84 (-15.8, 0.85)
				Ages 60–80		-4.86 (-17, 9.01)
			MEHP	Ages 12–20	0.73–2.79	-9.23 (-27.1, 13.0)
				Ages 20–<40	0.97–3.08	1.16 (-6.26, 9.17)
				Ages 40–<60	0.68–1.94	-8.48 (-17.5, 1.57)
				Ages 60–80	0.58–2.09	0.81 (-13.2, 17.1)
			MEHHP	Ages 12–20	4.83–11.9	-2.63 (-19.5, 17.8)
				Ages 20–<40	4.85–11.3	0.69 (-5.17, 6.91)
				Ages 40–<60	4.58–11.4	-7.30 (-14.7, 0.76)
				Ages 60–80	5.08–11.8	-1.78 (-13.8, 11.9)
			MEOHP	Ages 12–20	3.04–7.41	-7.61 (-24.7, 13.3)
				Ages 20–<40	2.77–7.06	1.29 (-5.29, 8.34)
				Ages 40–<60	2.89–5.92	-7.93 (-15.9, 0.84)
				Ages 60–80	3.42–7.92	-6.24 (-18.9, 8.4)
			MECPP	Ages 12–20	7.97–21.6	-10.9 (-26.5, 7.99)
				Ages 20–<40	6.95–17.7	0.20 (-5.64, 6.4)
				Ages 40–<60	7.65–15.9	-7.21 (-15.3, 1.61)
				Ages 60–80	8.45–19.7	-6.61 (-18.5, 7.06)

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Coefficient (β) (95% CI) unless otherwise specified[a]
Joensen et al. 2012, Cross-sectional (Denmark)	881 young Danish men from the general population recruited during 2007–2009 (mean age 19.5 years; range ~18–22 years). Urine and blood samples collected same day.	Linear regression adjusted for age, BMI, smoking, alcohol intake, and time of day of blood sample	Regression coefficient for difference in ln-transformed hormone level between the highest and lowest quartiles of % MEHP		
			ΣDEHP	15–260 (5^{th}–95^{th} percentile) [2.9–17% MEHP, 5^{th}–95^{th} percentile]	NR
			MEHP	0.4–18	TT -0.07 (-0.13, -0.01)* FT -0.07 (-0.12, -0.003)* E2 0.01 (-0.05, 0.07) SHBG 0.01 (-0.06, 0.09) LH 0.01 (-0.07, 0.10) FSH -0.14 (-0.25, -0.03)* Inhibin-B -0.02 (-0.09, 0.06)
			MEHHP	4.3–79	NR
			MEOHP	2.4–55	NR
			MECPP	3.0–54	NR
Jönsson et al. 2005, Cross-sectional (Sweden)	234 men ages 18–21 (28% smokers) living within 60 km of Mälmo, recruited at medical conscript examination in 2000; urine and serum samples collected at examination.	Linear regression (abstinence time and smoking considered as covariates but not included in final model)	Mean difference in serum hormone level between highest and lowest quartiles of Cr-adjusted urinary phthalate metabolite concentration		
			MEHP	<LOD–5.1 nmol/mmol Cr	TT 0.8 (-1.1, 2.7) E2 -0.6 (-6.3, 5.2) SHBG 3.1 (-0.3, 6.4) LH 0.1 (-0.4, 0.6) FSH 0.2 (-0.3, 0.8) Inhibin B 4.9 (-16, 26)

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Coefficient (β) (95% CI) unless otherwise specified[a]
Populations recruited from fertility clinics					
Mendiola et al. 2012Cross-sectional (United States [California, Massachusetts, Minnesota, Missouri, New York, Iowa])	850 men; 425 male partners (mean age 32.2 years) of pregnant women who conceived without assistance, recruited at prenatal clinics in five U.S. cities between 1999 and 2005 (subset of the Study for Future Families multicenter study; Mendiola et al. 2011) and 425 male partners (mean age 36 years) of infertile couples seeking fertility evaluation at Massachusetts General Hospital between January 2000 and May 2004 (Meeker et al. 2009a). Urine and blood samples collected at baseline.	Linear regression adjusted for age, age squared, BMI, smoking status, ethnicity, study center time of sample collection, time of collection squared, and urinary dilution (Cr or specific gravity)	Association between log-transformed serum hormone level and log-transformed urinary metabolite concentration in fertile and infertile men (combined)		
			MEHP	0.9–39.2 (10^{th}–90^{th} percentile)	TT -0.01 (-0.03, 0.005) FT -0.02 (-0.04, -0.004)* E2 -7.9 (-12.4, -3.5)* SHBG 0.01 (-0.01, 0.03) LH -0.01 (-0.03, 0.01) FSH 0.01 (-0.01, 0.04)
			MEHHP	5.4–170	TT -0.01 (-0.03, 0.02) FT -0.02 (-0.04, -0.001)* E2 -3.4 (-8.8, 1.9) SHBG 0.03 (0.002, 0.06)* LH -0.02 (-0.05, 0.01) FSH -0.01 (-0.04, 0.03)
			MEOHP	3.2–110	TT -0.01 (-0.03, 0.02) FT -0.02 (-0.04, -0.001)* E2 -3.0 (-8.4, 2.3) SHBG 0.03 (0.005, 0.06)* LH -0.02 (-0.05, 0.01) FSH -0.01 (-0.05, 0.02)
			Among fertile men (Mendiola et al. 2011), a significant positive association was seen between MEHP and SHBG, but not for other metabolites or hormones. Among infertile men, significant negative associations were seen between SG-adjusted MEHP and total testosterone and estradiol levels (Meeker et al. 2009a).		

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)			Coefficient (β) (95% CI) unless otherwise specified[a]
Wang et al. 2016, Cross-sectional (China)	1,040 male partners of couples attending infertility clinic in Wuhan China. Two urine samples at least 2 hours apart and one blood sample were collected.	Linear regression, adjusted for age, BMI, alcohol use, smoking status, daily cigarette consumption, and urinary Cr	Association between in serum hormone level and ln-transformed Cr-adjusted urinary metabolite concentration			
			MEHP	1st sample: 2.37–7.35 µg/g Cr 2nd sample: 2.53–8.80 µg/g Cr		Significant (p<0.05) associations between ↓ TT, FT, and E2 and ↑ MEHP in urine. No significant association between MEHP and FSH or LH, or between MEHHP and MEOHP and any hormone level (data shown graphically)
			MEHHP	1st sample: 6.80–15.07 µg/g Cr 2nd sample: 6.86–16.70 µg/g Cr		
			MEOHP	1st sample: 3.91–8.45 µg/g Cr 2nd sample: 3.94–9.27 µg/g Cr		
Chang et al. 2015, Case-control (Taiwan)	176 men (25–45 years) recruited between 2010 and 2012, including infertile men (n=141) recruited through infertility clinics in Taiwan and fertile men (n=35) recruited from childbirth preparation classes. Infertile men were classified as Infertile 1 (normal semen quality) and Infertile 2 (abnormal semen quality based on WHO reference values for semen volume and sperm concentration, motility and morphology). Urine and blood samples collected same day.	Linear regression adjusted for age, BMI, cigarettes/day, and season during which blood was collected; TT and E2 also adjusted for SHBG.	Change in ln-transformed serum hormone level per IQR increase in ln-transformed Cr-adjusted urinary metabolite concentration			
			ΣDEHP	Fertile Infertile 1 Infertile 2	0.11 (0.07) µmol/g Cr 0.12 (0.06) µmol/g Cr 0.14 (0.15) µmol/g Cr GM (GSD)	TT 0.98 (0.91, 1.06) FT 0.95 (0.79, 1.14) E2 0.99 (0.90, 1.09) SHBG 1.05 (0.95, 1.16) LH 1.05 (0.95, 1.17) FSH 1.03 (0.91, 1.16) Inhibin B 1.00 (0.87, 1.15) INSL3 1.07 (0.94, 1.21)
			MEHP	Fertile Infertile 1 Infertile 2	3.21 (0.30) µg/g Cr 4.11 (0.28) µg/g Cr 4.52 (0.33) µg/g Cr	TT 0.93 (0.87, 0.99)* FT 0.84 (0.71, 0.99)* E2 0.99 (0.91, 1.09) SHBG 1.00 (0.90, 1.10) LH 1.06 (0.96, 1.16) FSH 1.03 (0.92, 1.16) Inhibin B 1.00 (0.88, 1.14) INSL3 0.93 (0.83, 1.05)

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)			Coefficient (β) (95% CI) unless otherwise specified[a]
			MEHHP	Fertile	8.30 (0.79) µg/g Cr	TT 1.00 (0.94, 1.07) FT 1.06 (0.89, 1.25) E2 0.99 (0.91, 1.08) SHBG 1.04 (0.95, 1.14) LH 1.08 (0.98, 1.18) FSH 1.05 (0.95, 1.08) Inhibin B 0.97 (0.85, 1.10) INSL3 1.06 (0.95, 1.19)
				Infertile 1	9.94 (0.70) µg/g Cr	
				Infertile 2	10.1 (0.78) µg/g Cr	
			MEOHP	Fertile	6.14 (0.72) µg/g Cr	TT 0.99 (0.93, 1.06) FT 1.01 (0.85, 1.21) E2 0.99 (0.90, 1.09) SHBG 1.09 (1.01, 1.19)* LH 1.05 (0.95, 1.16) FSH 1.05 (0.94, 1.18) Inhibin B 1.01 (0.89, 1.15) INSL3 1.06 (0.99, 1.30)
				Infertile 1	5.85 (0.39) µg/g Cr	
				Infertile 2	5.66 (0.38) µg/g Cr	
			MECPP	Fertile	9.15 (1.01) µg/g Cr	TT 0.99 (0.93, 1.06) FT 0.91 (0.77, 1.08) E2 1.01 (0.92, 1.10) SHBG 1.04 (0.95, 1.15) LH 1.04 (0.94, 1.14) FSH 0.99 (0.89, 1.11) Inhibin B 1.02 (0.89, 1.16) INSL3 1.05 (0.93, 1.18)
				Infertile 1	11.9 (0.83) µg/g Cr	
				Infertile 2	12.4 (0.85) µg/g Cr	

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Coefficient (β) (95% CI) unless otherwise specified[a]
Pan et al. 2015, Cross-sectional (China)	1,066 male partners (mean age 29.1 years) of infertile couples recruited from the Reproductive Medical Center at Nanjing Jinling Hospital in Nanjing, China, between November 2012 and July 2014. Urine and nonfasting blood samples collected at recruitment.	Linear regression adjusted for age, BMI, smoking, drinking, time of blood draw, and urinary Cr	Percent change in ln-transformed serum hormone level with IQR increase in ln-transformed urinary metabolite concentration		
			MEHP	2.4–8.7	TT -1.2 (-3.5, 1.1) E2 −4.3% (−8.2, −0.2%)* SHBG 0.9% (−2.0, 3.8%) LH −0.2% (−3.5, 3.3%) FSH 3.1% (−3.4, 4.2%) INSL3 −4.3% (−7.7, −0.8%)*
			MEHHP	7.6–22.5	NR
			MEOHP	4.8–14.3	NR
			MECPP	9.9–27.1	NR
Jurewicz et al. 2013, Cross-sectional (Poland)	269 men <45 years of age (mean age 32 years) attending infertility clinic for diagnostic purposes, with sperm concentration ≥15x10^6/mL. Urine, semen, and blood samples collected same day.	Linear regression adjusted for age, smoking, abstinence period, past diseases, and urinary Cr	Regression coefficient for association between serum hormone level and log-transformed urinary metabolite concentration		
			MEHP	0.5–399.3 µg/g Cr (min–max)	TT -0.29* (NR) E2 0.14 (NR) FSH 0.08 (NR)
			MEOHP	1.2–131.0 µg/g Cr	TT 0.16 (NR) E2 -0.06 (NR) FSH 0.12 (NR)

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Coefficient (β) (95% CI) unless otherwise specified[a]
Occupationally exposed populations					
Fong et al. 2015, Occupational (Taiwan)	82 male PVC production workers (mean age 38 years) who worked for at least 1 year at one of three Taiwanese plants using only DEHP as plasticizer. Urine and blood samples collected on the last day of each subject's work week.	Linear regression adjusted for age, seniority in current job, BMI, current smoking and drinking (within 1 month), and SHBG level	Association between ln-transformed serum hormone level and log-transformed post-shift Cr-adjusted urinary metabolite concentration		
			MEHP	11.5–36.0 µg/g Cr	TT 0.041 (NR) E2 0.153 (NR) SHBG -0.019 (NR) LH 0.014 (NR) FSH 0.015 (NR) Inhibin B -0.003 (NR)
			MEHHP	46.2–150.5 µg/g Cr	TT 0.035 (NR) E2 0.160 (NR) SHBG -0.035 (NR) LH 0.018 (NR) FSH -0.001 (NR) Inhibin B 0.029 (NR)
			MEOHP	38.8–111.3 µg/g Cr	TT 0.055 (NR) E2 0.163 (NR) SHBG -0.014 (NR) LH 0.046 (NR) FSH 0.009 (NR) Inhibin B 0.031 (NR)

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Coefficient (β) (95% CI) unless otherwise specified[a]
Pan et al. 2006, Occupational (China)	74 exposed male PVC workers (mean age 33.5 years) and 63 unexposed male construction workers (mean age 34.3 years). Urine and blood samples collected on same day (not first work day of week or day after night shift).	Linear regression (age and alcohol intake, evaluated in separate models, were also significantly associated with free testosterone)	Association between log-transformed serum hormone level and log-transformed urinary metabolite concentration		
			MEHP	Exposed: 209.6–1,884.4 µg/g Cr Unexposed: 3.7–9.9 µg/g Cr	FT -0.235* (NR) No association with E2, LH, or FSH

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CI = confidence interval; Cr = creatinine; Cr-adj = creatinine-adjusted; DEHP = di(2-ethylhexyl)-phthalate; E2 = estradiol (pmol/L or pg/mL); FSH = follicle-stimulating hormone (IU/L); FT = free testosterone (nmol/L); GM = geometric mean; GSD = geometric standard deviation; INSL3 = insulin-like factor 3 (pg/mL); IQR = interquartile range; LH = luteinizing hormone (IU/L); LOD = limit of detection; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; NHANES = National Health and Nutrition Examination Survey; NR = not reported; PVC = polyvinyl chloride; SG-adj = specific gravity-adjusted; SHBG = sex hormone-binding globulin (nmol/mL or nmol/L); TT = total testosterone (nmol/L, ng/dL, ng/mL); WHO = World Health Organization

A number of cross-sectional studies have investigated relationships between urinary DEHP metabolite levels and semen parameters such as concentration, count, motility, and morphology. The studies selected for inclusion are in Table 2-10. Most of the studies evaluating sperm morphology suggested potential weak associations between exposure to DEHP and increased odds of sperm morphology below the World Health Organization (WHO) reference value for normal morphology (Han et al. 2014; Herr et al. 2009; Wirth et al. 2008) or a lower percent normal sperm with increasing DEHP exposure (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Huang et al. 2014b).

A negative relationship was suggested between reduced sperm count and/or concentration and DEHP metabolites in urine in most studies evaluating these endpoints (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Han et al. 2014; Hauser et al. 2006; Herr et al. 2009; Huang et al. 2014b; Jurewicz et al. 2013; Pan et al. 2015; Wirth et al. 2008). When percent motile sperm was evaluated as a continuous variable, negative relationships were reported in five (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Huang et al. 2014b; Jurewicz et al. 2013; Pan et al. 2015) of seven studies. In contrast, most studies that dichotomized percent motile sperm (above and below WHO reference values) reported reduced odds of low motility sperm (Table 2-10).

The extent to which effects on semen quality affect fertility in exposed men has not been well-studied. In the only identified prospective cohort study evaluating potential associations between time-to-pregnancy and urinary metabolite levels (n=439 couples), DEHP exposure in men was not associated with increased time to pregnancy; fecundability-adjusted odds ratios did not differ from 1.0 ($p>0.05$) for urinary levels of MECPP (FOR 0.89, 95% CI 0.77–1.03), MEHHP (FOR 0.93, 95% CI 0.82–1.07), MEOHP (FOR 0.91, 95% CI 0.79–1.05), or MEHP (FOR 0.98, 95% CI 0.87–1.10) (Buck Louis et al. 2014).

Nonhuman Primate Studies—Male Reproductive Effects. Studies conducted in nonhuman primates generally indicate that they are not susceptible to DEHP-induced reproductive toxicity. A dose of 2,000 mg/kg/day given to 12–18-month-old marmoset monkeys for a 14-day period had no effect on testicular weight or histology (ICI Americas Inc 1982; Rhodes et al. 1986). A 13-week gavage study in marmosets of unspecified age showed no significant treatment-related effects on gross or microscopic appearance of the testis or testicular zinc content at doses up to 2,500 mg DEHP/kg/day (Kurata et al. 1998).

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Sperm morphology					
Axelsson et al. 2015, Cross-sectional (Sweden)	314 men, ages 17–20, residing within 60 km of Malmo, Sweden; participant and mother born and raised in Sweden; recruited between 2008 and 2010 from general population. Urine and semen samples collected at baseline visit.	Regression adjusted for abstinence time, BMI, and own and parental smoking	Mean difference in percent normal sperm between highest and lowest quartiles of Cr-adjusted urinary metabolite concentration		
			MEHP	0.01–19 nmol/mmol Cr (min–max)	Difference = -1.3 (-3.3, 0.66)
			MEHHP	0.5–340 nmol/mmol Cr	Difference = -1.2 (-3.2, 0.8)
			MEOHP	0.2–200 nmol/mmol Cr	Difference = -0.42 (-2.4, 1.6)
			MECPP	0.3–110 nmol/mmol Cr	Difference = -1.0 (-3.0, 0.98)
Bloom et al. 2015a, 2015b, Cohort (United States [Michigan, Texas])	473 male partners (ages 19–51 years; mean age 31.8 years) of couples trying to conceive after discontinuing contraception; participants in the LIFE cohort; recruited from general population of 16 counties in Michigan and Texas from 2005 to 2009. Urine samples were collected at baseline, and semen samples collected at baseline and 1 month later.	Linear regression adjusted for age, race, BMI, income, serum cotinine, urine Cr, abstinence time, and study site	Difference in Box-Cox-transformed percent normal sperm (WHO criteria; baseline semen sample only) per IQR increase in ln-transformed urinary metabolite concentration		
			MEHP	0[b]–4.87	β -0.78 (-13.29, 11.72)
			MEHHP	5.56–37.94	β -4.33 (-12.89, 4.23)
			MEOHP	3.06–17.9	β -3.35 (-11.36, 4.67)
			MECPP	8.60–46.4	β -3.37 (-12.61, 5.86)

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Pan et al. 2015, Cross-sectional (China)	1,066 male partners (median age 29.1 years) of infertile couples recruited from the Reproductive Medical Center at Nanjing Jinling Hospital in Nanjing, China, between November 2012 and July 2014. Urine and semen samples collected at recruitment.	Linear regression adjusted for age, BMI, smoking, drinking, abstinence time, and urinary Cr	Percent change in percent normal sperm associated with IQR increase in ln-transformed urinary metabolite concentration		
			MEHP	2.4–8.7	β -0.7 (-3.7, 2.4)
			MEHHP	7.6–22.5	NR
			MEOHP	4.8–14.3	NR
			MECPP	9.9–27.1	NR
Huang et al. 2014b, Occupational (Taiwan)	47 exposed male PVC workers <60 years of age and 15 unexposed male graduate students (mean age 25.3 years); the exposed group was further divided into those expected to have high exposure (n=36, mean age 35.5 years, direct contact with DEHP in manufacturing process) and those expected to have low exposure (n=11, mean age 36.3 years, administrative, sales, or guard officers). Urine and semen samples collected same day.	Multiple linear regression adjusted for age, smoking status, and coffee consumption	Regression coefficient for association between percent normal sperm morphology and Cr-adjusted urinary metabolite concentration		
			MEHP	Control: 4.4–13.5 µg/g Cr Low: 9.2–21.4 µg/g Cr High: 11.5–31.9 µg/g Cr	β 0.090 (-0.123, 0.304)
			MEHHP	Control: 13.0–28.5 µg/g Cr Low: 29.7–54.2 µg/g Cr High: 47.1–111.5 µg/g Cr	β -0.005 (-0.065, 0.055)
			MEOHP	Control: 10.1–19.9 µg/g Cr Low: 20.4–48.5 µg/g Cr High: 41.0–99.4 µg/g Cr	β -0.001 (-0.074, 0.071)

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Jurewicz et al. 2013, Cross-sectional (Poland)	269 men <45 years of age (mean age 32 years) attending infertility clinic for diagnostic purposes, with sperm concentration ≥15x10^6/mL. Urine and semen samples collected same day.	Linear regression adjusted for age, smoking, abstinence period, past diseases, and urinary Cr	Regression coefficient for association between percent normal morphology sperm and log-transformed urinary metabolite concentration		
			MEHP	0.5–399.3 µg/g Cr (min–max)	β 1.29 (NR)
			MEOHP	1.2–131.0 µg/g Cr	β 1.31 (NR)
Joensen et al. 2012, Cross-sectional (Denmark)	881 young Danish men from the general population recruited during 2007–2009 (mean age 19.5 years; range ~18–22 years). Urine and semen samples collected same day.	Linear regression (no adjustments)	Regression coefficient for difference in square-root-transformed percent of morphologically normal sperm between the highest and lowest quartiles of percent MEHP		
			ΣDEHP	15–260 (5^{th}–95^{th} percentile) [2.9–17% MEHP, 5^{th}–95^{th} percentile]	NR
			MEHP	0.4–18	β 0.11 (-0.08, 0.3)
			MEHHP	4.3–79	NR
			MEOHP	2.4–55	NR
			MECPP	3.0–54	NR
Han et al. 2014, Cross-sectional (China)	232 men between 20 and 40 years of age, with no known exposure to phthalate esters, recruited in 2007 at Chongqing Family Planning Research Institute and Reproductive Center as part of study on semen quality in general population (mean age 32 years).	Logistic regression adjusted for age and abstinence time	OR for percent normal sperm below the WHO reference value (≥15% normal) comparing those with Cr-adjusted urinary metabolite concentration greater than the median with those less than the median		
			MEHP	<LOD–31.4 µg/g Cr (5^{th}–95^{th} percentile)	OR 1.18 (0.58, 2.39)

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Herr et al. 2009, Cross-sectional (Germany)	349 male partners of subfertile couples recruited between April 2004 and November 2005 from the Centre of Dermatology and Andrology at the University Medical Center, Giessen Germany (mean age 34.2 years). Urine and semen samples collected same day.	Logistic regression adjusted for age, smoking, duration of abstinence, and urine Cr	OR for sperm morphology below the WHO reference value (≥4% normal morphology) comparing highest quartile of urinary metabolite concentration with lowest quartile		
			ΣDEHP	23.20–74.70	OR 1.95 (0.74, 5.16)
			MEHP	1.97–9.17	NR
			MEHHP	6.91–22.09	NR
			MEOHP	5.10–16.19	NR
			MECPP	8.03–27.23	NR
Wirth et al. 2008, Cross-sectional (United States [Michigan])	45 male partners of subfertile couples seen for semen analysis at Michigan infertility clinic (mean age 34.8 years; timing of recruitment not reported). Urine and semen samples collected same day.	Multivariate logistic regression adjusted for specific gravity	OR for sperm morphology below the WHO reference value (≥4% normal morphology) comparing highest tertile of urinary metabolite concentration with lowest tertile		
			ΣDEHP	NA	OR 1.2 (0.3, 5.6)
			MEHP	4.6–22.1	NR
			MEHHP	32.7–137.1	NR
			MEOHP	20.1–79.3	NR
Hauser et al. 2006, Cross-sectional (United States [Massachusetts]) (Update of Duty et al. 2003 with larger population size)	463 male partners (ages 20–54 years) of subfertile couples seen for semen analysis Massachusetts General Hospital between January 2000 and May 2004. Urine and semen samples collected same day.	Multivariate logistic regression adjusted for age, abstinence time, and smoking	OR for sperm morphology below WHO reference value (≥4% normal morphology) comparing highest quartile of SG-adjusted urinary metabolite concentration with lowest quartile		
			MEHP	3.1–20.9	OR 0.7 (0.4, 1.5)
			MEHHP	23.4–113	OR 0.7 (0.3, 2.0)
			MEOHP	15.8–73.0	OR 0.7 (0.3, 2.0)

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Sperm motility (%)					
Axelsson et al. 2015, Cross-sectional (Sweden)	314 men, ages 17–20, residing within 60 km of Malmo, Sweden; participant and mother born and raised in Sweden; recruited between 2008 and 2010 from general population. Urine and semen samples collected at baseline visit.	Regression adjusted for abstinence time, BMI, and own and parental smoking	Mean difference in percent progressively motile sperm comparing highest and lowest quartiles of Cr-adjusted urinary metabolite concentration		
			MEHP	0.01–19 nmol/mmol Cr (min–max)	Difference = -7.8 (-14, -2)
			MEHHP	0.5–340 nmol/mmol Cr	Difference = -8.7 (-15, -2.8)
			MEOHP	0.2–200 nmol/mmol Cr	Difference = -6.9 (-13, -1.1)*
			MECPP	0.3–110 nmol/mmol Cr	Difference = -11 (-17, -5.0)*
Bloom et al. 2015a, 2015b, Cohort (United States [Michigan, Texas])	473 male partners (ages 19–51 years; mean age 31.8 years) of couples trying to conceive after discontinuing contraception; participants in the LIFE cohort; recruited from general population of 16 counties in Michigan and Texas from 2005 to 2009. Urine samples were collected at baseline, and semen samples collected at baseline and 1 month later.	Linear regression adjusted for age, race, BMI, income, serum cotinine, urine Cr, abstinence time, and study site	Change in Box-Cox-transformed percent motile sperm per IQR increase in ln-transformed urinary metabolite concentration		
			MEHP	0[b]–4.87	β 0.93 (-1.6, 3.46)
			MEHHP	5.56–37.94	β -1.46 (-3.18, 0.26)
			MEOHP	3.06–17.9	β -1.61 (-3.2, 0.00)*
			MECPP	8.60–46.4	β -1.88 (-3.73, -0.03)*

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Pan et al. 2015, Cross-sectional (China)	1,066 male partners (median age 29.1 years) of infertile couples recruited from the Reproductive Medical Center at Nanjing Jinling Hospital in Nanjing, China, between November 2012 and July 2014. Urine and semen samples collected at recruitment.	Linear regression adjusted for age, BMI, smoking, drinking, abstinence time, and urinary Cr	Percent change in progressively motile sperm (%) with IQR increase in ln-transformed urinary metabolite concentration		
			MEHP	2.4–8.7	β -2.1 (-4.9, 0.7)
			MEHHP	7.6–22.5	NR
			MEOHP	4.8–14.3	NR
			MECPP	9.9–27.1	NR
Huang et al. 2014b, Occupational (Taiwan)	47 exposed male PVC workers <60 years of age and 15 unexposed male graduate students (mean age 25.3 years); the exposed group was further divided into those expected to have high exposure (n=36, mean age 35.5 years, direct contact with DEHP in manufacturing process) and those expected to have low exposure (n=11, mean age 36.3 years, administrative, sales, or guard officers). Urine and semen samples collected same day.	Multiple linear regression adjusted for age, smoking status, and coffee consumption	Regression coefficient for association between percent motile sperm motility and Cr-adjusted urinary metabolite concentration		
			MEHP	Control: 4.4–13.5 µg/g Cr Low: 9.2–21.4 µg/g Cr High: 11.5–31.9 µg/g Cr	β -0.549 (-0.952, -0.146)*
			MEHHP	Control: 13.0–28.5 µg/g Cr Low: 29.7–54.2 µg/g Cr High: 47.1–111.5 µg/g Cr	β -0.155 (-0.267, -0.043)*
			MEOHP	Control: 10.1–19.9 µg/g Cr Low: 20.4–48.5 µg/g Cr High: 41.0–99.4 µg/g Cr	β -0.201 (-0.336, -0.066)*

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Jurewicz et al. 2013, Cross-sectional (Poland)	269 men <45 years of age (mean age 32 years) attending infertility clinic for diagnostic purposes, with sperm concentration ≥15x10^6/mL. Urine and semen samples collected same day.	Linear regression adjusted for age, smoking, abstinence period, past diseases, and urinary Cr	Regression coefficient for association between percent motile sperm and log-transformed urinary metabolite concentration		
			MEHP	0.5–399.3 µg/g Cr (min–max)	β -3.85* (NR)
			MEOHP	1.2–131.0 µg/g Cr	β -3.94* (NR)
Joensen et al. 2012, Cross-sectional (Denmark)	881 young Danish men from the general population recruited during 2007–2009 (mean age 19.5 years; range ~18–22 years). Urine and semen samples collected same day.	Linear regression adjusted for time to semen analysis	Regression coefficient for difference in squared percent of progressively motile sperm between the highest and lowest quartiles of percent MEHP		
			ΣDEHP	15–260 (5^{th}–95^{th} percentile) [2.9–17% MEHP, 5^{th}–95^{th} percentile]	NR
			MEHP	0.4–18	β 289 (-40, 617)
			MEHHP	4.3–79	NR
			MEOHP	2.4–55	NR
			MECPP	3.0–54	NR
Jönsson et al. 2005, Cross-sectional (Sweden)	234 men ages 18–21 (28% smokers) living within 60 km of Mälmo, recruited at medical conscript examination in 2000; urine and semen samples collected at examination.	Linear regression (abstinence time and smoking considered as covariates but not included in final model)	Mean difference in sperm motility (%) between the highest and lowest quartiles of Cr-adjusted urinary metabolite concentration		
			MEHP	<LOD–12 nmol/mmol Cr	Difference = 0.1 (-5.8, 6.1)

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Han et al. 2014, Cross-sectional (China)	232 men between 20 and 40 years of age, with no known exposure to phthalate esters, recruited in 2007 at Chongqing Family Planning Research Institute and Reproductive Center as part of study on semen quality in general population (mean age 32 years).	Logistic regression adjusted for age and abstinence time	OR for percent motile sperm below the WHO reference values (grade A+B ≥50% or grade A ≥25%) comparing those with Cr-adjusted urinary metabolite concentration greater than the median with those less than the median		
			MEHP	<LOD–31.4 µg/g Cr (5^{th}–95^{th} percentile)	OR 0.48 (0.08, 2.76)
Liu et al. 2012, Cross-sectional (China)	97 male partners of subfertile couples (mean age 31.5 years) seeking fertility assessment at The Reproduction Department of the Chongqung Institute of Science and Technology for Population and Family Planning from July 2009 to August 2010. Urine and semen samples collected same day.	Multivariate logistic regression adjusted for age, BMI, abstinence time, smoking, and drinking behavior	OR for percent motile sperm below WHO reference value (≥50% motile) comparing highest tertile of urinary metabolite concentration, with lowest tertile		
			MEHP	0.35–1.93 µg/g Cr (33^{rd}–66^{th} percentile)	OR 0.8 (0.3, 2.4)
			MEOHP	1.89–3.05 µg/g Cr	OR 0.6 (0.2, 1.8)
Herr et al. 2009, Cross-sectional (Germany)	349 male partners of subfertile couples recruited between April 2004 and November 2005 from the Centre of Dermatology and Andrology at the University Medical Center, Giessen Germany (mean age 34.2 years). Urine and semen samples collected same day.	Logistic regression adjusted for age, smoking, duration of abstinence, and urine Cr	OR for sperm motility below the WHO reference value (>50% motile) comparing highest quartile of urinary metabolite concentration with lowest quartile		
			ΣDEHP	23.20–74.70	OR 0.86 (0.26, 2.86)
			MEHP	1.97–9.17	NR
			MEHHP	6.91–22.09	NR
			MEOHP	5.10–16.19	NR
			MECPP	8.03–27.23	NR

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Sperm Morphology or Motility

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Wirth et al. 2008, Cross-sectional (United States [Michigan])	45 male partners of subfertile couples seen for semen analysis at Michigan infertility clinic (mean age 34.8 years; timing of recruitment not reported). Urine and semen samples collected same day.	Multivariate logistic regression adjusted for age, servings per week of alcohol, and urinary specific gravity	OR for sperm motility below the WHO reference value (>50% motile) comparing highest tertile of urinary metabolite concentration with lowest tertile		
			ΣDEHP	NA	OR 0.7 (0.1, 4.4)
			MEHP	4.6–22.1	NR
			MEHHP	32.7–137.1	NR
			MEOHP	20.1–79.3	NR
Hauser et al. 2006, Cross-sectional (United States [Massachusetts])	463 male partners (ages 20–54 years) of subfertile couples seen for semen analysis Massachusetts General Hospital between January 2000 and May 2004. Urine and semen samples collected same day.	Multivariate logistic regression adjusted for age, abstinence time, and smoking	OR for sperm motility below WHO reference value (≥50% motile) comparing highest quartile of SG-adjusted urinary metabolite concentration with lowest quartile		
			MEHP	3.1–20.9	OR 1.1 (0.6, 1.9)
			MEHHP	23.4–113	OR 0.8 (0.4, 1.8)
			MEOHP	15.8–73.0	OR 0.8 (0.3, 1.6)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.
[b]Value reported in study was less than zero, reflecting correction for analytical blank; adjusted to 0 for reporting in this table.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; IQR = interquartile range; LIFE = Longitudinal Study of Infertility and Environment; LOD = limit of detection; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; NA = not applicable; NR = not reported; OR = odds ratio; PVC = polyvinyl chloride; SG-adj = specific gravity-adjusted; WHO = World Health Organization

Rodent Studies—Male Reproductive Effects. In the only available inhalation study evaluating male reproductive performance, no changes in fertility or mating performance of male Wistar rats were observed following exposure to DEHP during adulthood at concentrations up to 63 ppm for 6 hours/day, 5 days/week for 4 weeks (Klimisch et al. 1991, 1992). Mating with unexposed females was carried out at 2 and 6 weeks after the end of the DEHP exposure period. At sacrifice, there were no observable effects of DEHP on testicular structure.

Several studies evaluated reproductive performance in rats following oral exposure to DEHP. Two-generation studies in Wistar rats reported decreased F1 fertility after exposure to doses ≥1,040 mg/kg/day, but not ≤380 mg/kg/day (Schilling et al. 1999, 2001). It is likely that decreased fertility in F1 adults was due (at least in part) to male reproductive toxicity, because testes exhibited focal tubular atrophy at 113 mg/kg/day, and higher doses (≥1,040 mg/kg/day) resulted in aspermia, gross reproductive tract abnormalities, and decreased reproductive organ weights (Schilling et al. 1999, 2001). Testicular atrophy was also observed in F0 males at 1,088 mg/kg/day (Schilling et al. 2001). Clear evidence of decreased male fertility in F1 and F2 generations was observed at doses ≥447 mg/kg/day in a 3-generation study in Sprague-Dawley rats via cross-over mating experiments; complete sterility was observed in F1 males at 659 mg/kg/day (Blystone et al. 2010; NTP 2005). Additional effects observed at doses ≥17 mg/kg/day included reproductive tract malformations in F1 and F2 adult offspring, and decreased reproductive organ weights, seminiferous tubule atrophy, epididymal aspermia, and decreased sperm counts in one or more generations. In 1-generation studies in which exposed male rats were mated to unexposed females following exposure for 21 days, decreased male fertility was only seen at ≥5,000 mg/kg/day (Dalgaard et al. 2000). This finding was accompanied by severe atrophy of seminiferous tubules, diffuse Leydig cell hyperplasia, and decreased testicular weights, with decreased seminal vesicle and epididymides weights occurring at 10,000 mg/kg/day (Dalgaard et al. 2000).

In a chronic exposure 2-generation study in Sherman rats, no changes in fertility or reproductive organ histology were observed; however, the highest dose evaluated was 200 mg/kg/day (Carpenter et al. 1953). Exposure to doses up to 1,156 mg/kg/day for 21–60 days prior to mating had no effect on male fertility (Agarwal et al. 1986; Dalgaard et al. 2000), even though male rats exposed to 1,156 mg/kg/day showed testicular atrophy, decreased sperm density and mobility, increased abnormal sperm, and decreased testes, epididymides, and prostate weights (Agarwal et al. 1986).

Reproductive performance has also been evaluated in mice following oral DEHP exposure. In a continuous breeding study, decreased fertility, and decreased numbers of litters/pair, pups/litter, live-born

pups were observed at 130 mg/kg/day, with no litters produced at 390 mg/kg/day (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984). Decreased fertility was attributed to both males and females in a cross-over mating trial, as fertility issues were observed when males exposed at 390 mg/kg/day were mated to unexposed females or vice versa. Additional reproductive effects observed in exposed males from the cross-over trial included decreased testes, epididymides, and prostate gland weights, decreased sperm concentration and motility, and increased percentages of abnormal sperm.

Additional studies that did not evaluate reproductive performance indicate that the testes are a primary target tissue of DEHP toxicity in adult rats. In an acute study, moderate to severe changes in seminiferous tubules and decreased testes weight were observed at doses ≥1,000 mg/kg/day (Dostal et al. 1988). In intermediate-duration studies, the lowest doses associated with mild to moderate testicular lesions were 37.6 mg/kg/day (Poon et al. 1997) and 142 mg/kg/day (Gray et al. 1977; lowest dose tested). Additional effects, including testicular atrophy and degeneration, degeneration of the Leydig cells, decreased spermatogenesis/hypospermia, and decreased testicular weights, were observed at ≥300 mg/kg/day (CMA 1984; Exxon Chemical Americas 1990; Myers 1992b; NTP 1982; Shaffer et al. 1945). However, two intermediate-duration studies reported no histopathological changes in rat testes at doses up to 200 mg/kg/day for 28 days (Akingbemi et al. 2001) or 930 mg/kg/day for 3 weeks (Astill et al. 1986). In chronic studies, the lowest doses associated with testicular effects (spermatogenesis and seminiferous tubule degeneration) were 14 and 29 mg/kg/day (David et al. 2000a; Ganning et al. 1991). Severe degeneration, atrophy, and decreased testes weights were reported at chronic doses ≥300 mg/kg/day (David et al. 2000a; Kluwe et al. 1982a; Price et al. 1987; Voss et al. 2005).

Similarly, studies that did not evaluate reproductive performance also clearly indicate that the testes are a primary target tissue of DEHP toxicity in adult mice. In A/J mice, Sertoli cell vacuolation and germ cell sloughing in seminiferous tubules were observed after exposure to dietary doses ≥12.3 mg/kg/day for 2–8 weeks (Kitaoka et al. 2013). Lymphocyte infiltration in the testes and hypospermia in the seminiferous tubules were also observed at ≥12.3 and 125 mg/kg/day, respectively, after 8 weeks (Kitaoka et al. 2013). However, testicular effects, including testicular atrophy, decreases/absent spermatogenesis, and decreased testes/epididymides weights, were observed in B6C3F1 mice after intermediate-duration exposure to doses ≥2,579 mg/kg/day, but not ≤2,500 mg/kg/day (Myers 1992a; NTP 1982). In C57Bl/6J/BALBcByJ hybrid mice, exposure to 1,100 mg/kg/day (only dose tested) for 26 weeks resulted in decreased testes weights and focal testicular atrophy (Toyosawa et al. 2001). Chronic exposure of B6C3F1 mice resulted in bilateral hypospermia, immature/abnormal sperm in the epididymides, and decreased testes weights at

doses ≥292 mg/kg/day and seminiferous tubule degeneration at 1,325 mg/kg/day (David et al. 2000b; Kluwe et al. 1982a; NTP 1982).

There is some evidence for altered male reproductive hormones in adult rats exposed to high levels of DEHP. While no changes in serum testosterone or LH were observed in adult Long-Evans rats following exposure to doses up to 750 mg/kg/day for 14 days, exposure for 21–35 days resulted in decreased serum testosterone and increased serum LH at doses ≥10 mg/kg/day (Li et al. 2012a). No changes in serum testosterone or LH levels were observed in adult Long-Evans rats at doses up to 200 mg/kg/day for 28 days (Akingbemi et al. 2001).

To evaluate the antiandrogenic potential of DEHP, Lee and Koo (2007) and Stroheker et al. (2005) conducted Hershberger Assays in Sprague-Dawley and Wistar rats, respectively. In these studies, male rats were castrated and subsequently supplemented with testosterone so control and exposed animals had equivalent testosterone levels. Following DEHP exposure for 10 days, Lee and Koo (2007) observed significantly decreased ventral prostate weights at ≥20 mg/kg/day (lowest dose tested), decreased seminal vesicle weights and increased serum LH at ≥100 mg/kg/day, and decreased levator ani/bulbocavernosus (LABC) muscle weights at 500 mg/kg/day. Similarly, Stroheker et al. (2005) observed significantly decreased LABC muscle weights at ≥100 mg/kg/day, decreased prostate weights at ≥200 mg/kg/day, and decreased seminal vesicles weights at ≥400 mg/kg/day; no exposure-related findings were observed at ≤20 mg/kg/day. As expected, no exposure-related changes in serum testosterone were observed in either study. Reproductive organ histology was not assessed. These studies indicate that DEHP exhibits some antiandrogenic activity.

Observed alterations in hormone levels may be due to Leydig cell toxicity. In Long-Evans rats, exposure to DEHP at doses ≥10 mg/kg/day for 7–11 days resulted in an increase in the number of Leydig cells in the testes (Guo et al. 2013). When mature Leydig cells were eliminated using ethane dimethane sulfonate (EDS), a significant increase in the number and proliferation of Leydig cell precursors was observed following exposure to ≥10 mg/kg/day for 11–35 days (Guo et al. 2013; Li et al. 2012a). However, no changes were observed in Leydig cell testosterone production *in vivo* in cells harvested from adult Long-Evans rats exposed to doses up to 200 mg/kg/day for 28 days (Akingbemi et al. 2001).

Other Mammalian Species—Male Reproductive Effects. In ferrets, absence of germinal epithelium in the seminiferous tubules was observed in 3/7 animals exposed to 1,200 mg/kg/day for 14 months (only

dose tested) (Lake et al. 1976). Relative testes weights were also elevated at this dose, but this effect appeared to be secondary to exposure-related weight loss.

Mechanisms of Male Reproductive Toxicity. As discussed above, several studies suggest associations between diminished semen quality and DEHP metabolite levels in urine. Additionally, Zhang et al. (2006) reported an association between increased DEHP metabolite levels in semen and altered semen parameters (decreased semen volume, increased rate of sperm malformation). Some studies have indicated that oxidative stress may potentially be a mechanism of toxicity for observed alterations in male semen quality. In a study in PVC workers, increased urinary DEHP metabolite levels were associated with both decreased sperm quality and sperm ROS generation (Huang et al. 2014b). Other studies reported associations between urinary DEHP metabolite levels and urinary markers of oxidative stress (e.g., 8-hydroxy-2'-deoxyguanosine [8-OHdG], isoprostane, carnitines) in couples planning to become pregnant (Guo et al. 2014), couples seeking fertility treatment (Wu et al. 2017), and men from a fertility cohort (Zhang et al. 2016); however, these studies do not have concurrent evaluations of male reproductive parameters. Direct damage to sperm DNA may also underlie observed male reproductive effects, as increased urinary levels of DEHP metabolites were associated with DNA damage in men from a fertility cohort (Hauser et al. 2007).

Decreased testosterone production was observed in adult human testes explants cultured with DEHP or MEHP (Desdoits-Lethimonier et al. 2012). No effects were observed on INSL3 production by Leydig cells, inhibin B production by Sertoli cells, or germ cell apoptosis, suggesting that effects were limited to steroidogenesis. DEHP can alter sterologenesis in the liver of rodents, which may have an impact on steroid-dependent functions. For example, feeding male rats DEHP at an estimated dose of 500 mg/kg/day for 7–18 days significantly inhibited sterologenesis from ^{14}C-mevalonate in liver and adrenal minces (Bell 1976, 1980). Other mechanisms may include apoptosis, as germ cell apoptosis was observed following gavage administration of MEHP to prepubertal rats and mice (Lagos-Cabre and Moreno 2012). Germ cell apoptosis appears to be mediated by upregulation of FasL (an apoptosis-related protein in Sertoli cells) (Lagos-Cabre and Moreno 2012).

Mechanisms of male reproductive toxicity occurring after gestational or early postnatal exposure to DEHP are in Section 2.17 (Developmental; Mechanisms of Altered Male Reproductive Development).

Epidemiology Studies —Female Reproductive Effects. Few epidemiological studies evaluating the effects of exposure to DEHP on the female reproductive system met inclusion criteria (Appendix B).

Many of the available studies (Barrett et al. 2014; Buck Lewis et al. 2013; Grindler et al. 2015; Huang et al. 2010, 2014b; Itoh et al. 2009; Kim et al. 2015; Pollack et al. 2015; Sun et al. 2015, 2016; Upson et al. 2013; Weuve et al. 2010; Velez et al. 2015) measured exposure using urine samples collected after the outcome of interest (e.g., pregnancy, endometriosis, fibroids, early menopause, etc.) had occurred, limiting their utility for assessing the potential cause and effect relationship. Others were excluded because exposure was assessed using biomarkers other than urinary metabolites (Caserta et al. 2013; Cobellis et al. 2003; Du et al. 2016; Kim et al. 2011; La Rocca et al. 2014; Reddy et al. 2006; Romani et al. 2014; Specht et al. 2015).

Three prospective cohort studies of couples discontinuing birth control to become pregnant did not observe associations between DEHP exposure and prolonged time to pregnancy (Buck Louis et al. 2014; Jukic et al. 2016; Thomsen et al. 2017; Table 2-11). One of these studies (Jukic et al. 2016) evaluated the menstrual cycle, observing that DEHP metabolites were not associated with altered follicular phase length. A cohort study of women (n=215) seeking evaluation for fertility problems observed decreases in ovarian antral follicle counts (AFCs) associated with higher DEHP metabolite concentrations in urine samples collected before AFCs were determined (Messerlian et al. 2016a). Multiple urine samples were collected for some of the women in this study, improving exposure estimates; however, the small population size and lack of evidence for decreased fertility in prospective cohort studies make the findings inconclusive.

Four cross-sectional studies evaluating whether DEHP exposure alters reproductive hormones in women are limited and reported inconsistent findings (Table 2-11). A cross-sectional study in 591 pregnant women reported increased serum estrone and estradiol with increased MEHP and MEOHP urinary levels; no associations were observed with the sum of DEHP metabolites(Sathyanarayana et al. 2017). Two additional cross-sectional studies (n≤180) did not report an association between serum estradiol and urinary DEHP metabolites in pregnant women (Johns et al. 2015; Sathyanarayana et al. 2014). In addition, Johns et al. (2015) observed no association with serum sex hormone binding globulin (SBHG) or progesterone. Reduced free testosterone in pregnant women was associated with higher urinary MECPP levels, but not levels of other DEHP metabolites, and no associations were observed between DEHP metabolites and total testosterone (Sathyanarayana et al. 2017). Sathyanarayana et al. (2014) observed associations between reduced total and free serum testosterone and higher urinary metabolite concentrations in women delivering female infants, but no association in women delivering male infants. In a cross-sectional study of women between 20 and 80 years of age who participated in the 2011–2012

Table 2-11. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Thomsen et al. 2017, Cohort (Denmark)	229 women (ages 20–35 years) recruited between 1992 and 1995, for the Danish First Pregnancy Planner study. First morning urine samples collected from day 1 to 10 in each cycle until pregnancy achieved or 6 months passed. Urinary phthalate levels were measured in the first urine sample (day 1–10 of first cycle) and a second urine sample (the last taken prior to pregnancy or in the sixth cycle for women who did not become pregnant). Time of pregnancy was diagnosed by general practitioner.	Discrete-time Cox regression model adjusted for age, BMI, alcohol, and smoking	Fecundability odds ratio per ln unit increase in ln-transformed urinary metabolite concentration, conditional on not achieving pregnancy in previous cycle		
			MEHP	14.5 (0–348) (median [min–max])	0.99 (0.72, 1.35)
			MEHHP	NR	0.70 (0.48, 1.03)
			MEOHP	NR	0.83 (0.58, 1.18)
Buck Louis et al. 2014, Cohort (United States [Michigan, Texas])	454 women (ages 18–44) recruited when discontinuing contraception to become pregnant; recruited using population-based sampling from 16 counties in Michigan and Texas between 2005 and 2009 (members of Longitudinal Investigation of Fertility and the Environment cohort). Women completed daily journal regarding intercourse, menstruation, and home pregnancy tests; home fertility monitors that track rise in estrone-3-glucuronide and LH used to time intercourse. Single urine sample collected at baseline. Time to pregnancy determined by journals and fertility monitoring results.	Cox models for discrete survival time, adjusted for both partners' urinary metabolite and creatinine concentrations, age, BMI, serum cotinine, and research site	Fecundability odds ratio per SD increase in log-transformed and scaled (by SD) urinary metabolite concentration, conditional on not achieving pregnancy in previous cycle		
			MEHP	Pregnant: 4.56 (3.40–6.11) Not pregnant: 5.60 (3.81–8.24)	0.99 (0.87, 1.12)
			MEHHP	Pregnant: 15.24 (13.01–17.86) Not pregnant: 14.46 (11.52–18.14)	1.06 (0.91, 1.24)
			MEOHP	Pregnant: 8.65 (7.40–10.10) Not pregnant: 7.55 (5.86–9.74)	1.08 (0.92, 1.27)
			MECPP	Pregnant: 21.18 (18.25–24.58) Not pregnant: 21.21 (16.94–26.55)	1.06 (0.91, 1.24)

Table 2-11. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Jukic et al. 2016, Cohort (United States [North Carolina])	221 healthy women recruited when discontinuing contraception to become pregnant, between 1982 and 1986, from communities in North Carolina (members of North Carolina Early Pregnancy Study). First morning urine samples collected daily until pregnancy achieved or 6 months passed; three stored samples per cycle were pooled for phthalate metabolite analysis. Time to pregnancy measured as numbers of ovulatory cycles (identified by urinary analysis for estrone 3-glucuronide and pregnanediol 3-glucuronide) between enrollment and conception.	Discrete-time, time-to-event model adjusted for age, age at menarche, current smoking, alcohol intake, BMI, caffeine consumption, and education	Fecundability ratio comparing highest and lowest tertiles of urinary metabolite concentrations		
			ΣDEHP	NR	FRs for DEHP metabolites were ≥1, indicating no association or improved fecundability; none of the FRs were statistically significant (p>0.05) and there was no significant trend across tertiles of any metabolite (data shown graphically)
			MEHP	3.8–11.2	
			MEHHP	31.8– 80.8	
			MEOHP	19.5–48.9	
			MECPP	42.2–100.0	
			DEHP metabolites were not associated with follicular phase length; higher MECPP levels were associated with longer luteal phase length (increase of ~0.5 days; p=0.02).		
Messerlian et al. 2016a; Hauser et al. 2015, Cohort (United States [Massachu-setts])	215 women ages 18–46 years seeking infertility investigation; members of Environmental and Reproductive Health cohort, recruited between November 2004 and April 2012; excluding women with oophorectomies, unreadable ovary scans, and polycystic ovaries. Urine samples collected at study entry, twice during next treatment cycle, and at time of unstimulated AFC determination. All samples taken before AFC determination were pooled and geometric means of metabolite concentrations used in analysis.	Generalized linear models, adjusted for maternal age, BMI, and smoking status	Percent change in AFC comparing highest and lowest quartiles of urinary metabolite concentration		
			ΣDEHP	0.10–0.46 µmol/L	-14% (-23, -5)*
			MEHP	1.6–6.7	-13% (-22, -3)*
			MEHHP	8.2–41.1	-7% (-16, 4)
			MEOHP	5.1–25.0	-16% (-24, -6)*
			MECPP	13.5–59.1	-17% (-25, -7)*
			p for trend across quartiles >0.05 for all metabolites (p=0.06 for MEOHP).		
			Hauser et al. (2015) observed statistically significant reductions in total and mature oocyte counts with higher urinary concentrations of DEHP metabolites in this cohort (n=256).		

Table 2-11. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Sathyanarayana et al. 2017 Cross-Sectional (United States [California, Minnesota, New York, Washington])	591 pregnant women recruited from clinics in California, Minnesota, New York, and Washington between 2010 and 2012; members of Study for Future Families cohort. Urine and blood sample collected same day (59.5% at ≤12 weeks of gestation, 39.9% at >12–20 weeks of gestation, 0.5% at >20 weeks of gestation).	Linear regression, adjusted for study center, maternal age, maternal race/ethnicity, gestational age at serum draw, first-trimester BMI, and infant sex	Percent change in maternal hormone concentration per (unspecified) change in log-transformed SG-adjusted urinary metabolite concentration		
			ΣDEHP	15.73–39.70	Estrone 14.10 (-4.32, 36.08) Estradiol 11.02 (-4.02, 28.38) Total testosterone -5.57 (-15.08, 5.03) Free testosterone -9.18 (-18.57, -1.30)
			MEHP	1.38–4.35	Estrone 28.23 (9.85, 49.69)* Estradiol 24.97 (10.00, 41.97)* Total testosterone 0.00 (-9.01, 9.90) Free testosterone -3.46 (-12.38, 6.37)
			MEHHP	4.35–12.66	Estrone 12.62 (-3.88, 31.95) Estradiol 10.28 (-3.22, 25.69) Total testosterone -3.57 (-12.36, 6.10) Free testosterone -5.07 (-13.96, 4.74)
			MEOHP	3.22–8.46	Estrone 19.34 (1.39, 40.51)* Estradiol 14.71 (0.25, 31.22)* Total testosterone

Table 2-11. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
					-4.79 (-13.72, 5.10) Free testosterone -6.59 (-15.61, 3.37)
			MECPP	5.89–15.71	Estrone 4.95 (-11.71, 24.74) Estradiol 3.18 (-10.55, 18.99) Total testosterone -7.87 (-16.98, 2.21) Free testosterone -12.30 (-21.17, -2.43)*
Johns et al. 2015, Cross-sectional (Puerto Rico)	106 pregnant women aged 18–40 years, members of Puerto Rico Test Site for Exploring Contamination Threats birth cohort, recruited at 14 weeks of gestation from prenatal clinics and hospitals. Urine and serum samples collected at 1st and 3rd prenatal visits (16–20 and 24–28 weeks of gestation).	Linear mixed models adjusted for age at enrollment, prepregnancy BMI, and urinary specific gravity	Percent change in serum estradiol, sex hormone binding globulin, and progesterone with IQR increase in urinary metabolite concentration (longitudinal analysis)		
			ΣDEHP	NR	Estradiol -0.56 (-9.17, 8.06) SBHG -4.11 (-9.83, 1.62) Ln-Progesterone 1.79 (-5.17, 9.39)
			MEHP	Visit 1: 1.61–6.36; Visit 3: 1.69–6.73 (SG-adj)	NR
			MEHHP	Visit 1: 6.14–19.9; Visit 3: 7.28–16.9	NR
			MEOHP	Visit 1: 5.57–16.5; Visit 3: 6.22–14.8	NR
			MECPP	Visit 1: 12.7–31.4; Visit 3: 13.4–29.3	NR
			Cross-sectional analyses by visit did not yield any statistically significant association or consistent pattern of change.		

Table 2-11. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)			Effect estimate (95% CI)[a]
Meeker and Ferguson 2014, Cross-sectional (United States)	697 women including 262 ages 20–40, 230 ages 40–60, and 205 ages 60–80; participants in NHANES 2011–2012. Urine and blood samples collected same day.	Linear regression adjusted for urinary Cr, age, poverty-income ratio, BMI, race/ethnicity, and session of sample collections	Percent change in serum total testosterone (ng/dL) with IQR increase in urinary metabolite concentration			
			ΣDEHP	Ages 20–<40	NR	-1.27 (-11.5, 10.1)
				Ages 40–<60		-20.1 (-30.9, -7.72)
				Ages 60–80		-2.24 (-21.0, 20.9)
			MEHP	Ages 20–<40	1.07, 3.57	2.54 (-10.9, 18.0)
				Ages 40–<60	0.90, 2.90	-13.4 (-27.0, 2.71)
				Ages 60–80	0.70, 1.94 (Cr-adj)	2.07 (-23.9, 36.9)
			MEHHP	Ages 20–<40	5.44, 14.6	-1.55 (-11.7, 9.77)
				Ages 40–<60	5.82, 15.4	-17.8 (-28.3, -5.72)
				Ages 60–80	5.27, 13.7	-2.46 (-19.6, 18.4)
			MEOHP	Ages 20–<40	3.62, 10.0	-0.19 (-10.5, 11.3)
				Ages 40–<60	3.73, 10.0	-21.8 (-31.6, -10.7)
				Ages 60–80	3.41, 8.38	-1.67 (-19.5, 20.2)
			MECPP	Ages 20–<40	9.06, 21.7	-2.69 (-11.8, 7.31)
				Ages 40–<60	10.4, 23.9	-18.7 (-29.2, -6.64)
				Ages 60–80	9.98, 23.9	0.63 (-14.9, 19.0)

Table 2-11. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Sathyanarayana et al. 2014, Cross-sectional (United States [California, Minnesota, Missouri])	180 pregnant women recruited from prenatal clinics in California, Minnesota, and Missouri between September 1999 and August 2002; members of Study for Future Families cohort. Urine and blood sample collected same day (60% after 30th week of gestation).	Linear regression adjusted for maternal age, gestational age at blood draw, urinary creatinine, study center, parity, and education	Association between serum hormone level and log-transformed urinary metabolite concentration in women with male fetuses (n=94)		
			ΣDEHP (MEHP, MEHHP, MEOHP)	5.53–21.05 µmol/L (all women)	Total testosterone -0.07 (-0.20, 0.06) Free testosterone -0.04 (-0.18, 0.10) Estradiol -0.06 (-0.17, 0.04)
			Association between log-transformed serum hormone level and log-transformed urinary metabolite concentration in women with female fetuses (n=86)		
			ΣDEHP (MEHP, MEHHP, MEOHP)	5.53–21.05 µmol/L (all women)	Total testosterone -0.15 (-0.26, -0.04)* Free testosterone -0.15 (-0.27, -0.03)* Estradiol -0.08 (-0.18, 0.01)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; AFC = antral follicle count; BMI = body mass index; CI = confidence interval; Cr = creatinine; Cr-adj = creatinine-adjusted; DEHP = di(2-ethylhexyl)phthalate; FR = fecundability ratio; IQR = interquartile range; LH = luteinizing hormone; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl) phthalate; min = minimum; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; SD = standard deviation; SG-adj = specific gravity adjusted

NHANES survey, while urinary metabolite levels were generally associated with lower serum total testosterone, no association was seen for any DEHP metabolite or age group (Meeker and Ferguson 2014).

Epidemiology Studies—Pregnancy Outcomes. Preterm birth as a categorical measure (<37 weeks of gestation) was evaluated in four epidemiological studies summarized in Table 2-12. Studies reporting associations between the odds of preterm birth and urinary DEHP metabolites include a nested case-control study (n=130 cases and 352 controls) by Ferguson et al. (2014a, 2014b) and a case-control study (n=30 cases and 30 controls) by Meeker et al. (2009b). Two cohort studies (Adibi et al. 2009; Shoaff et al. 2016; n=238 and 368, respectively) observed no association between exposure and preterm birth. In studies of gestational age as a continuous variable (Table 2-12), no clear relationship with urinary DEHP metabolite levels was seen. Of the six studies that evaluated gestational age, two (Adibi et al. 2009; Wolff et al. 2008) reported increased gestational age associated with increased urinary DEHP metabolite levels, and one (Whyatt et al. 2009) reported an association between decreasing gestational age and increasing metabolite levels. Inconsistencies among the studies may result from the varying times of urine sample collection, validity of outcome assessment, or selection or omission of important covariates. Importantly, the timing of urine sample collection may have a significant impact on a study's ability to detect an association. A systematic review of 15 studies recommends collection of samples in each trimester, standardization of sample collection to a specific time of day, and correction for specific gravity (not creatinine) to reduce intra- and within-individual variability (Yaghjyan et al. 2016).

Only one study (Ferguson et al. 2014a) distinguished spontaneous preterm birth (spontaneous labor or membrane rupture) from other causes of preterm birth (i.e., intrauterine growth retardation [IUGR], preeclampsia, or other maternal complications). Ferguson et al. (2014a; Table 2-12) observed an association between spontaneous preterm birth and the sum of DEHP metabolites in urine; this association exhibited an exposure-related trend across quartiles of exposure (geometric mean across three visits), and also held true for three of the four individual metabolites measured (MEHP, MEOHP, and MECPP). Ferguson et al. (2014a) proposed that increased risk of preterm birth may be associated with pro-inflammatory activities of DEHP based on positive associations between DEHP exposure and systemic markers of inflammation and oxidative stress (Ferguson et al. 2012). In support of this proposed mechanism, follow-up studies in this birth cohort showed a positive association between maternal urinary levels of DEHP metabolites and urinary levels of the oxidative stress marker, 8-isoprostane (Ferguson et al. 2015). Additionally, the association between urinary DEHP metabolites

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Preterm birth and gestational age					
Casas et al. 2016, Cohort (Spain)	Population-based birth cohort (INMA study) of 657 pregnant women recruited 2004–2006 during first prenatal visit.	Linear regression (considering these covariates: maternal education, smoking during pregnancy, parity, birth season, and urinary cotinine levels during pregnancy)	Estimated difference in gestational age (weeks) per doubling of log2-transformed exposure levels		
			ΣDEHP	26.5–1,670 µg/g Cr (min–max)	β -0.13 (-1.72, 1.46)
			MEHP	1.8–266.9 µg/g Cr	NA
			MEHHP	5.3–503.4 µg/g Cr	NA
			MEOHP	4.1–378.3 µg/g Cr	NA
			MECPP	7.7–718.9 µg/g Cr	NA
Ferguson et al. 2014a, Case-control (United States [Massachu-setts])	130 preterm births (<37 weeks) and 352 random controls selected from a prospective cohort of pregnant women recruited (2006-2008) early in pregnancy at Brigham and Women's Hospital in Boston.	Logistic regression (adjusting for specific gravity, maternal age at first visit, race/ethnicity, and education)	Risk of preterm birth per ln-unit increase in urinary phthalate metabolite level		
			ΣDEHP	20.2–63.2 µmol/mL (IQR; SG-adj)	OR 1.33 (1.04, 1.70)*
			MEHP	5.51–18.1 (SG-adj)	OR 1.34 (1.07, 1.68)*
			MEHHP	17.2–55.3	OR 1.03 (0.82, 1.30)
			MEOHP	9.33–29.7	OR 1.16 (0.91, 1.47)
			MECPP	20.6–73.8	OR 1.40 (1.13, 1.74)*
	Gestational age determined by ultrasound and LMP recall. Spot urine samples collected during weeks 10, 18, and 26 of gestation.		Risk of spontaneous preterm birth per ln-unit increase in SG-adj urinary phthalate metabolite level		
			ΣDEHP	20.2–63.2 µmol/mL (IQR; SG-adj)	OR 1.63 (1.15, 2.31)*
			MEHP	5.51–18.1 (SG-adj)	OR 1.65 (1.20, 2.26)*
			MEHHP	17.2–55.3	OR 1.27 (0.91, 1.78)
			MEOHP	9.33–29.7	OR 1.47 (1.04, 2.08)*
			MECPP	20.6–73.8	OR 1.56 (1.15, 2.13)*

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Su et al. 2014, Cohort (Taiwan)	130 mother-infant pairs recruited and followed from November 2001–August 2009; TMICS.	Simple linear and binary logistic regression	Association between gestational age (weeks) and maternal urinary phthalate metabolite levels		
			ΣDEHP	42.28–60.83 µg/g Cr (95% CI)	β 0.001 (NR)
			MEHP	14.56–20.19 µg/g Cr	β 0.004 (NR)
			MEHHP	5.49–10.53 µg/g Cr	β 0.005 (NR)
			MEOHP	10.05–17.58 µg/g Cr	β 0.003 (NR)
			MECPP	NA	NA
Adibi et al. 2009, Cohort (United States [California, Iowa, Minnesota, Mississippi])	283 pregnant women in four states (Study for Future Families cohort; mean maternal age 30.2 years), recruited at the beginning of the 3rd trimester from prenatal clinics from March 2000 to August 2004.	Linear and logistic regression (considering these covariates: creatinine, high blood pressure, and nongestational diabetes)	Change in log odds preterm birth per log-unit increase in urinary phthalate metabolite concentration		
			ΣDEHP	NA	NA
			MEHP	1.1–8.2	OR 0.5 (0.3, 0.9)*
			MEHHP	5.6–25.5	OR 0.5 (0.3, 0.9)*
			MEOHP	5.1–24.6	OR 0.4 (0.2, 0.9)*
			MECPP	NA	NA
	Gestational age determined by LMP recall and clinical estimate. Spot urine sample collected during 3rd trimester.	Linear and logistic regression (considering these covariates: creatinine, geographic center, mother's educational level, job-related stress, nongestational diabetes, thyroid disorders, fibroids, and parity)	Change in gestational age (weeks) at delivery per log-unit increase in urinary phthalate metabolite concentration		
			ΣDEHP	NA	NA
			MEHP	1.1–8.2	β 0.16 (0.02, 0.3)*
			MEHHP	5.6–25.5	β 0.16 (0.01, 0.31)*
			MEOHP	5.1–24.6	β 0.19 (0.03, 0.35)*
			MECPP	NA	NA

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Meeker et al. 2009b, Case-control (Mexico)	30 preterm births and 30 controls selected from a large Mexican birth cohort study; pregnant women were recruited during prenatal visits at one of four clinics of the Mexican Institute of Social Security in Mexico City between 2001 and 2003. Gestational age calculated from LMP recall. Spot urine sample collected during 3rd trimester.	Multivariate logistic regression (considering these covariates: marital status, maternal education, infant sex, and gestational age at time of urine sample)	Odds of having Cr-adjusted urinary phthalate metabolite concentrations above the median in cases, compared with controls		
			ΣDEHP	Controls: 0.16–0.55 µg/g Cr (IQR); Cases: 0.28–0.45 µg/g Cr	OR 4.1 (1, 17.5)*
			MEHP	Controls: 1.7–7.4 µg/g Cr; Cases: 3.3–7.4 µg/g Cr	OR 3.2 (0.9, 11.3)
			MEHHP	Controls: 11.4–52.1 µg/g Cr; Cases: 24.1–41.5 µg/g Cr	OR 2.9 (0.8, 10.8)
			MEOHP	Controls: 9.5–42.1 µg/g Cr; Cases: 20.6–29.2 µg/g Cr	OR 3.2 (0.9, 11)
			MECPP	Controls: 27.3–98.6 µg/g Cr; Cases: 52.7–77.4 µg/g Cr	OR 2.9 (0.8, 11)
Wolff et al. 2008, Cohort (United States [New York])	404 mother-infant pairs enrolled prior to delivery at Mount Sinai Medical Center between March 1998 and March 2002 (Children's Environmental Health Study); mean±SD age: 24±6.2 years.	Multivariable linear regression (considering these covariates: Race, infant sex, ln-creatinine, smoking during pregnancy, maternal education, marital status, prepregnancy BMI, and restricted to observations with creatinine ≥20 mg/dL)	Association between gestational age (weeks) and ln-transformed maternal urinary phthalate metabolite concentration		
			ΣDEHP	0.13–0.5 µmol/L (IQR)	β 0.1 (-0.05, 0.24)
			MEHP	2.9–14	β 0.15 (0.02, 0.29)*
			MEHHP	9.5–39	β 0.06 (-0.07, 0.2)
			MEOHP	8.3–36	β 0.05 (-0.09, 0.2)
			MECPP	16–70	β 0.07 (-0.08, 0.21)

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Spontaneous abortion/pregnancy loss					
Jukic et al. 2016, Cohort (United States [North Carolina])	221 healthy women (median age 26 years, 96% white, 7% smokers) without fertility problems, recruited prior to conception between 1982 and 1986. Early pregnancy loss determined by decrease in urinary hCG level. Urine samples collected daily until clinical pregnancy demonstrated or 6 months after discontinuation of contraception. Samples analyzed 20 years later.	Unconditional logistic regression, considering these covariates: age, current smoking, alcohol intake, BMI, caffeine consumption, education, and season of conception	Adjusted odds of early pregnancy loss comparing highest tertile of exposure to lowest tertile		
			ΣDEHP		Significantly ($p<0.05$) decreased odds of spontaneous abortion with higher MEOHP and sum DEHP metabolite levels (data shown graphically).
			MEHP	3.8–11.2	
			MEHHP	31.8–80.8	
			MEOHP	19.5–48.9	
			MECPP	42.2–100.0	
Messerlian et al. 2016b Cohort (United States [Massachu-setts])	256 women with 303 conceived pregnancies (average age 34.9 years), recruited from women undergoing medically-assisted reproduction between 2004 and 2012 (Environment and Reproductive Health Study cohort).	Log-binomial regression models, adjusted for age, BMI, smoking status, and infertility diagnosis	Relative risk for biochemical pregnancy loss comparing highest quartile of exposure (SG-adj) with lowest quartile (p for trend)		
			ΣDEHP	0.10–0.40 µmol/L (IQR)	3.4 (0.97, 1.17) (p for trend = 0.04)
			MEHP	1.5–6.4	2.8 (0.99, 8.1) (p for trend = 0.03)
			MEHHP	7.8–35.4	3.1 (0.91, 10.5) (p for trend = 0.03)
			MEOHP	5.5–24.4	5.2 (1.2, 21.9)* (p for trend = 0.006)

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
	Biochemical pregnancy loss defined as urinary hCG-confirmed pregnancy never visualized on ultrasound. Total pregnancy loss defined as any pregnancy loss <20 weeks of gestation (including biochemical pregnancy loss). Urine samples collected at study entry and up to 2 times per fertility treatment cycle.		MECPP	14.3–57.2	2.4 (0.78, 7.6) (p for trend = 0.07)
			Relative risk for total pregnancy loss (<20 weeks of gestation) between quartiles of SG-adjusted ln-transformed urinary metabolite		
			ΣDEHP	0.10–0.40 µmol/L (IQR)	1.6 (0.96, 2.7) (p for trend =0.06)
			MEHP	1.5–6.4	1.6 (0.99, 2.7) (p for trend = 0.06)
			MEHHP	7.8–35.4	1.7 (1.0, 2.9)* (p for trend = 0.07)
			MEOHP	5.5–24.4	2.0 (1.1, 3.5)* (p for trend = 0.03)
			MECPP	14.3–57.2	1.4 (0.85, 2.4) (p for trend = 0.09)
Mu et al. 2015, Case-control (China)	132 cases of spontaneous abortion and 172 controls, aged 20–45 years, recruited prior to 20 weeks of gestation at time of ultrasound. Clinical pregnancy loss determined by transvaginal ultrasound. Urine sample collected on the 4th day after ultrasound examination.	Logistic regression, adjusted for age, week of gestation, BMI, household income, smoking status, alcohol consumption, and occupation	Adjusted OR for clinical pregnancy loss comparing highest quartile of exposure with lowest quartile		
			ΣDEHP	NA	NA
			MEHP	Cases: 1.53–103 µg/g Cr (5th–95th percentiles) Controls: 1.27–20.8 µg/g Cr	OR 1.30 (0.66–2.55)

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Toft et al. 2012, Cohort (Denmark)	128 pregnant women with at least one urine sample, from prospective cohort of 430 couples aged 20–35 years recruited from trade unions in Denmark. Early pregnancy loss determined by decrease in urinary hCG level. Urine sample collected day 10 after last menstrual period.	Logistic regression, adjusted for age, BMI, smoking, alcohol consumption, caffeine consumption, and exposure to the specific compound analyzed in the preconception cycle	Adjusted OR (95% CI) for early pregnancy loss comparing highest tertile of exposure to lowest tertile.		
			MEHP	<LOD–84 (pregnancy loss) (min–max) <LOD–64 (liveborn child)	OR 40.67 (4.48, 369.50)*
			MEHHP	9.5–207.1 (pregnancy loss) 3.6–215.3 (liveborn child)	OR 2.12 (0.67, 6.67)
			MEOHP	5.7–245.9 (pregnancy loss) 2.7–222.2 (liveborn child)	OR 2.73 (0.78, 9.54)
			Adjusted OR (95% CI) for clinical pregnancy loss comparing highest tertile of exposure to lowest tertile.		
			MEHP	<LOD–84 µg/L (pregnancy loss) (min–max) <LOD–64 µg/L (liveborn child)	OR 0.25 (0.05, 1.28)
			MEHHP	9.5–207.1 µg/L (pregnancy loss) 3.6–215.3 µg/L (liveborn child)	OR 0.90 (0.23, 3.61)
			MEOHP	5.7–245.9 µg/L (pregnancy loss) 2.7–222.2 µg/L (liveborn child)	OR 0.55 (0.13, 2.35)

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Cantonwine et al. 2016, Case-control (United States [Massachu-setts])	Nested case-control study (n=50 cases of preeclampsia and 431 pregnancies without preeclampsia) within prospective birth cohort at hospital in Boston. Preeclampsia defined by blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) and positive urinary protein testing. Maternal urine samples collected at 9.7, 17.9, 26.0, and 35.1 weeks of pregnancy.	Cox proportional hazard (considering these covariates: specific gravity, maternal age, race, BMI, smoking during pregnancy, and infant sex)	Adjusted hazard ratio (95% CI) associated with IQR increase in concentration (average of three visits)		
			ΣDEHP	0.33–0.46 nmol/L (GMs on four visits)	HR = 1.79 (1.3, 2.46)*
			MEHP	9.8–12.7	HR = 1.4 (1.03, 1.89)*
			MEHHP	27.1–40.8	NR
			MEOHP	15.8–20.1	NR
			MECPP	38.5–41.8	NR

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; hCG = human chorionic gonadotropin; INMA = Infancia y Medio Ambiente; IQR = interquartile range; LMP = last menstrual period; LOD = limit of detection; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; NA = not applicable; NR = not reported; OR = odds ratio; SD = standard deviation; SG-adj = specific gravity adjusted; TMICS = Taiwan Maternal and Infant Cohort Study

and spontaneous preterm birth was mediated by maternal urinary levels of 8-isoprostane using complex regression models (Ferguson et al. 2017).

Pregnancy loss, or spontaneous abortion, was evaluated in three cohort studies and one case-control study that measured exposure using urinary metabolites of DEHP (Table 2-12). When evaluating early (or biochemical) pregnancy loss, one study observed decreased odds with increased urinary metabolite levels (Jukic et al. 2016), while two others reported increased risk of early pregnancy loss with an increase in urinary levels of one or more DEHP metabolites (Messerlian et al. 2016b; Toft et al. 2012). However, none of the three studies evaluating clinical pregnancy loss observed an association with exposure to DEHP (Messerlian et al. 2016b; Mu et al. 2015; Toft et al. 2012).

Cantonwine et al. (2016) observed increased hazard ratios for preeclampsia with interquartile range increases in maternal urinary levels of MEHP and the sum of DEHP metabolites. No other studies of this endpoint were identified in the available literature.

Nonhuman Primates—Female Reproductive Effects. Few female reproductive studies of DEHP have been conducted in nonhuman primates. A 13-week gavage study in marmosets of unspecified age showed no significant treatment-related effects on gross or microscopic appearance of the uterus, vagina, or ovary at doses up to 2,500 mg DEHP/kg/day (Kurata et al. 1998).

Rodent Studies—Female Reproductive Effects. Two-generation studies in Wistar rats reported decreased F1 fertility and increased postimplantation loss in F0 dams after exposure to doses ≥1,040 mg/kg/day, but not ≤380 mg/kg/day (Schilling et al. 1999, 2001). Evidence of decreased growing ovarian follicles and corpora lutea in F0 and F1 females exposed to 1,088 mg/kg/day suggest that alterations in the female reproductive system may contribute to decreased F1 fertility; however, these studies provide strong evidence for damage to the male reproductive system (discussed above). In a chronic exposure 2-generation study in Sherman rats, no changes in fertility or reproductive organ histology were observed; however, the highest dose evaluated was 200 mg/kg/day (Carpenter et al. 1953). In a 3-generation, continuous breeding study with cross-over mating, decreased fertility in the F1 and F2 generation was attributed to effects in males, with no clear evidence of decreased female fertility in the cross-over mating trial at 659 mg/kg/day (Blystone et al. 2010; NTP 2005). Additionally, no changes were observed in female reproductive organ weights or histology.

In CD-1 mice, decreased fertility in a continuous breeding study at doses ≥130 mg/kg/day was attributed to both males and females in a cross-over trial, as fertility issues were observed when females exposed at 390 mg/kg/day were mated to unexposed males or vice versa (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984). In the main mating trial, decreased fertility, decreased numbers of litters/pair, decreased numbers of pups/litter, and decreased numbers of live-born pups were observed at 130 mg/kg/day, with no litters produced at 390 mg/kg/day. The combined weight of the ovaries, oviducts, and uteri of exposed females from the crossover trial was significantly decreased compared with controls. In a shorter-duration study, a complete absence of corpora lutea was observed in female B6C3F1 mice exposed to dietary doses of approximately 7,899 mg/kg/day DEHP; ovarian histology was not evaluated at lower doses in the study (Myers 1992a). Altered estrous cycles (increased percentage of days spent in estrus) were also observed in CD-1 mice exposed to 200 mg/kg/day for 30 days, but not at doses ≤20 mg/kg/day (Hannon et al. 2014). No dose-related changes were observed in the number of follicles in ovaries or uterine weight. Gene expression analysis showed significant alterations in genes within the PI3K pathway, which regulates early folliculogenesis, including decreased Pten at ≥20 mg/kg/day and decreased Tsc1 at 200 mg/kg/day (Hannon et al. 2014).

Increased resorptions and post-implantation losses, and decreased uterine weights, were observed in Wistar rat dams exposed to 1,000 mg/kg/day from GD 6 to 15, but not ≤200 mg/kg/day (Hellwig et al. 1997). Vaginal hemorrhage was observed in two of nine dams exposed to 1,000 mg/kg/day. Increased postimplantation losses and decreased litter sizes were also observed in Wistar rat dams exposed to 500 mg/kg/day during gestation, but not ≤100 mg/kg/day (Dalsenter et al. 2006). In mice, gestational exposure resulted in decreased numbers of live pups/litter at doses ≥95 mg/kg/day, increased resorptions and late fetal deaths at ≥341 mg/kg/day, and complete litter losses at ≥500 mg/kg/day (Pocar et al. 2012; Price et al. 1988b; Schmidt et al. 2012; Shiota and Nishimura 1982; Shiota et al. 1980; Tyl et al. 1988). No changes in pregnancy outcomes were observed at ≤91 mg/kg/day. In 15 other studies, no changes in gestation length, litter sizes, or sex ratios were observed following gestational exposure to DEHP at doses up to 900 mg/kg/day in rats or 500 mg/kg/day in mice (Table 2-2).

Additional studies in rodents that did not evaluate reproductive performance show limited evidence of reproductive effects in non-pregnant female mice. A significant 25% decrease in serum estradiol levels was observed on GD 12.5 in dams exposed to 0.04 mg/kg/day via gavage from GD 0.5 to 19.5, compared with controls (Zhang et al. 2015); however, since no other dose levels were tested and no other reproductive endpoints were evaluated, the adversity of this finding is unclear. Therefore, reproductive effects from Zhang et al. (2015) were not included in the LSE table. In other intermediate-duration oral

studies, no changes in ovary weights or reproductive organ histology were observed in rats or mice at doses up to 3,000 or 2,500 mg/kg/day, respectively (Gray et al. 1977; Myers 1992b; NTP 1982; Toyosawa et al. 2001), although decreased uterine weights were observed in rats at 1,858 mg/kg/day (Myers 1992b). In chronic-duration studies, no changes in female reproductive organ histology were observed in rats at doses up to 939 mg/kg/day (David et al. 2000a; Kluwe et al. 1982a; NTP 1982). In mice, suppurative inflammation in the uterus/endometrium was observed following exposure to 1,821 mg/kg/day for 2 years, with no adverse histological effects at doses up to 1,458 mg/kg/day (David et al. 2000b; Kluwe et al. 1982b; NTP 1982). However, reduced uterus weights were also observed in female B6C3F1 mice exposed to 1,458 mg/kg/day for 2 years (David et al. 2000b).

In a study that evaluated the estrogenic activity of DEHP and other phthalate esters, DEHP did not affect the degree of vaginal epithelial cell cornification in mature ovariectomized rats following exposure to doses up to 2,000 mg/kg/day for 4 days (Zacharewski et al. 1998).

Mechanisms of Female Reproductive Toxicity. DEHP has been shown to affect various stages of mammalian folliculogenesis following *in vivo* and *in vitro* exposure, including altered development of the primordial germ cell, impaired primordial follicle assembly, impaired oocyte survival and meiosis, cell cycle arrest and apoptosis in ovarian granulosa cells, reduced oocyte nest breakdown, acceleration of primordial follicle activation, altered follicle steroidogenesis, increased follicle atresia, and impaired growth of antral follicles (Li et al. 2012b, 2016; Mu et al. 2015; Zhang et al. 2013b, 2014, 2015). Folliculogenesis effects appear to be mediated, in part, by DEHP or MEHP binding to PPARs and/or estrogen receptors (ERs). Although the exact mechanism is unknown, binding to these receptors appears to alter the ability of endogenous hormones to regulate normal ovarian development (Zhang et al. 2015). Lovekamp-Swan and Davis (2003) suggested that MEHP interacts with PPARs to decrease aromatase activity and estradiol production in the ovary, resulting in decreased ovulation and reduced fertility. In *in vitro* studies, co-exposure of DEHP with an ER antagonist (ICI 182,780) reversed DEHP-mediated impairments during primordial follicle assembly (Mu et al. 2015).

Other than studies evaluating potential mechanisms for altered ovarian folliculogenesis, data on mechanisms of female reproductive toxicity are extremely limited. One study suggests that DEHP impairs endometrial receptivity to embryo implantation, which could result in decreased fertility (Li et al. 2012c). In this study, decreased implantation was associated with elevated protein expression levels of ERα, progesterone receptor (PR), and E-cadherin in the mouse endometrium. The E-cadherin finding suggests that the MAPK and NF-κB signaling pathways may be influenced by DEHP exposure. DEHP

can also alter sterologenesis in the liver of rodents, which may have an impact on steroid-dependent functions. For example, feeding female rats DEHP at an estimated dose of 500 mg/kg/day for 13 days significantly inhibited sterologenesis from ^{14}C-mevalonate in liver and adrenal minces (Bell 1980).

Additional mechanisms of female reproductive toxicity occurring after gestational or early postnatal exposure to DEHP are in Section 2.17 (Developmental; Mechanisms of Altered Female Reproductive Development).

Summary. Human epidemiological studies suggest potential associations between DEHP exposure and decreased serum testosterone and diminished semen quality in adult men. Available studies on fertility effects in humans are limited, but do not indicate an association between DEHP exposure and infertility. Numerous studies in rodents have shown that the mature male reproductive systems, particularly the testes, are susceptible to DEHP toxicity, and that DEHP exposure leads to decreased male fertility in both rats and mice. Limited data indicate that nonhuman primates are not susceptible or less susceptible to male reproductive toxicity following exposure to DEHP. Alterations in female reproductive systems, including decreased fertility, have been reported in animals at higher doses than those associated with male reproductive effects. Taken together, available human and animal data indicate that the adult male reproductive system is a sensitive target of DEHP toxicity.

2.17 DEVELOPMENTAL

Overview. Many human and animal studies have evaluated whether DEHP may affect development. The most studied endpoints include birth size and growth, and development of the reproductive and neurological systems. The development of the hepatic and renal systems as well as metabolic function (glucose homeostasis) have also been evaluated. In addition, meta-analyses and systematic review regarding developmental reproductive effects in male humans and animals have been conducted by NAS. Studies discussed in this section include those with prenatal, early postnatal, and/or pre-pubescent exposure. For studies that exposed animals both prior to and through sexual maturation into adulthood (e.g., multigenerational studies), endpoints evaluated after sexual maturation are in the respective organ system section of this profile (e.g., reproductive), while endpoints evaluated prior to sexual maturation are below.

Epidemiology Studies—Birth Size and Growth. Measures of birth size evaluated in epidemiological studies of DEHP include birth length, birth weight, and head circumference (Table 2-13). Only two of the seven selected studies that examined infant length, weight, or head circumference observed an association with DEHP metabolites in maternal or newborn urine (Sathyanarayana et al. 2016a; Zhao et al. 2014). Zhao et al. (2014) observed exposure-related increases in the odds of IUGR across tertiles of maternal urinary DEHP metabolites in a case-control study in China (42 infants with IUGR and 84 controls matched on maternal age). A relationship between lower birth weight and higher urinary levels of MEHHP and MEOHP, especially among male infants, was also observed. In contrast, Sathyanarayana et al. (2016a) reported increased birth weight in female infants, but not male infants, with increasing DEHP metabolite levels in maternal urine. Other studies did not observe an association between DEHP exposure and measures of birth size (Casas et al. 2016; Kim et al. 2016a; Shoaff et al. 2016; Su et al. 2014; Wolff et al. 2008).

Epidemiological studies evaluating the effects of prenatal exposure to DEHP and growth or obesity parameters in children have not shown consistent results, as shown in Table 2-14. Generally, the associations between maternal metabolite levels and BMI, waist circumference, and percent fat mass were negative, with higher DEHP exposures associated with lower BMI, waist circumference, and percent fat mass (Agay-Shay et al. 2015; Buckley et al. 2016a, 2016b; Maresca et al. 2016; Valvi et al. 2015). In contrast to the other studies, Harley et al. (2017) reported increased odds (Table 2-14) of being overweight or obese at 12 years of age when DEHP metabolite levels were doubled in maternal urine; however, sensitivity analysis indicated that maternal BMI influenced these results. A positive association was also reported between waist circumference z-score and maternal urinary DEHP levels at 5 years of age, but not at 7–12 years (Harley et al. 2017). No associations were observed between BMI z-score at 5–12 years or percent body fat at 9–12 years and maternal urinary DEHP levels. Kim et al. (2016a) also reported increased odds of higher growth (increase in BMI z-score more than the 50^{th} percentile change between birth and 3 months of age) with higher levels of MEHHP and MEOHP in newborn urine. However, birth weight and length at 3 months of age were obtained by telephone interview with mothers rather than clinical examination and measurement by a physician, rendering the growth estimates uncertain.

Animal Studies—Fetotoxicity, Teratology, and Physical Growth and Development. A single inhalation study evaluated fetal skeletal and visceral effects in GD 20 offspring of female Wistar rats exposed to 0.6–21 ppm for 6 hours/day during the period of organogenesis (GDs 6–15) (Merkle et al. 1988).

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β [95% CI]) unless otherwise specified[a]
Casas et al. 2016, Cohort (Spain)	Population-based birth cohort (INMA study) of 657 pregnant women recruited 2004–2006 during first prenatal visit.	Linear regression adjusted for maternal education, smoking during pregnancy, parity, birth season, and urinary cotinine levels during pregnancy	Estimated difference per doubling of log2-transformed urinary metabolite concentrations		
			ΣDEHP	26.5–1,670 µg/g Cr (min–max)	Birth length: Difference 0.38 (-1.59, 2.35) Birth weight: Difference 15.56 (-28.75, 59.87) Head circumference: Difference 0.16 (-1.15, 1.47)
			MEHP	1.8–266.9 µg/g Cr	NR
			MEHHP	5.3–503.4 µg/g Cr	NR
			MEOHP	4.1–378.3 µg/g Cr	NR
			MECPP	7.7–718.9 µg/g Cr	NR
Kim et al. 2016a, Cohort (Korea)	128 infants (65 boys and 63 girls) from birth cohort (Children's Health and Environmental Chemicals in Korea cohort); pregnant women recruited from five hospitals in four cities just prior to delivery of singleton birth. Newborns' first urine samples collected within 2 days of birth; infants' weights and heights recorded at birth, and obtained through telephone interview with mothers at 3 months of age.	Linear regression adjusted for maternal age, maternal BMI, gestational period, caesarean section, delivery experience, and urinary Cr	Association between birth size metrics and log-transformed urinary metabolite concentrations in newborn urine in boys Birth length		
			ΣDEHP	NR	0.050 (0.017, 0.082)*
			MEHHP	3.21–11.87	0.048(0.015, 0.080)*
			MEOHP	1.51–6.50)	0.052 (0.019, 0.085)*
			Birth weight		
			ΣDEHP	NR	-0.001 (-0.050, 0.048)
			MEHHP	3.21–11.87	-0.003 (-0.052, 0.045)
			MEOHP	1.51–6.50	0.003 (-0.046, 0.052)
			Head circumference		
			ΣDEHP	NR	-0.001 (-0.050, 0.048)
			MEHHP	3.21–11.87	-0.0004 (-0.021, 0.020)
			MEOHP	1.51–6.50	0.003 (-0.018, 0.024)
			No significant associations were seen in girls or analysis of combined genders		

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β [95% CI]) unless otherwise specified[a]
Sathyanarayana et al. 2016a, Cohort (United States [California, Minnesota, New York, Washington])	753 mother-infant pairs recruited from one of four study centers (University of California, San Francisco, University of Minnesota, University of Rochester Medical Center, Seattle Children's Hospital) between 2010 and 2012 (TIDES study).	Linear regression adjusted for race, smoking during pregnancy, study center, parity, income, and gestational age at birth	Change in birth weight in per log-unit increase in SG-adjusted urinary phthalate metabolite concentration		
			ΣDEHP	NR	Males: -0.03 (-0.16, 0.10) Females: 0.16 (0.03, 0.29)*
			MEHP	1.37–4.35	Males: -0.02 (-0.14, 0.10) Females: 0.13 (0.01, 0.24)*
			MEHHP	4.35–12.77	Males: -0.03 (-0.15, 0.08) Females: 0.15 (0.03, 0.27)*
			MEOHP	3.13–8.70	Males: -0.05 (-0.17, 0.07) Females: 0.13 (0.00, 0.25)*
			MECPP	5.90–15.95	Males: -0.01 (-0.14, 0.12) Females: 0.14 (0.02, 0.26)*
Shoaff et al. 2016, Cohort (United States [Ohio])	368 mother-infant pairs recruited from one of seven prenatal care clinics in Cincinnati, Ohio between 2003 and 2006 (HOME study).	Linear regression adjusted for maternal race, age, income, education, marital status, insurance, parity, food security, prenatal vitamin use, fish consumption, fruit/ vegetable consumption, BMI, BDI score, and serum cotinine level	Change in birth weight per 10-fold increase in urinary phthalate metabolite concentration		
			ΣDEHP	16 weeks: 0.14–0.72 nmol/mL 26 weeks: 0.10–0.52 nmol/mL	Presented graphically; non-significant for sum DEHP metabolites
			MEHP	16 weeks: 1.30–13.00 26 weeks: 1.60–10.40	
			MEHHP	16 weeks: 11.60–61.50 26 weeks: 8.30–46.60	
			MEOHP	16 weeks: 9.10–45.80 26 weeks: 7.00–37.50	
			MECPP	16 weeks: 15.80–89.30 26 weeks: 12.70–63.50	

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β [95% CI]) unless otherwise specified[a]
Su et al. 2014, Cohort (Taiwan)	130 mother-infant pairs recruited and followed from November 2001 to August 2009; TMICS.	Simple linear and binary logistic regression adjusted for gestational age (used to calculate z-score)	Association with maternal urinary metabolite concentrations		
			Birth length		
			ΣDEHP	42.28–60.83 µg/g Cr (95% CI)	0.001 (NR)
			MEHP	14.56–20.19 µg/g Cr	0.002 (NR)
			MEHHP	5.49–10.53 µg/g Cr	0.002 (NR)
			MEOHP	10.05–17.58 µg/g Cr	0.001 (NR)
			Birth weight		
			ΣDEHP	42.28–60.83 µg/g Cr (95% CI)	0.001 (NR)
			MEHP	14.56–20.19 µg/g Cr	0.001 (NR)
			MEHHP	5.49–10.53 µg/g Cr	0.002 (NR)
			MEOHP	10.05–17.58 µg/g Cr	0.001 (NR)
			Head circumference		
			Sum	42.28–60.83 µg/g Cr (95% CI)	0.001 (NR)
			MEHP	14.56–20.19 µg/g Cr	0.002 (NR)
			MEHHP	5.49–10.53 µg/g Cr	0.003 (NR)
			MEOHP	10.05–17.58 µg/g Cr	0.002 (NR)

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β [95% CI]) unless otherwise specified[a]
Wolff et al. 2008, Cohort (United States [New York])	404 mother-infant pairs enrolled prior to delivery at Mount Sinai Medical Center between March 1998 and March 2002 (Children's Environmental Health Study); mean±SD age: 24±6.2 years.	Multivariable linear regression adjusted for race, infant sex, gestational age, ln-creatinine, smoking during pregnancy, maternal education, marital status, prepregnancy BMI, and restricted to observations with creatinine ≥20 mg/dL	Association with ln-transformed maternal urinary metabolite concentrations		
			Birth length		
			ΣDEHP	0.13–0.5 µmol/L	0.07 (-0.13, 0.27)
			MEHP	2.9–14	0.01 (-0.18, 0.19)
			MEHHP	9.5–39	0.08 (-0.10, 0.27)
			MEOHP	8.3–36	0.07 (-0.12, 0.27)
			MECPP	16–70	0.04 (-0.16, 0.24)
			Birth weight		
			ΣDEHP	0.13–0.5 µmol/L	10 (-29, 49)
			MEHP	2.9–14	4.9 (-28, 38)
			MEHHP	9.5–39	6.6 (-27, 40)
			MEOHP	8.3–36	5.1 (-29, 40)
			MECPP	16–70	4.2 (-31, 40)
			Head circumference		
			ΣDEHP	0.13–0.5 µmol/L	0.00 (-0.14, 0.14)
			MEHP	2.9–14	0.01 (-0.11, 0.14)
			MEHHP	9.5–39	0.00 (-0.13, 0.13)
			MEOHP	8.3–36	0.01 (-0.12, 0.14)
			MECPP	16–70	0.01 (-0.13, 0.14)

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β [95% CI]) unless otherwise specified[a]
Zhao et al. 2014, Case-control (China)	42 IUGR infants and 84 controls (2 per case, matched for maternal age); mother-infant pairs were recruited during 3rd trimester sonogram examination at the Second Affiliated Hospital of Wenzhou Medical College between March 2012 and January 2013.	Logistic regression adjusted for maternal age, gestational age at delivery, maternal education, prepregnancy BMI, passive smoking, and other urinary phthalate metabolite concentrations	Risk of IUGR in the highest tertile of urinary phthalate metabolite concentration, compared with lowest (cases and controls combined)		
			ΣDEHP	All: 13.6–46.3 Cases: 16.4–54.5; Controls: 9.3 -41.5	No significant ($p<0.05$) association between birth length and urinary levels of metabolites after adjustment for covariates (data presented graphically)
			MEHP	All: 1.5–17.4 Cases: 3.5–16.7 Controls: 0.7–17.4	
			MEHHP	All: 3.9–19.2 Cases: 6.6–29.8 Controls: 3.2–15.8	Significant ($p<0.05$) association between lower birth weight and increasing urinary levels of MEHHP and MEOHP (data presented graphically)
			MEOHP	All: 1.7–9.7 Cases: 2.4–15.0 Controls: 1.4–6.4	Significantly increased adjusted OR for IUGR and MEHHP (data presented graphically)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BDI = Beck Depression Inventory; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)-phthalate; HOME = Health Outcomes and Measures of the Environment; INMA = Infancia y Medio Ambiente; IQR = interquartile range; IUGR = intrauterine growth retardation; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono-(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; NR = not reported; OR = odds ratio; SD = standard deviation; TIDES = The Infant Development and Environment Study; TMICS = Taiwan Maternal and Infant Cohort Study

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Fat Mass

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Harley et al. 2017, Cohort (United States [California])	345 children from the CHAMACOS birth cohort in California enrolled between 1999 and 2000. Maternal urine samples collected at mean gestation weeks 14.0 and 26.9; children's weight, height, and waist circumference were recorded at 5, 7, 9, 10.5, and 12 years.	Logistic and linear regression adjusted for maternal age, education, marital status; mother's years of residence in the United States and family income at the time of pregnancy; smoking during pregnancy; and repeated measures of family food insecurity and child's fast food consumption at each time point 1st and 2nd trimester urinary metabolite concentration pooled for analysis	Odds of being overweight or obese (BMI ≥85th percentile) at 5–12 years per doubling of log-transformed maternal urinary metabolite concentration		
			ΣDEHP	0.1–0.3 µmol/L	5 years: OR 1.1 (0.9, 1.4) 7, 9, 10.5 years: OR 1.2 (1.0, 1.5) 12 years: OR 1.3 (1.0, 1.6)*
			MEHP	2.1–7.0	NR
			MEHHP	8.6–27.8	NR
			MEOHP	6.6–20.8	NR
			MECCP	15.7–43.1	NR
			Change in BMI z-score at ages 5–12 years per each doubling of log-transformed maternal urinary metabolite		
			ΣDEHP	0.1–0.3 µmol/L	5 years: β 0.05 (-0.05, 0.16) 7 years: β 0.08 (-0.02, 0.18) 9 years: β 0.09 (-0.01, 0.20) 10.5 years: β 0.09 (-0.02, 0.19) 12 years: β 0.08 (-0.03, 0.19)
			Change in waist circumference z-score at ages 5–12 years per each doubling of log-transformed maternal urinary metabolite		
			ΣDEHP	0.1–0.3 µmol/L	5 years: β 0.14 (0.05, 0.23)* 7 years: β 0.00 (-0.08, 0.09) 9 years: β 0.00 (-0.09, 0.09) 10.5 years: β 0.10 (0.00, 0.19) 12 years: β 0.09 (-0.01. 0.20)
			Change in percent body fat at ages 9–12 years per each doubling of log-transformed maternal urinary metabolite		
			ΣDEHP	0.1–0.3 µmol/L	9 years: β 1.0 (-0.2, 2.2) 10.5 years: β 1.0 (-0.2, 2.2) 12 years: β 1.1 (-0.2, 2.4)

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Fat Mass

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)	Effect estimate (95% CI)[a]
Buckley et al. 2016a, Cohort (United States [New York and Ohio])	707 children from three birth cohorts (Mount Sinai Children's Environmental Health and Disease Prevention Research Center in New York, The CCCEH in New York, and Health Outcomes and Measures of the Environment in Ohio) enrolled between 1998 and 2006. Maternal urine samples collected at mean gestation weeks between 27 and 34; children's weights and heights recorded at ages between 4 and 7 years.	Linear mixed-effects regression adjusted for cohort; maternal race/ethnicity, age at delivery, education, work status during pregnancy, prepregnancy BMI, height, gestational weight gain, smoking during pregnancy, natural log Cr, calendar date of urine collection, parity, breast feeding, and child's sex and months of age at followup	Change in BMI z-score at ages 4–7 years per 1 SD increase in ln-transformed maternal urinary metabolite concentration (data pooled across cohorts)	
			ΣDEHP	
			0.128–0.562 µmol/L	β -0.04 (-0.15, 0.06)
			MEHP 2.00–11.9	NR
			MEHHP 9.20–45.1	NR
			MEOHP 8.00–37.5	NR
			MECPP 16.1–74.4	NR
			Analyses by child's sex, race/ethnicity, and cohort also did not identify any significant association with DEHP metabolites. Maresca et al. (2016) evaluated the same outcome in a subset of this cohort (members of the CCCEH cohort); no significant association was observed.	
Buckley et al. 2016b, Cohort (United States [New York])	180 children (82 girls and 98 boys) from birth cohort (Mount Sinai Children's Environmental Health Study); mothers recruited between 1998 and 2002 from Mount Sinai Hospital and two private practices. Maternal urine samples collected between 25 and 40 weeks of gestation. Children's fat mass was measured at ages 4 and 9 years.	Linear mixed-effects regression adjusted for prepregnancy BMI, gestational weight gain, maternal smoking during pregnancy, and breastfeeding	Change in percent fat mass in children 4–9 years old per 1 SD increase in ln-transformed maternal urinary metabolite concentration	
			ΣDEHP	
			125–530 nmol/L	β -0.89 (-2.24, 0.47)
			MEHP 3.00–14.2	NR
			MEHHP 8.80–41.3	NR
			MEOHP 8.20–38.3	NR
			MECPP 15.1–72.7	NR
			Analyses stratified by child's sex did not result in statistically significant effect estimates or change the direction of change.	

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Fat Mass

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Kim et al. 2016a, Cohort (Korea)	128 infants (65 boys and 63 girls) from birth cohort (Children's Health and Environmental Chemicals in Korea cohort); pregnant women recruited from five hospitals in four cities just prior to delivery of singleton birth. Newborns' first urine samples collected within 2 days of birth; infants' weights and heights recorded at birth, and obtained through telephone interview with mothers at 3 months of age.	Logistic regression adjusted for sex, birth weight, birth length, head circumference at birth, ponderal index (ratio of height to weight) at birth and 3 months; and leptin, total cholesterol, and triglyceride in cord blood and at 3 months	OR for BMI z-score increase >50th percentile from birth to 3 months per log-unit increase in newborn urinary metabolite concentration		
			ΣDEHP	NR	OR 4.35 (1.2, 15.72)*
			MEHHP	3.21–11.87	OR 4.43 (1.22, 16.04)*
			MEOHP	1.51–6.50	OR 3.91 (1.12, 13.65)*
			Association between triglyceride or cholesterol in cord blood and log-transformed newborn urinary metabolite concentration		
			ΣDEHP	NR	Total cholesterol β -0.019 (-0.103, 0.065) Triglyceride β 0.144 (0.020, 0.267)*
			MEHHP	3.21–11.87	Total cholesterol β -0.021 (-0.104, 0.062) Triglyceride β 0.146 (0.024, 0.267)*
			MEOHP	1.51–6.50	Total cholesterol β -0.014 (-0.098, 0.070) Triglyceride β 0.132 (0.009, 0.256)*
Agay-Shay et al. 2015; Valvi et al. 2015, Cohort (Spain)			Difference in BMI z-score (at age 7 years) between the highest and lowest tertiles of maternal urinary metabolite concentrations, without imputation of missing exposure data (Agay-Shay et al. 2015)		
			MEHP	1.8–266.9 µg/g Cr (min–max)	β -0.03 (-0.32, 0.27)
			MEHHP	5.3–503.4 µg/g Cr (	β -0.09 (-0.39, 0.21)
			MEOHP	4.1–378.3 µg/g Cr	β -0.14 (-0.44, 0.16)
			MECPP	7.7–718.9 µg/g Cr	β -0.26 (-0.55, 0.04)
			Inclusion of imputed values did not significantly alter the results.		

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Fat Mass

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
	Children from birth cohort (INMA or Environment and Childhood cohort); mothers were >16 years old with singleton pregnancy, enrolled at ultrasound during first trimester between 2004 and 2006. Maternal urine samples collected during 1st and 3rd trimesters, at mean gestational weeks 13 and 34 weeks, respectively. Children's heights and weights measured at birth and ages 6 months and 1, 4, and 7 years. Agay-Shay et al. (2015) included 470 children with followup data from 7 years of age. Valvi et al. (2015) evaluated subset of 391 children with complete data, including measurements at 1, 4, and 7 years.	Agay-Shay et al. (2015): Linear regression adjusted for child's sex, gestational age, birth weight, exact age at the time that the outcome was measured (months), maternal country of origin, maternal age at delivery, maternal prepregnancy BMI, maternal weight gain during pregnancy, maternal social class, breastfeeding duration, and maternal smoking during pregnancy Valvi et al. (2015): Generalized estimating equations adjusted for child's exact age at examination and maternal characteristics (country of origin, age at delivery, parity, education, social class, prepregnancy BMI, and smoking in pregnancy)	Association between BMI z-score and log-transformed, Cr-adjusted average maternal urinary metabolite concentration (Valvi et al. 2015) (urine concentrations shown for boys and girls combined)		
			ΣDEHP	64.9–139 µg/g Cr (as MEHP)	Boys: β -0.32 (-0.64, -0.02)* Girls: β 0.21 (-0.11, 0.53)
			MEHP	7.3–17.2 µg/g Cr	NR
			MEHHP	17.9–41.5 µg/g Cr	NR
			MEOHP	14.3–30.3 µg/g Cr	NR
			MECPP	31.0–61.2 µg/g Cr	NR

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Fat Mass

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Maresca et al. 2016, Cohort (United States [New York])	424 children from birth cohort (Columbia Center for Children's Environmental Health cohort); pregnant African-American or Dominican women between 18 and 35 years of age recruited from two New York city hospitals between 1998 and 2006. Maternal urine samples collected during 3rd trimester. Children's anthropometric parameters measured at age 7.	Linear regression adjusted for maternal race/ethnicity, receipt of public assistance during pregnancy, prepregnancy obesity status, child birth weight, child age in months at time of followup, and urine specific gravity	Change in waist circumference at age 7 per unit increase in ln-transformed maternal urinary metabolites		
			ΣDEHP	292.89 (3.24) nmol/L (GM [GSD])	Boys: β -0.65 (-2.16, 0.87) Girls: β -0.13 (-1.37, 1.12)
			MEHP	4.91 (4.21)	NR
			MEHHP	22.03 (3.56)	NR
			MEOHP	18.30 (3.48)	NR
			MECPP	39.04 (3.08)	NR
			Change in percent body fat at age 7 per unit increase in ln-transformed maternal urinary metabolites		
			ΣDEHP	292.89 (3.24) nmol/L (GM [GSD])	Boys: β -0.39 (-1.57, 0.79) Girls: β -0.13 (-1.09, 0.84)
			MEHP	4.91 (4.21)	NR
			MEHHP	22.03 (3.56)	NR
			MEOHP	18.30 (3.48)	NR
			MECPP	39.04 (3.08)	NR

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; BMI = body mass index; CCCEH = Columbia Center for Children's Environmental Health; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; GSD = geometric standard deviation; INMA = Infancia y Medio Ambiente; IQR = interquartile range; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; NR = not reported; OR = odds ratio; SD = standard deviation

Skeletal and visceral effects were classified as retardations (delays in development), variations (changes that regularly occurred), or anomalies (changes that progressed beyond the degree of retardations and variations). No exposure-related skeletal retardations, variations, or anomalies or visceral variations or anomalies were observed. However, there was a statistically significant increase in the percent of litters with visceral retardations at 21 ppm, identified as "mainly" renal pelvis dilatations by the study authors (incidence data not reported). In similarly exposed dams that were allowed to deliver, no change was observed in offspring survival, growth, or development (Merkle et al. 1988).

In oral studies, increased fetal and neonatal mortality was observed in rats and mice following developmental exposure to DEHP. Fetal deaths were generally associated with maternal doses ≥340 mg/kg/day in rats and ≥95 mg/kg/day in mice (Hellwig et al. 1997; Nakamura et al. 1979; Price et al. 1988b; Schilling et al. 1999, 2001; Tanaka 2002; Tomita et al. 1982a; Yagi et al. 1980). Several studies also reported malformations and variations following gestational exposure to similar doses. In Wistar rats, maternal exposure to 1,000 mg/kg/day on GDs 6–15 increased the incidence of fetuses with external, soft tissue, or skeletal malformations in the tail, brain, urinary tract, gonads, vertebral column, and/or sternum (Hellwig et al. 1997). Variations and skeletal retardations were also increased at 1,000 mg/kg/day. No teratogenic effects were observed at maternal doses of 200 mg/kg/day. In CD-1 mice exposed throughout gestation, a significant increase in malformations of the external viscera and skeleton was apparent at maternal doses ≥91 mg/kg/day (Tyl et al. 1988). Specific abnormalities included protrusion of the eyeball, exencephaly, blood vessel abnormalities, fused or branched ribs, misaligned and fused thoracic vertebrae, and tail malformations. No adverse effects were seen at a maternal dose of 44 mg/kg/day. In ICR mice, 25.8% of fetuses were malformed following exposure to a maternal dose of 341 mg/kg/day from GD 1 to 18; observed malformations included club foot, exencephaly, open eyelids, tail anomalies, myeloschisis, gastroschisis, and generalized edema (Shiota and Nishimura 1982). No fetal malformations were observed in controls or low-dose animals (85 mg/kg/day), and only 5% of fetuses were malformed at 170 mg/kg/day (Shiota and Nishimura 1982). No gross malformations were observed in offspring of CD-1 mice exposed to doses up to 100 mg/kg/day from GD 11 to 19 (Maranghi et al. 2010). Acquisition of developmental landmarks was not altered in CD-1 mice following maternal exposure to 95 mg/kg/day from GD 0 to 17 (Price et al. 1988b).

Numerous studies reported body weight effects in rats following developmental exposure to DEHP; however, findings are inconsistent among species, strains, and studies. Following gestation-only exposure, decreases in pup body weight ≥10% were observed in Sprague-Dawley rats at doses ≥10 mg/kg/day (Chen et al. 2010) and ≥37.5 mg/kg/day (Piepenbrink et al. (2005); however, Vo et al.

(2009a) did not observe decreased body weights until doses of 500 mg/kg/day. Findings in Sprague-Dawley rats following gestation plus lactation exposure were more consistent with the Vo et al. (2009a) study, reporting no body weight changes in offspring until maternal doses ≥447 mg/kg/day (Andrade et al. 2006a, 2006c; Blystone et al. 2010; Grande et al. 2006, 2007; Gray et al. 2009; Kobayashi et al. 2006; NTP 2005). Similarly, decreased offspring body weight in Long-Evans rats was only observed at 750 mg/kg/day, not at 10 mg/kg/day (Lin et al. 2009). Most studies in Wistar rats also reported no changes in offspring body weight following gestational and lactational exposure to maternal doses up to 500 mg/kg/day (Carbone et al. 2010, 2012; Dalsenter et al. 2006; Schilling et al. 1999, 2001); however, Christiansen et al. (2010) reported decreased offspring weights at doses ≥300 mg/kg/day. Additionally, two very low dose studies reported decreased offspring weight, body fat percentage, and adipocyte size at maternal doses ≥0.25 mg/kg/day during gestation and lactation (Lin et al. 2011; Wei et al. 2012).

Gestational studies in mice showed more consistent effects, with decreased offspring body weights at ≥191 mg/kg/day, but not ≤100 mg/kg/day (Maranghi et al. 2010; Price et al. 1988b; Shiota et al. 1980; Shiota and Nishimura 1982; Tyl et al. 1988). Similarly, a 1-generation study reported a lack of body weight effects in offspring at maternal doses up to 180.77 mg/kg/day (Tanaka 2002). However, decreased offspring body weight and abdominal fat were observed in mouse offspring following gestational plus lactation exposure to maternal doses ≥0.05 mg/kg/day (Pocar et al. 2012; Tanida et al. 2009). In contrast, another 1-generation study reported a significant *increase* in F1 offspring body weight and visceral adipose tissue at doses ≥0.05 mg/kg/day (Schmidt et al. 2012). No changes in body weight or visceral or inguinal adipose tissue were observed in postnatal week (PNW) 22 mouse offspring following maternal exposure to 0.05 or 500 mg/kg/day throughout gestation and lactation followed by high-fat diet consumption for 19 weeks, compared with unexposed high-fat diet controls (Hunt et al. 2017). Due to use of a high-fat diet, this study was not included in the LSE table.

In female weanling Wistar rats, an approximate 10% decrease in terminal body weight was observed following inhalation exposure to DEHP at 1.6 ppm for 6 hours/day, 5 days/week for the first 9 weeks post-weaning (Ma et al. 2006). However, no body weight effects were observed in young male or female Wistar rats exposed to concentrations up to 1.6 ppm for the first 3–8 weeks post-weaning (Kurahashi et al. 2005; Ma et al. 2006). In weanling Long-Evans rats, a 13% decrease in body weight was observed following exposure to 750 mg/kg/day for 28 days, but not at 500 mg/kg/day for 14 or 28 days (Ge et al. 2007). Similarly, no body weight effects were observed in young Sprague-Dawley rats exposed to 500 mg/kg/day for 15 days post-weaning (Vo et al. 2009b). Unspecified body weight decreases and increased mortality were observed in neonatal and weanling rats exposed to ≥1,000 mg/kg/day DEHP via

gavage for 5 days (Dostal et al. 1987). Similarly, a 14-day dietary study reported a >15% decrease in body weight in sexually immature male and female F344 rats at ≥5,700 and 6,200 mg/kg/day, respectively, and male and female B6C3F1 mice at ≥4,900 and 11,000 mg/kg/day, respectively (NTP 1982).

In nonhuman primates exposed post-weaning, no exposure-related body weight effects were observed in sexually immature Cynomolgus monkeys exposed to 500 mg/kg/day for 14 days (Pugh et al. 2000) or marmoset monkeys exposed to doses up to 2,500 mg/kg/day for 65 weeks from weaning until sexual maturation (Tomonari et al. 2006).

Mechanisms of Fetotoxicity and Altered Growth. Several mechanisms have been proposed to contribute to DEHP-induced pregnancy loss, preterm birth, low birth weight, and IUGR, including alteration of ovarian steroidogenesis, thyroid dysfunction, placental alterations, and intrauterine inflammation (Marie et al. 2015).

Developmental exposure to DEHP may contribute to obesity later in life via disruption of adipose tissue homeostasis. *In vitro* exposure of mouse embryonic preadipocytes to MEHP resulted in PPARγ activation, perturbation of PPARγ-induced regulators of adipogenesis and lipogenesis, and increased adipocyte differentiation (Hao et al. 2012). Perturbation of PPARγ-induced regulators of adipogenesis and lipogenesis was also observed in PND 60 mice following gestational and lactational exposure to MEHP, along with increased body and fat pad weight, increased serum cholesterol, increased triacylglycerol, and increase glucose levels (Hao et al. 2012). Specifically, DEHP exposure may result in increased adipocyte maturation via proliferating cell nuclear antigen (PCNA) phosphorylation (Hunt et al. 2017). *In vitro* studies confirm the DEHP stimulates adipogenesis in mouse embryo fibroblasts expressing wild-type PCNA, but not in mouse embryos expressing mutated PCNA (which blocks phosphorylation) (Hunt et al. 2017).

Animal Studies—Liver System Development. As observed in the adult rodent, evidence of hepatomegaly was also observed in young animals following developmental exposure. As discussed in detail in Section 2.9 (Hepatic effects), increased liver weight without histological evidence of hepatobiliary damage is not considered adverse or relevant for human risk assessment unless at least two of the following are observed: (1) 2–3 times increase in ALT levels; (2) biologically significant change in other biomarkers of hepatobiliary damage (ALP, AST, GGT, etc.); or (3) biologically significant change in

another clinical pathology marker indicating liver dysfunction (Hall et al. 2012). Therefore, evidence of increased liver weight alone is not used as a basis for a LOAEL.

In nonhuman primates, no histopathological changes in liver histology, changes in hepatic serum enzymes, evidence of liver enlargement, or peroxisomal proliferation were observed in sexually immature Cynomolgus monkeys exposed to 500 mg/kg/day via gavage for 14 days (Pugh et al. 2000) or marmoset monkeys exposed to doses up to 2,500 mg/kg/day for 65 weeks from weaning at 3 months to sexual maturity at 18 months (Tomonari et al. 2006).

Transient increases in liver weights (partially recovered by PND 56) and reversible subendothelial edema of the centrilobular vein and portal space (recovered by PND 42) were seen in offspring of Long-Evans rat dams exposed to DEHP at ≥3 mg/kg/day during all of gestation and lactation (Arcadi et al. 1998). Transient liver lesions, including pyknotic nuclei and hepatocyte vacuolation, were also observed in PND 21 offspring of CD-1 mice exposed to doses ≥25 mg/kg/day from GD 11 to 19 (Maranghi et al. 2010). Decreased glycogen storage was also observed. These effects were no longer evident at PND 35.

In a gestational/lactational exposure study in Sprague-Dawley rats, significant increases in liver weights were observed in offspring at PND 1 at maternal doses ≥135 mg/kg/day, but not at weaning or during adulthood at maternal doses up to 405 mg/kg/day (Andrade et al. 2006a, 2006c; Grande et al. 2006, 2007). Similarly, no exposure-related changes in liver weights were observed at PND 21 or 63 in offspring born to Sprague-Dawley rat dams exposed to DEHP at doses up to 400 mg/kg/day from GD 6 to PND 20 (Kobayashi et al. 2006). In a 2-generation study in Wistar rats, increased liver weights were observed in F1 and F2 pups on PND 21 following exposure to ≥113 mg/kg/day (lowest dose tested) (Schilling et al. 2001). No exposure-related changes were observed in Wistar rat offspring on PND 16 following maternal exposure to doses up to 900 mg/kg/day from GD 7 to PND 16 (Christiansen et al. 2010). Measures of liver function and liver histology were not assessed in these studies. As discussed in Section 2.9 (Hepatic), the biological relevance of elevated liver weight in the absence of altered function or histology is unclear.

Liver weight was significantly elevated in adult male rat offspring following gestational, lactational, and direct post-lactational exposure to DEHP through PND 65 at doses ≥100 mg/kg/day, but not at doses up to 33 mg/kg/day (Gray et al. 2009). Elevated liver weight at PND 65 was not observed if DEHP exposure ceased at weaning (no direct exposure).

Age-dependent effects on enzyme activities were examined in rats of three ages: 3, 6, and 10 weeks old (Parmar et al. 1994). Single administration of 2,000 mg DEHP/kg decreased the cytochrome P-450 contents in the liver, as well as the activities of aryl hydrocarbon hydroxylase (AHH), aniline hydroxylase, and ethylmorphine N-demethylase in all age groups, while repeated exposure induced them with maximum increases occurring in 3-week-old rats. Administration of DEHP for 15 days decreased cytochrome P-450 and the activity of the three enzymes only in the 3-week-old rats. Six- and 10-week-old rats showed an inhibition of AHH and increased activities of aniline hydroxylase and ethylmorphine N-demethylase, which were lower than seen after 7 days of exposure in their respective groups. The potential adversity of observed changes in the MFO enzymes on the liver is difficult to determine in the absence of evaluation of other hepatic endpoints. Changes could potentially lead to altered metabolism of endogenous and exogenous chemicals, resulting in decreased detoxification of chemicals and/or decreased formation of toxic intermediates.

Animal Studies—Renal System Development. In the only inhalation study evaluating potential effects on the developing renal system following DEHP exposure, no changes in kidney weights were observed in female weanling rats exposed to DEHP at concentrations up to 1.6 ppm for 6 hours/day, 5 days/week for 3 or 9 weeks (Ma et al. 2006). No other renal parameters were measured.

In orally exposed nonhuman primates, no changes in clinical chemistry measures of renal function, urinalysis parameters, or kidney weight or histology were observed in 14-day studies in sexually immature Cynomolgus monkeys at 500 mg/kg/day (Pugh et al. 2000).

In a developmental study in Wistar rats, impaired kidney development and function were observed in adult offspring following maternal exposure to 0.25 or 6.25 mg/kg/day from GD 0 to PND 21 (Wei et al. 2012). Creatinine clearance (measured at PNW 21) was significantly reduced in all exposed offspring. Serum creatinine was only significantly elevated in low-dose female offspring. Serum BUN was significantly elevated in low-dose females and low- and high-dose males, and urinary total protein was significantly elevated in low- and high-dose females and high-dose males. Serum renin and angiotensin levels were reduced at birth but increased at PNW 3. The glomerular number per kidney was significantly decreased (compared with control) at PNWs 3 and 33 in all exposed offspring; total glomerular volume was also decreased at PNW 33 in all exposed offspring. The average individual glomerular volume was increased in high-dose females and all exposed males at PNW 3, but decreased in all exposed males at PNW 33. Histological examination showed decreased glomerular size, glomerular swelling, and reduction in Bowman’s capsule size in both exposure groups from PND 0 to PNW 33.

Electron microscopy showed renal tubular dilation, tubular atrophy, interstitial fibrosis, and scarring. Additionally, significant increases in blood pressure in exposed offspring were considered secondary to impaired kidney function. Significant changes observed in offspring kidney weights included decreased absolute weight in high-dose females at PNW 15, increased absolute weight in high-dose males at PNW 21, increased relative weight in high-dose pups at PNDs 0 and 3, increased relative weight in low-dose females at PNW 15, and increased relative weight in high-dose males at PNWs 15 and 21 (Wei et al. 2012).

Reversible decreases in kidney weights (recovered by PND 56), reversible glomerulonephritis and dilation of renal tubule (recovered by PND 42), and persistent light renal fibrosis (no recovery at PND 56) were seen in offspring of Long-Evans rat dams exposed to DEHP at ≥3 mg/kg/day during all of gestation and lactation (Arcadi et al. 1998). In Sprague-Dawley rat offspring, decreased kidney weight was observed in adulthood following gestation and lactational exposure to a maternal dose of 300 mg/kg/day, but not at maternal doses up to 100 mg/kg/day (Gray et al. 2009). A subset of male offspring continued direct exposure post-weaning through PND 65; decreased kidney weight was also observed at 300 mg/kg/day in these animals. However, no exposure-related changes in kidney weights were observed in weanling or adult offspring born to Sprague-Dawley rat dams exposed to DEHP at doses up to 405 mg/kg/day during gestation and lactation (Andrade et al. 2006a; Grande et al. 2007; Kobayashi et al. 2006). In a 2-generation study in Wistar rats, absolute kidney weights were decreased in F2 weanlings exposed to 1,088 mg/kg/day, but relative kidney weights were increased at lower doses (113 and 340 mg/kg/day); no exposure-related changes were observed in kidney weights in F1 weanlings (Schilling et al. 2001). No exposure-related changes were observed in Wistar rat offspring on PND 16 following maternal exposure to doses up to 900 mg/kg/day from GD 7 to PND 16 (Christiansen et al. 2010). Increased relative kidney weights were observed in neonatal and weanling rats exposed to ≥1,000 mg/kg/day DEHP via gavage for 5 days (Dostal et al. 1987). Measures of renal function and kidney histology were not assessed in these studies.

Epidemiology Studies—Neurodevelopment. Many epidemiological studies assessed neuro-developmental outcomes. The types of neurodevelopmental effects that have been evaluated include infant neurological state; cognitive, mental and psychomotor development; behavior and emotional development; social development and autism spectrum disorders; and gender-related behaviors. All of the selected studies are birth cohort studies that evaluated exposure using maternal urine samples.

In a study using the neonatal intensive care unit (NICU) Network Neurobehavioral Scale (NNNS) to evaluate infant neurological state, Yolton et al. (2011) observed an association between increased frequency of nonoptimal reflexes in male infants (n=158 boys) and the sum of DEHP metabolites in maternal urine samples collected at 26±4 weeks of gestation (β =0.216, SE=0.090, p=0.02). No association was seen between female infants (n=174 girls) and DEHP metabolites in maternal urine samples collected at 26 weeks, or in either sex using maternal urine samples collected at 16 weeks. No other subscales of the NNNS (e.g., attention, arousal, regulation, handling, etc.) were affected in boys or girls.

The database for epidemiological studies of cognitive/mental and psychomotor development includes eight studies of birth cohorts evaluating 110–460 children (Table 2-15). These studies used standard instruments for assessing development; typically, the Bayley Score for Infant Development (BSID) was used in children up to 3 years of age and the Wechsler Intelligence Scale for Children (WISC) was used in older children. Most studies administered the tests at one point in time, although Tellez-Rojo et al. (2013) and Huang et al. (2015) conducted longitudinal analyses, using repeated test scores in the same children. Two studies suggested associations between poorer performance on the mental development index at 6 months (Kim et al. 2011) and 2–3 years of age (Tellez-Rojo et al. 2013) and prenatal DEHP exposure. The affected sex differed between the studies with Kim et al. (2011) reporting an association for male infants and Tellez-Rojo et al. (2013) observing an association only in female infants. Two studies (Kim et al. 2011; Polanska et al. 2014) reported associations between prenatal DEHP exposure and psychomotor development in young children (6 months and 2 years, respectively). Other studies (Doherty et al. 2017; Factor-Litvak et al. 2014; Gascon et al. 2015b; Huang et al. 2015; Whyatt et al. 2012) did not observe associations between cognitive, mental, or psychomotor development and maternal urinary metabolites of DEHP (Table 2-15). However, the available studies measuring these endpoints are not strictly comparable, due to differences in the instruments used to assess development, varying ages at assessment, gestational timing of maternal urine collection, nature and number of covariates considered in the analyses, differences in study populations, and specific DEHP metabolites measured in urine.

Studies examining potential relationships between DEHP exposure and autism spectrum disorders are limited to case-control studies in which exposure was measured after the diagnosis (Kardas et al. 2016; Stein et al. 2013; Testa et al. 2012); these studies were not considered useful for hazard identification. Miodovnik et al. (2011) and Braun et al. (2014) examined autism-related behavior in two U.S. birth

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Infant neurological status					
Yolton et al. 2011, Cohort (United States [Ohio])	350 infants (163 boys, 187 girls); members of birth cohort (HOME); mothers at ~16 weeks of gestation recruited from nine obstetrical clinics between 2003 and 2006. Maternal urine collection at 16 and 26 weeks of gestation. NNNS at 5 weeks of age.	Linear regression adjusted for urinary creatinine, infant age at exam and weight change since birth, and maternal income	ΣDEHP	16 weeks: 311 (269–360) 26 weeks: 245 (213–281) (GM [95% CI], in nmol/L)	NNNS at 5 weeks: ↑ frequency of nonoptimal reflexes in male infants with ↑ ∑DEHP metabolites in 26-week (but not 16-week) maternal urine β 0.216* 95% CIs not reported No significant association in female infants, or on other subscales of the NNNS in males or females.
			MEHP	16 weeks: 4.9 (4.2–5.7) 26 weeks: 4.2 (3.7–4.9)	
			MEHHP	16 weeks: 26.9 (23.0–31.3) 26 weeks: 20.4 (17.6–23.5)	
			MEOHP	16 weeks: 19.9 (17.1–23.2) 26 weeks: 16.5 (14.3–19.1)	
			MECPP	16 weeks: 38.0 (33.0–43.7) 26 weeks: 29.9 (26.1–34.2)	

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)	Results[a]
Mental, psychomotor, and cognitive development (by age at evaluation, youngest to oldest)				
Kim et al. 2011, Cohort (Korea)	460 children (235 boys and 225 girls) aged 6 months; members of birth cohort (Mothers and Children's Environmental Health); mothers in their 1st trimester were recruited at obstetric clinics in three cities between 2006 and 2009. Single maternal urine sample collected between 36 and 42 weeks of gestation; BSID-II (MDI and PDI) administered to infants at 6 months of age.	Linear regression adjusted for infant birth weight, infant sex, maternal age, maternal education level, family income, breastfeeding status, and residential area	MEHHP 4.3–21.4 MEOHP 3.8–17.1	BSID II at 6 months: ↓ MDI scores in male infants with ↑ MEHHP and MEOHP in maternal urine β -1.46* and -1.57*, respectively ↓ PDI scores in male infants with ↑ MEHHP and MEOHP in maternal urine β -2.36* and -2.05*, respectively 95% CIs not reported No significant association in female infants; in analyses grouping across sex, significant associations between MDI and PDI and DEHP metabolites were also seen. Significant association also seen in subgroup analysis that controlled for maternal intelligence score.
Gascon et al. 2015b, Cohort (Spain)	367 children (187 boys, 178 girls); members of birth cohort (INMA or Environment and Childhood); mothers recruited at 1st trimester prenatal visit at hospital or health center between 2004 and 2006. Maternal urine samples collected at 12 and 32 weeks of gestation and results averaged. BSID (MDI and PDI) administered to infants at 1 year of age, and MSCA administered at age 4.	Linear regression adjusted for sex, maternal age and education, maternal smoking during pregnancy, birth season, breastfeeding, maternal country of origin, number of siblings, and child's age (BSID not adjusted for child's age)	ΣDEHP 68–146 µg/g Cr MEHP 7–17 µg/g Cr MEHHP 18–41 µg/g Cr MEOHP 14–30 µg/g Cr MECPP 27–59 µg/g Cr	BSID at 1 year: No significant association between MDI or PDI scores and ∑DEHP metabolites in maternal urine; no sex-specific associations observed. MSCA at 4 years: No significant association between any test subscore and ∑DEHP metabolites in maternal urine; no sex-specific associations observed.

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Doherty et al. 2017, Cohort (United States [New York])	250 children (134 boys, 116 girls); from a cohort of 404 pregnant women; mothers recruited at first prenatal visit (<26 weeks) at hospital or health center 1998-2002. Single maternal urine sample (n=258) collected at 25-40 weeks of gestation. BSID (MDI and PDI) administered at approximately 24 months of age.	Linear regression adjusted for urinary creatinine, pre-pregnancy BMI, maternal race, maternal education, HOME Score, duration of breastfeeding, maternal age, child age at testing, child's sex (male/female), and maternal marital status	ΣDEHP	0.28 (3.7) µmol/L (GM [SE])	BSID at 24 months: No significant association between MDI or PDI scores and ∑DEHP metabolites in maternal urine; no sex-specific associations were observed.
			MEHP	6.2 (3.8)	
			MEHHP	20 (4.0)	
			MEOHP	18 (3.9)	
			MECPP	35 (3.7)	
Polanska et al. 2014, Cohort (Poland)	165 children (72 boys, 93 girls); members of birth cohort (Polish Mother and Child Cohort); mothers recruited during first trimester of pregnancy at maternity units or clinics (time of recruitment not reported). Single maternal urine sample collected during 3rd trimester (30–34 weeks of gestation); child urine sample collected at 24 months of age. BSID-III administered to infants at 24 months of age.	Linear regression adjusted for examiner, parental age, parental education, child gender, pre- and postnatal ETS exposure, cognitive development, marital status, and child nursery attendance	ΣDEHP	0.0004–1.5 µmol/g Cr (min–max)	BSID-III at 2 years: No significant association with cognitive or language scores after adjustment for covariates. ↓ motor scores with ↑ log-transformed Cr-adjusted MEHHP, MEOHP, and ∑DEHP metabolites in maternal urine β -1.2*, -1.8*, and -2.2*, respectively 95% CIs not reported Analyses using child urine samples were not considered, as outcome was measured concurrently.
			MEHP	0.02–4.3 µg/g Cr	
			MEHHP	0.02–431 µg/g Cr	
			MEOHP	0.04–140 µg/g Cr	

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Tellez-Rojo et al. 2013, Cohort (Mexico)	135 children (64 boys, 71 girls); members of birth cohort (Early Life Exposure in Mexico to Environmental Toxicants); mothers recruited during 1st trimester (no further details). Single maternal urine sample collected during 3rd trimester. BSID-II administered to children at 24, 30, and 36 months of age (results combined in analysis).	Linear regression for longitudinal data adjusted for birth weight, breastfeeding practices, Z-scores for weight-for-age, child's current age, mother's age, mother's educational level, and laboratory where urine analyzed	ΣDEHP	0.35 (0.30, 0.40) nmol/mL (GM [95% CI], SG-adj)	BSID-II between 2 and 3 years: ↓ MDI scores in girls* with ↑ ln-transformed MEHP, MEHHP, MEOHP, MECPP, and ∑DEHP metabolites in maternal urine β -2.11*, -1.89*, -1,80*, -2.52*, and -3.41*, respectively 95% CIs not reported No significant association with MDI in boys or combined analyses. No significant association with PDI in combined or sex-stratified analyses.
			MEHP	6.56 (5.72, 7.53)	
			MEHHP	22.08 (18.77, 25.96)	
			MEOHP	14.23 (12.05, 16.80)	
			MECPP	39.65 (34.32, 45.81)	
Whyatt et al. 2012, Cohort (United States [New York])	319 children (151 boys, 168 girls); members of birth cohort (CCCEH); black or Dominican mothers recruited prior to 20th week of pregnancy (no further details). Single maternal urine sample collected during 3rd trimester (mean 33 weeks of gestation). BSID-II administered to infants between 27 and 42 months of age (mean 36.4 months).	Linear regression adjusted for child sex, race/ethnicity, quality of proximal care-taking environment, gestational age, maternal marital status, maternal prenatal alcohol use, and urine specific gravity	MEHP	<LOD–613 (min–max)	BSID-II at 3 years: No significant association with ∑DEHP metabolites in maternal urine in combined or sex-stratified linear regression analyses. No significant associations with ∑DEHP metabolites in maternal urine in combined or sex-stratified logistic regression analyses dichotomizing scores ≤85 and >85 (score ≤85 associated with risk of developmental delay on both MDI and PDI).
			MEHHP	1.1–1,750	
			MEOHP	0.7–1,320	
			MECPP	3.0–1,840	

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Factor-Litvak et al. 2014, Cohort (United States [New York])	328 children (155 boys, 173 girls); members of CCCEH cohort (see Whyatt et al. [2012] above for study population and urine collection). WISC administered to children at 7 years of age.	Linear regression adjusted for specific gravity, maternal IQ, ethnicity, alcohol use during pregnancy, education, marital status, total HOME score, and sex of child	MEHP	1.9–12.4	WISC at 7 years: No significant association between full scale or subscale scores and MEHHP or MEHP in maternal urine.
			MEHHP	10.6–47.2	
Huang et al. 2015, Cohort (Taiwan)	110 children (58 boys, 52 girls); members of birth cohort (TMICS); mothers 25–34 years of age recruited during 3rd trimester at medical center between December 1, 2000 and November 30, 2001. Single maternal urine sample collected during 3rd trimester; children's urine samples collected at ages 2, 5, 8, and 11 years. BSID-II administered at age 2; WPPSI-R at age 5; WISC-III at age 8, and WISC-IV at age 11.	Mixed-model repeat measures analysis adjusted for gender, HOME score, birth weight, maternal education, lactation, and children's age MDI portion of BSID-II used as estimate of IQ in infants	ΣDEHP	58.69 (48.32, 71.30) µg/g Cr; GM (95% CI)	IQ between 2 and 11 years: No significant association with MEHP, MEHHP, or MEOHP in maternal urine. ↓ IQ with ↑ MEOHP and ∑DEHP metabolites in child's urine; however, samples were taken at the same time as tests administered.
			MEHP	19.79 (16.38, 23.92) µg/g Cr;	
			MEHHP	8.49 (5.97, 12.09) µg/g Cr	
			MEOHP	12.97(9.23, 18.21) µg/g Cr	

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Behavioral development					
Whyatt et al. 2012, Cohort (United States [New York])	319 children (151 boys, 168 girls); members of birth cohort (CCCEH); black or Dominican mothers recruited prior to 20th week of pregnancy (no further details). Single maternal urine sample collected during 3rd trimester (mean 33 weeks of gestation). Mothers completed CBCL when children were between 33 and 48 months of age (mean 36.6 months).	Linear regression adjusted for child age in months at the time of test administration, child sex, race/ethnicity, maternal IQ; maternal satisfaction with living conditions; maternal perceived hardship; maternal demoralization[b]; maternal prenatal PAH exposure; maternal prenatal urinary BPA concentrations, and SG	MEHP	<LOD–613 (min–max)	CBCL at 3 years: No significant association with ∑DEHP metabolites in maternal urine in combined or sex-stratified linear regression analyses. No significant association with ∑DEHP metabolites in maternal urine in combined or sex-stratified logistic regression analyses categorizing scores as normal, borderline, or clinical.
			MEHHP	1.1–1,750	
			MEOHP	0.7–1,320	
			MECPP	3.0–1,840	

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Gascon et al. 2015b, Cohort (Mexico)	367 children (187 boys, 178 girls); members of birth cohort (INMA or Environment and Childhood); mothers recruited at 1st trimester prenatal visit at hospital or health center between 2004 and 2006. Maternal urine samples collected at 12 and 32 weeks of gestation and results averaged. CPSCS and ADHD criteria form filled out by teachers when children were age 4. Parents filled out SDQ and short form of CSRS; includes ADHD index) when children were age 7.	Linear regression (CPSCS scores) or negative binomial generalized linear models (ADHD, SDQ, and CSRS) adjusted for sex, maternal age and education, maternal smoking during pregnancy, birth season, breastfeeding, maternal country of origin, number of siblings, and child's age	ΣDEHP MEHP MEHHP MEOHP MECPP	68–146 µg/g Cr 7–17 µg/g Cr 18–41 µg/g Cr 14–30 µg/g Cr 27–59 µg/g Cr	↑ (improved) social competence score at 4 years with ↑ ∑DEHP metabolites in maternal urine β 2.00* 95% CIs not reported ↓ (improved) risk of inattention symptoms at 4 and 7 years with ↑ ∑DEHP metabolites in maternal urine IRR [95% CI] = 0.84 [0.72, 0.98]* at 4 years and 0.83 [0.71, 0.95]* at 7 years ↓ (improved) risk of ADHD symptoms at 7 years with ↑ ∑DEHP metabolites in maternal urine IRR [95% CI] 0.88 [0.77, 1.00]*
Lien et al. 2014, Cohort (Taiwan)	122 children (sex distribution not reported); members of birth cohort (TMICS); mothers 25–34 years of age recruited during 3rd trimester at medical center between December 1, 2000 and November 30, 2001. Single maternal urine sample collected during 3rd trimester. Child's urine collected at 8 years of age. Mothers completed CBCL when children were 8 years of age.	Linear and logistic regression adjusted for child's IQ, sex, and family income (logistic regression results shown to right)	MEHP MEHHP MEOHP	16.93 (14.32, 20.02) µg/g Cr (GM [95% CI]) 7.91 (5.69, 11.02) µg/g Cr 13.59 (10.27, 18.00) µg/g Cr	CBCL at 8 years: ↑ OR for scores in clinical range (versus normal range) for delinquent behavior with ↑ log-unit ↑ Cr-adjusted MEOHP in maternal urine OR 22.91* ↑ OR for scores in clinical range (versus normal range) for aggressive behavior with log-unit ↑ Cr-adjusted MEHP, MEHHP, and MEOHP in maternal urine ORs 9.77*, 4.99*, and 6.88*, respectively ↑ OR for scores in clinical range versus normal range) for externalizing problems

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)	Results[a]
				with log-unit ↑ Cr-adjusted MEHP, MEHHP, and MEOHP in maternal urine ORs 31.01*, 7.41*, and 28.49*, respectively. Significant ORs also seen for borderline or borderline/clinical scores for all three behavior categories and DEHP metabolites. 95% CIs not reported.
Kobrosly et al. 2014, Cohort (United States [California, Minnesota, Missouri, Iowa])	153 children (77 boys, 76 girls) born between 2000 and 2005; members of birth cohort (Study for Future Families); mothers recruited between 1999 and 2005 (no further details). Single maternal urine sample collected between 10 and 39 weeks of gestation (mean 26.6 weeks). Mothers completed CBCL when children were 72–126 months of age (mean 102 months or 8.5 years).	Linear regression adjusted for child sex, child age, mother's education, urinary creatinine, and family stress score	MEHP 1.1, 9.9 MEHHP 6.1, 24.2 MEOHP 5.1, 22.0	↓ (improved) score for anxious/depressed among female children with ↑ ln-transformed ∑DEHP metabolites in maternal urine β -0.21* 95% CI not reported No significant effect on other behavioral scores, or among male children or male and female combined.

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)		Results[a]
Gender-related play					
Percy et al. 2016, Cohort (United States [Ohio])	227 children (101 boys, 126 girls) born between 2003 and 2006; part of HOME cohort; mothers (16±3 weeks of gestation) recruited at Cincinnati Children's Hospital. Maternal urine samples were collected at 16 and 26 weeks of gestation (on average). Mothers completed GIQ and children completed PPPSI at the child's 8-year clinic visit.	Linear regression analysis for continuous scores, and logistic regression of scores dichotomized by sex at the lower 25th percentile. Analyses adjusted for race, mother's education, and relational frustration score	ΣDEHP	16 weeks: 87.9 (73.4, 105.3) nmol/L 26 weeks: 65.9 (55.2, 78.5) nmol/L (GM [95% CI])	No association between GIQ or PPPSI scores and mean maternal urinary metabolites in either boys or girls. Odds of having atypical gender-related play were not associated with maternal urinary metabolites in either boys or girls.
			MEHP	16 weeks: 4.9 (4.1, 6) 26 weeks: 4.3 (3.6, 5)	
			MEHHP	16 weeks: 27 (22.3, 32.7) 26 weeks: 19.4 (16.1, 23.4)	
			MEOHP	16 weeks: 20.1 (16.7, 24.2) 26 weeks: 15.9 (13.2, 19.2)	
			MECPP	16 weeks: 39.3 (33, 46.9) 26 weeks: 29.1 (24.5, 34.6)	

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference and study type	Population	Method of analysis	Metabolite concentration in urine (IQR in ng/mL unless otherwise specified)	Results[a]
Swan et al. 2010 Cohort (United States [California, Minnesota, Missouri, Iowa])	145 children (74 boys, 71 girls) born between 2000 and 2003; members of birth cohort (Study for Future Families); mothers recruited from prenatal clinics between 1999 and 2005. Single maternal urine sample collected midpregnancy. Mothers completed PSAI when children were approximately 5 years old.	Linear regression analysis adjusted for child's age, mother's age, mother's education, parents' attitude towards boy's play, and interaction of mother's education and attribute toward boy's play	Change in PSAI scores for masculine play in boys per log-unit increase in maternal urinary metabolite	
			ΣDEHP 11.7, 40.3	β (95% CI) -3.18 (6.26, 0.10)*
			MEHP 1.4, 6.2	β (95% CI) -0.95 (-3.85, 1.95)
			MEHHP 5.2, 17.3	β (95% CI) -3.29 (-6.14, -0.43)*
			MEOHP 4.7, 17.9	β (95% CI) -2.94 (-5.78, -0.10)*
			No associations were observed between composite or feminine play scores in boys and maternal urinary metabolite levels. No associations were observed between composite, masculine play, or feminine play scores in girls and maternal urinary metabolite levels.	

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.
[b]Demoralization is defined as "a psychological state characterized by helplessness, hopelessness, a sense of failure and the inability to cope" or a "giving up-given up" complex (Tecuta et al. 2015); maternal demoralization was assessed via questionnaire.

ΣDEHP = sum DEHP metabolites; ADHD = attention-deficit/hyperactivity disorder; BPA = bisphenol A; BSID = Bayley Scales of Infant Development; CBLC = child behavior checklist; CCCEH = Columbia Center for Children's Environmental Health; CI = confidence interval; CPSCS = California Preschool Social Competence Scale; Cr = creatinine; CSRS = Connors' Parent Rating Scales; DEHP = di(2-ethylhexyl)phthalate; ETS = environmental tobacco smoke; GIQ = Gender Identity Questionnaire; GM = geometric mean; HOME = Health Outcomes and Measures of the Environment; INMA = Infancia y Medio Ambiente; IQ = intelligence quotient; IQR = interquartile range; IRR = incidence rate ratio; LOD = limit of detection; max = maximum; MDI = Mental Development Index; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; MSCA = McCarthy Scales of Children's Abilities; NICU = neonatal intensive care unit; NNNS = NICU Network Neurobehavioral Scale; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon; PDI = Psychomotor Development Index; PPPSI = Playmate and Play Style Preferences Structured Interview; PSAI = pres-School Activities Inventory; SDQ = Strengths and Difficulties Questionnaire; SG = specific gravity; SG-adj = specific gravity adjusted; TMICS = Taiwan Maternal and Infant Cohort Study; WISC = Wechsler Intelligence Scale for Children; WWPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised

cohorts in which prenatal exposure was assessed using maternal urine samples during pregnancy. Both studies were small (137 children in New York and 175 children in Ohio), limiting their power to detect an effect on autism-related behaviors.

The Social Responsiveness Scale (SRS), a validated scale for autistic behaviors, in which a higher score reflects social impairment related to the autism spectrum, is used to assess children's behaviors. In a New York study (Miodovnik et al. 2011), maternal urinary levels of DEHP metabolites measured between 25 and 40 weeks of pregnancy were not associated with scores on the SRS at ages 7–9 years (n=137 children). All regression coefficients adjusted for covariates showed weak positive associations (0.46–0.83) for the total score as well as all subscale scores. In an Ohio study (Braun et al. 2014), when SRS total T-scores were obtained in children 4–5 years old, the regression coefficients between SRS scores and maternal urinary metabolite levels were positive for MEHP and MECPP, whereas MEHHP was not (note that this analysis only used the sensitive covariates in adjustment). Other risk factors (e.g., birth weight; gestational diabetes, depression; Apgar score, birth order; Jeddi et al. 2016) were not considered in either study.

Two cohort studies evaluated potential associations between gender-related play in children and maternal urinary DEHP metabolite levels (Table 2-15). Swan et al. (2010) evaluated whether prenatal DEHP exposure altered the nature of children's play behaviors. In a group of 145 children (74 boys and 71 girls, on average 5 years of age) who were members of a multicenter U.S. birth cohort, prenatal maternal urinary metabolite levels were associated with reduced scores on the Pre-School Activities Inventory (PSAI), indicative of decreased masculine play activities, among boys. In contrast, the U.S. Health Outcomes and Measures of the Environment (HOME) birth cohort did not observe associations between maternal urinary metabolite levels and scores on the Gender Identity Questionnaire (GIQ) and the Playmate and Play Style Preferences Structured Interview (PPSI) measures of gender-related play in 227 children (101 boys and 126 girls, 8 years old) (Percy et al. 2016). Results from these studies are difficult to compare, primarily due to use of different metrics and different ages at analysis.

Animal Studies—Neurodevelopment. One inhalation developmental study in Wistar rats evaluated neurodevelopment in the offspring of females exposed to up to 21 ppm for 6 hours/day from GD 6 to 15 (Merkle et al. 1988). Newborn rats did not show any evidence of altered neurological development in the righting test on PND 6, gripping reflex on PND 13, pupillary reflex on PND 20, or hearing test on PND 21.

In oral developmental studies, neurobehavioral changes have been observed following gestational or gestational plus lactational exposure to DEHP. Impaired performance on the learned avoidance test was observed in PND 30 female offspring of Long-Evans rat dams exposed to 30 mg/kg/day during gestation and lactation; this was not observed in female offspring after maternal exposure to 3 mg/kg/day or in male offspring after maternal doses up to 30 mg/kg/day (Arcadi et al. 1998). The study authors reported that it was unclear whether the observed neurobehavioral effects were due to learning and memory deficits, muscle weakness, impaired motor coordination (particularly of the hindlimbs), or alterations in motivation (fear) and attentional components. Locomotor activity measured during both light and dark cycles was significantly decreased by up to 40% in adult offspring of Sprague-Dawley rat dams exposed to 300 mg/kg/day from GD 14 to PND 0 (only dose tested) (Martinez-Arguelles et al. 2013). No other measures of neurobehavior were conducted. No changes in spontaneous locomotion were observed in offspring of CD-1 mouse dams exposed to doses up to 95 mg/kg/day from GD 0 to 17 (Price et al. 1988b).

Altered behavior has also been reported at 30 mg/kg/day following early postnatal exposure. In a series of experiments that evaluated anxiety-like behavior in Wistar rats using the elevated plus maze, male rats exposed to 30 mg/kg/day from PND 1 to 21 (via lactation) plus PNDs 22–45 or 22–60 (via drinking water) showed increased anxiety-like behavior (Carbone et al. 2013). Observed effects included fewer entries into the open and closed arms, less time in the open arms, and more time in the closed arms. No behavioral changes were observed in similarly exposed females. When direct exposure ceased at PND 30, altered behavior in the elevated plus maze was not observed in either sex (Carbone et al. 2013).

In a 2-generation study in Wistar rats evaluating doses up to approximately 1,088 mg/kg/day, F2 offspring were evaluated for neurological effects using FOB on PND 28 and water maze testing (for learning and memory) on PNDs 28 and 35 (Schilling et al. 2001). The only changes observed in the FOB were decreased grip strength and foot splay in high-dose animals; however, these effects were attributed to decreased body weights observed at this dose. No exposure-related changes were observed in the water maze. However, in a 1-generation study in CD-1 mice (4 weeks premating through PNW 9), a delayed surface righting reflex was observed at PND 4 and 7 in female F1 offspring at ≥20.62 mg/kg/day (lowest dose tested) and at PND 7 in male F1 offspring at ≥60.42 mg/kg/day (Tanaka 2002). No exposure-related changes were observed in negative geotaxis on PNDs 4 and 7, cliff avoidance on PND 7, swimming behavior on PNDs 4 and 14, olfactory orientation on PND 14, exploratory behavior on PNDs 21 and 56, or learning and memory in a multiple water T-maze on PND 49 at doses up to 180.77 mg/kg/day (Tanaka 2002).

Brain weights and the numbers of dopaminergic neurons were evaluated at PNWs 2, 4, and 6 in ICR mice exposed to 0 or 1 mg/kg/day from GD 8 to 17 (via dams) and PNDs 3–7 (direct exposure) (Tanida et al. 2009). Significant changes included 4 and 8% decreases in absolute and relative brain weights at PNW 6, respectively, and a 15% decrease in relative brain weight at 2 weeks. The numbers of tyrosine hydroxylase- and Fos-immunoreactive neurons were significantly decreased at PNWs 4 and 6, indicating a decrease in dopaminergic neurons (tyrosine hydroxylase is a marker for biosynthetic activity of dopamine; Fos is a marker of neuronal activation).

In nonhuman primates, no changes in brain weight occurred in sexually immature Cynomolgus monkeys exposed to 500 mg/kg/day for 14 days (Pugh et al. 2000). In Sprague-Dawley rats, no exposure-related changes in brain weights were observed at PND 1 or 21 in offspring following maternal doses up to 405 mg/kg/day from GD 6 to PND 21 (Andrade et al. 2006c; Grande et al. 2006). Similarly, no exposure-related changes were observed in F1 or F2 pup brain weight in a 2-generation study in Sprague-Dawley rats at doses up to 1,088 mg/kg/day (Schilling et al. 2001).

Mechanisms of Neurodevelopmental Toxicity. Several animal studies indicate that DEHP alters hippocampal structural and functional plasticity following pre-, peri-, and post-natal exposure. Sun et al. (2014b) reported evidence of altered hippocampal function (impaired memory and learning) and impaired structural plasticity (elevated levels of phosphorylated Tau with no increase in total Tau) in adult rat offspring following perinatal exposure to DEHP. In mice, impaired functional plasticity was suggested by inhibition of ERK1/2 phosphorylation in the hippocampus following perinatal DEHP exposure (Xu et al. 2015). Structural changes in the hippocampus have also been observed in juvenile rats following postnatal exposure to DEHP, including decreased axonal innervation, decreased cell density, decreased dendritic spine density, and reduced neurogenesis (Smith and Holahan 2014; Smith et al. 2011).

Disruption of calcium homeostasis may contribute to DEHP-mediated neurotoxicity. Neuronal degeneration has been associated with increased intracellular calcium levels, resulting in inhibition of cellular membrane Na+/K+-ATPase activity, in rats following intraperitoneal exposure to DEHP (Dhanya et al. 2003). DEHP also increased intracellular calcium levels in rat neurohypophysial nerve terminals and pheochromocytoma cells (Tully et al. 2000). Additionally, DEHP decreased calcium signaling mediated through the nicotinic acetylcholine receptor in human neuroblastoma cells (Kaun-Yu et al. 2004).

As discussed extensively in Section 2.9 (Hepatic), DEHP activation of PPARs is a key mechanistic event for hepatic toxicity (Kushman et al. 2013; Rusyn and Corton 2012). Neurodevelopmental toxicity may also be mediated by PPAR activation. In support, Lin et al. (2011) indicated that PPARγ overexpression induced by DEHP may result in apoptosis of undifferentiated neurons. PPAR activation may also contribute to observed changes in fetal lipid metabolome, including reduction in the overall lipid content and alterations in fatty acid composition of the fetal rat brain observed following exposure to DEHP during gestation (Xu et al. 2007, 2008).

Observed DEHP-moderated alterations in oxidative stress and inflammatory pathways (Ferguson et al. 2012, 2015, 2017; Wu et al. 2017) could potentially contribute to neurodevelopmental toxicity of DEHP; however, the potential role(s) of these pathways has not been specifically evaluated with regard to neurodevelopment.

Epidemiology Studies—Male Reproductive Development. Studies of DEHP-induced effects on the development of the male reproductive system in humans have examined relationships with cryptorchidism, hypospadias, hydrocele, and AGD in infants and children.

Swan (2008) reported an association between decreased probability of normal testicular descent at 1 year of age and MEHP levels in maternal urine (sampled at ~29 weeks of gestation) in a prospective study of 106 male infants in the United States. In a case-control study nested within two large birth cohorts in France, Chevrier et al. (2012) observed no increase in the risk of either hypospadias or cryptorchidism at birth associated with maternal urinary DEHP metabolites. Sathyanarayana et al. (2016b) also did not find an increased risk of hypospadias and cryptorchidism and first trimester maternal urinary DEHP metabolites in male infants from a large birth cohort from four medical centers. However, increased maternal urinary DEHP levels were associated with an increased risk of hydrocele or all male genital anomalies combined. Based on a systematic review of available epidemiological data, NAS (2017) concluded that data are inadequate to evaluate the potential association between fetal exposure to DEHP and hypospadias in humans.

Eleven epidemiological studies have investigated the association between reduced AGD in male infants and prenatal DEHP exposure in seven different birth cohorts. Table 2-16 displays the findings of these studies in which prenatal maternal urine samples were used as a biomarker of fetal exposure to DEHP and AGD was measured in infants at various ages between birth and 2 years of age. Associations between

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
Male AGD					
Wenzel et al. 2018, Cohort (United States [South Carolina])	171 male newborns from birth cohort of 193 white and 187 African-American pregnant women (mean maternal age 27.4 years), recruited from the Medical University of South Carolina between 2011 and 2014. Maternal urine sample collected in first trimester for all women (n=380) and again in second trimester for a subset of women (n=219); AGD measured within 48 hours of birth.	Linear regression adjusted for body weight percentile, maternal smoking, race, and education.; a second analysis stratified by race was conducted	Change in anopenile distance (mm) per natural log-increase in SG-adjusted maternal urinary metabolite		
			ΣDEHP	36.3–92.8 nmol/L	-0.93 (-1.96, 0.09)
			MEHP	1.7–5.3	-1.57 (-2.93, -0.20)*
			MEHHP	4.5–12.2	-0.84 (-2.04, 0.35)
			MEOHP	3.8–9.0	-0.99 (-2.29, 0.30)
			Change in anoscrotal distance (mm) per natural log-increase in SG-adjusted maternal urinary metabolite		
			ΣDEHP	36.3–92.8 nmol/L	0.01 (-0.89, 0.91)
			MEHP	1.7–5.3	-0.10 (-1.31, 1.11)
			MEHHP	4.5–12.2	0.04 (-1.00, 1.09)
			MEOHP	3.8–9.0	-0.48 (-1.79, 0.82)
			In the analyses stratified by race, larger (but still not significant, except for MEHP) coefficients were observed for African-American infants, but the interaction term for race x phthalates was not statistically significant.		
Adibi et al. 2015; Barrett et al. 2016; Martino-Andrade et al. 2016; Swan et al. 2015, Cohort (United States [Minnesota,	366 male newborns from birth cohort of 738 pregnant women in four states (TIDES; mean maternal age 31.1 years), recruited from prenatal clinics from 2010 to 2012. Maternal urine sample collected in first trimester; AGD measured shortly after birth. Swan et al. (2015) evaluated the same cohort and endpoints but without accounting for maternal race	Linear regression adjusted for infant age at exam, gestational age at birth, study center, weight-for-length z-score, specific gravity, time of day of urine collection, maternal age, maternal race, and maternal first	Change in anopenile distance (mm) per natural log-increase in maternal urinary metabolite		
			ΣDEHP	71.7 (65.6–78.3)[b] nmol/L	-1.35 (-2.65, -0.05)*
			MEHP	1.93 (1.76–2.11)[b]	-1.21 (-2.41, 0.00)*
			MEHHP	6.04 (5.49–6.64)[b]	-1.29 (-2.28, -0.29)*
			MEOHP	4.22 (3.84–4.63)[b]	-1.6 (-2.81, -0.38)*
			MECPP	8.12 (7.42–8.89)[b]	-0.94 (-2.26, 0.37)
			Change in anoscrotal distance (mm) per natural log-increase in maternal urinary metabolite		
			ΣDEHP	71.7 (65.6–78.3)[b] nmol/L	-1.26 (-2.38, -0.15)*

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
California, New York, Washington])	and prenatal stress. Martino-Andrade et al. (2016) evaluated a subset of this cohort that had maternal urine samples for first, second, and third trimesters. Adibi et al. (2015) evaluated the same endpoint for a subset of the cohort (mothers with hCG measurements).	trimester life event stress	MEHP	1.93 (1.76–2.11)[b]	-1.14 (-2.18, -0.11)*
			MEHHP	6.04 (5.49–6.64)[b]	-1.47 (-2.62, -0.31)*
			MEOHP	4.22 (3.84–4.63)[b]	-1.44 (-2.48, -0.4)*
			MECPP	8.12 (7.42–8.89)[b]	-0.97 (-2.09, 0.16)
			Martino-Andrade et al. (2016) reported negative associations between AGD in male infants and maternal urinary metabolites in the first trimester, but not second or third trimester.		
Jensen et al. 2016, Cohort (Denmark)	273 male infants (3 months old) from Odense Child Cohort; pregnant women recruited between 8 and 16 weeks of gestation; maternal urine sample collected at 26–30 weeks of gestation; AGD measured in offspring at 3 months of age.	Multivariate linear regression adjusted for postconceptional age (sum of gestational age at birth and age at AGD measurement), and weight-for-age z-score	Change in anopenile distance (mm) between highest and lowest quartiles in osmolality-adjusted maternal urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	11.4–36.1 (molar sum expressed as excreted DEHP)	-0.45 (-2.56, 1.66)
			Change in anoscrotal distance (mm) between highest and lowest quartiles in osmolality-adjusted maternal urinary metabolite concentration		
			ΣDEHP	11.4–36.1 (molar sum expressed as excreted DEHP)	-1.16 (-3.08, 0.77)
			MEHP	0.4–2.3 (osmolality-adjusted)	NR
			MEHHP	2.4–9.1	NR
			MEOHP	2.2–7.1	NR
			MECPP	2.7–8.7	NR
			Sum DEHP metabolite concentration in 1st quartile: LOD–13.9 ng/mL; 4th quartile: ≥34 ng/mL		

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
Bornehag et al. 2015, Cohort (Sweden)	196 male infants from SELMA birth cohort (n=2,000 mother-child pairs recruited during 10th week of gestation), born between August 2009 and November 2010. Maternal urine measured at recruitment (9–11 weeks of gestation); AGD measured at mean age 20.8 months.	Linear regression, adjusted for infant age, gestational week of urine sampling, weight-for-age percentile, and creatinine	Change in anopenile distance (mm) per log-unit increase in maternal urinary metabolite		
			ΣDEHP	84.56–220.71 nmol/L	-1.39 (-4.49, 1.70)
			MEHP	1.91–5.86	-1.74 (-4.43, 0.95)
			MEHHP	8.69–22.85	-1.5 (-4.5, 1.49)
			MEOHP	5.67–15.60	-1.25 (-4.19, 1.70)
			MECPP	8.00–22.50	-0.64 (-3.69, 2.40)
			Increase in anoscrotal distance (mm) per log-unit increase in maternal urinary metabolite		
			ΣDEHP	84.56–220.71 nmol/L	-1.16 (-4.01, 1.68)
			MEHP	1.91–5.86	-1.28 (-3.74, 1.17)
			MEHHP	8.69–22.85	-1.24 (-3.99, 1.51)
			MEOHP	5.67–15.60	-0.77 (-3.48, 1.94)
			MECPP	8.00–22.50	-0.89 (-3.69, 1.95)
			In analyses using categorized AGD values (by quartile), the odds of infant with AGD <25th percentile was increased with log-transformed DEHP metabolite levels in maternal urine (ORs 1.47–1.82) but the increases were not statistically significant.		

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
Bustamante-Montes et al. 2013, Cohort (Mexico)	73 male infants from birth cohort (pregnant women >18 years of age, mean age 29.5 years, recruited in last trimester of pregnancy at single hospital). Maternal urine samples collected at recruitment; AGD measured 24–48 hours after birth.	Linear regression adjusted for creatinine and supine length at birth	Association between anoscrotal distance (mm) and maternal urinary metabolite level		
			MEHP	0.4–19.5	-0.0049 (NR)
			Association between distance from anus to posterior base of penis (mm) and maternal urinary metabolite level		
			MEHP	0.4–19.5	-0.0733 (NR)
			Association between distance from anus to posterior base of penis (mm) and maternal urinary metabolite level		
			MEHP	0.4–19.5	-0.0252 (NR)
Suzuki et al. 2012, Cohort (Japan)	111 male infants from a birth cohort of 224 mother-infant pairs who delivered at the Central Hospital of the Defense Force in Tokyo. Maternal urine samples collected at mean 29 weeks of gestation (range 9–40 weeks). AGD measured at birth.	Multiple linear regression adjusted for phthalate metabolite, maternal partner smoking, gestational week, birth order, maternal age, and log-transformed maternal urinary isoflavone concentrations	Change in body-weight corrected distance from anus to anterior genitalia (mm/kg) per log-unit increase in SG-adj maternal urinary metabolite Nonsmoking mothers (n=107)		
			MEHP	2.92–8.03	-0.246 (-0.435, -0.057)*
			MEHHP	6.79–14.4	NR
			MEOHP	6.92–15.2	NR
			Smoking and non-smoking mothers (n=111)		
			MEHP	2.92–8.03	-0.226 (-0.41, -0.042)*
			MEHHP	6.79–14.4	NR
			MEOHP	6.92–15.2	NR

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
Swan 2008, Cohort (United States [Minnesota, Missouri, California]) Swan et al. 2005 reported previous analysis of this cohort (smaller n)	106 male infants from birth cohort (Study for Future Families multi-center cohort). Maternal urine samples collected at mean gestation week 28.6; average infant age at AGD measurement was 12.8 months.	Mixed model regression adjusted for age and weight percentile	Association between distance from center of anus to cephalad base of penis (mm) and log-transformed maternal metabolite concentration		
			MEHP	Short AGD: 6.2 (median) Intermediate AGD: 2.9 Long AGD: 2.3	-3.503* (NR)
			MEHHP	Short AGD: 19.8 Intermediate AGD: 10.0 Long AGD: 8.2	-4.977* (NR)
			MEOHP	Short AGD: 21.3 Intermediate AGD: 11.7 Long AGD: 7.3	-5.126* (NR)
			MECPP	NA	NA
Hydrocele, hypospadias, and cryptorchidism					
Sathyanarayana et al. 2016b Cohort (United States [Minnesota, California, New York, Washington])	371 male newborns from birth cohort of pregnant women in four states (TIDES), recruited at 2010–2012. Maternal urine sample collected in first trimester; genital anatomical anomalies evaluated during physical exam at birth. In total, 37/371 male infants had a genital anomaly (5 cryptorchidism, 30 hydrocele, 3 hypospadias, and 4 with multiple anomalies).	Logistic regression adjusted for study center, maternal age, birth weight, and age at exam	Risk of male genital anomaly per log-unit increase in SG-adjusted maternal urinary metabolite concentration (µg/L)		
			ΣDEHP	14.86–38.80 nmol/L	OR 2.54 (1.09, 5.92)*
			MEHP	1.28–3.63	OR 2.49 (1.13, 5.50)*
			MEHHP	3.76–11.24	OR 2.52 (1.16, 5.46)*
			MEOHP	2.54–7.25	OR 2.49 (1.11, 5.58)*
			MECPP	6.42–16.21	OR 2.34 (0.96, 5.69)
			Risk of hydrocele per log-unit increase in SG-adjusted maternal urinary metabolite concentration (µg/L)		
			ΣDEHP	14.86–38.80 nmol/L	OR 3.01 (1.19, 7.62)*
			MEHP	1.28–3.63	OR 3.13 (1.31, 7.48)*
			MEHHP	3.76–11.24	OR 3.17 (1.35, 7.74)*
			MEOHP	2.54–7.25	OR 3.17 (1.30, 7.73)*

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
			MECPP	6.42–16.21	OR 2.52 (0.94, 6.77)
			Risk of hypospadias or cryptorchidism per log-unit increase in SG-adjusted maternal urinary metabolite concentration (µg/L)		
			ΣDEHP	14.86–38.80 nmol/L	OR 0.88 (0.09, 8.44)
			MEHP	1.28–3.63	OR 0.74 (0.09, 6.10)
			MEHHP	3.76–11.24	OR 0.77 (0.11, 5.44)
			MEOHP	2.54–7.25	OR 0.60 (0.07, 5.13)
			MECPP	6.42–16.21	OR 1.23 (0.13, 11.46)
			When evaluated by quartile of log-transformed SG-adjusted urinary metabolite concentrations, only the third quartile of MEHHP showed a statistically significant increase in odds for any male reproductive anomaly, OR: 3.89 (1.16, 13.04) (graphically reported data).		
Chevrier et al. 2012, Nested case-control (France) Exposure concentrations reported in Philippat et al. 2012	21 cases of hypospadias, 50 cases of cryptorchidism, and (for each) 3:1 control male infants matched on residence, and gestational age, day, and date of urine collection; members of two birth cohorts (EDEN and PELAGIE) of pregnant women recruited before the 28th week of pregnancy. Maternal urine samples collected between 6 and 19 weeks of gestation in PELAGIE cohort and between 24 and 30 weeks in the EDEN cohort. Case status determined at birth.	Conditional logistic regression, adjusted for maternal age, parity, educational level, gestational duration, and creatinine	OR for hypospadias comparing highest and lowest tertiles of maternal urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	NR	0.21 (0.04, 2.1)
			OR for cryptorchidism comparing highest and lowest tertiles of maternal urinary metabolite concentration		
			ΣDEHP	NR	0.6 (0.2, 1.7)
			MEHP	0.8–40.7 (5th–95th percentile)	NR
			MEHHP	4.6–147.0	NR
			MEOHP	3.6–112.0	NR
			MECPP	11.6–183.0	NR

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
Swan 2008, Cohort (United States [Minnesota, Missouri, California]) Swan et al. 2005 reported previous analysis of this cohort (smaller n)	106 male infants from birth cohort (Study for Future Families multi-center cohort). Maternal urine samples collected at mean gestation week 28.6; average infant age at testicular descent determination was 12.8 months.	Logistic regression adjusted for age and weight percentile	Association between probability of normal testicular descent and log-transformed maternal metabolite concentration		
			ΣDEHP	NR	-1.447 (NR)
			MEHP	Short AGD: 6.2 (median) Intermediate AGD: 2.9 Long AGD: 2.3	-1.258* (NR)
			MEHHP	Short AGD: 19.8 Intermediate AGD: 10.0 Long AGD: 8.2	-1.417 (NR)
			MEOHP	Short AGD: 21.3 Intermediate AGD: 11.7 Long AGD: 7.3	-1.350 (NR)
Female AGD					
Wenzel et al. 2018, Cohort (United States [South Carolina])	128 female newborns from birth cohort of 193 white and 187 African American pregnant women (mean maternal age 27.4 years), recruited from the Medical University of South Carolina between 2011 and 2014. Maternal urine sample collected in first trimester for all women and again in second trimester for 219 women; AGD measured within 48 hours of birth.	Linear regression adjusted for body weight percentile, maternal age, smoking, race, and education; a second analysis stratified by race was conducted	Change in anoclitoral distance (mm) per natural log-increase in SG-adjusted maternal urinary metabolite		
			ΣDEHP	36.3–92.8 nmol/L	-0.71 (-1.69, 0.27)
			MEHP	1.7–5.3	-1.17 (-2.60, 0.26)
			MEHHP	4.5–12.2	-0.94 (-2.18, 0.29)
			MEOHP	3.8–9.0	-0.86 (-2.30, 0.58)
			Change in anofourchette distance (mm) per natural log-increase in SG-adjusted maternal urinary metabolite		
			ΣDEHP	36.3–92.8 nmol/L	-0.38 (-0.99, 0.23)
			MEHP	1.7–5.3	-0.69 (-1.58, 0.20)
			MEHHP	4.5–12.2	-0.48 (-1.24, 0.29)
			MEOHP	3.8–9.0	-0.49 (-1.39, 0.40)

Table 2-16. Summary of Epidemiological Data on Reproductive Tract Development in Male and Female Infants

Reference, study type, and location	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Regression coefficient (β) (95% CI), unless otherwise indicated[a]
			Similar results were observed in the analysis stratified by race; the interaction term for race x phthalates was not statistically significant.		
Adibi et al. 2015; Barrett et al. 2016; Swan et al. 2015, Cohort (United States [Minnesota, California, New York, Washington])	373 female newborns from birth cohort of 738 pregnant women in four states (TIDES; mean maternal age 31.1 years), recruited from prenatal clinics from 2010 to 2012. Maternal urine sample collected in first trimester; AGD measured shortly after birth. Swan et al. (2015) evaluated the same cohort and endpoints but without accounting for maternal race and prenatal stress. Adibi et al. (2015) evaluated the same endpoint for a subset of the cohort (mothers with hCG measurements).	Linear regression adjusted for infant age at exam, gestational age at birth, study center, weight-for-length z-score, specific gravity, time of day of urine collection, maternal age, maternal race, and maternal first trimester life event stress	Change in anoclitoral distance (mm) per natural log-increase in urinary metabolite		
			ΣDEHP	71.7 (65.6–78.3)[b] nmol/L	-0.34 (-1.4, 0.72)
			MEHP	1.93 (1.76–2.11)[b]	-0.15 (-1.07, 0.78)
			MEHHP	6.04 (5.49–6.64)[b]	-0.3 (-1.29, 0.68)
			MEOHP	4.22 (3.84–4.63)[b]	0.01 (-1.01, 1.02)
			MECPP	8.12 (7.42–8.89)[b]	-0.44 (-1.41, 0.54)
			Change in anofourchette distance (mm) per natural log-increase in urinary metabolite		
			ΣDEHP	71.7 (65.6–78.3)[b] nmol/L	0.29 (-0.54, 1.13)
			MEHP	1.93 (1.76–2.11)[b]	0.05 (-0.68, 0.78)
			MEHHP	6.04 (5.49–6.64)[b]	0.27 (-0.51, 1.04)
			MEOHP	4.22 (3.84–4.63)[b]	0.33 (-0.47, 1.13)
			MECPP	8.12 (7.42–8.89)[b]	0.26 (-0.51, 1.03)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.
[b]GM (95% CI).

ΣDEHP = sum DEHP metabolites; AGD = anogenital distance; CI = confidence interval; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; hCG = human chorionic gonadotropin; IQR = interquartile range; LOD = limit of detection; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NA = not applicable; NR = not reported; OR = odds ratio; SELMA = Swedish Environmental Longitudinal Mother and child Asthma and Allergy; SG-adj = specific gravity adjusted; TIDES = The Infant Development and Environment Study

decreased AGD and DEHP metabolite levels in maternal urine have been reported in four birth cohorts (Barrett et al. 2016; Martino-Andrade et al. 2016; Suzuki et al. 2012; Swan 2008; Swan et al. 2015; Wenzel et al. 2018). In addition, the effect estimates in the remaining three cohorts (Bornehag et al. 2015; Bustamante-Montes et al. 2013; Jensen et al. 2016) also suggested a negative association between AGD (both anoscrotal and anopenile distances) in male infants and prenatal DEHP exposure. This finding was consistent across cohort studies in the United States, Scandinavia, Mexico, and Japan, and across ages from birth to 20 months.

A meta-analysis of five epidemiological studies (Bornehag et al. 2015; Bustamante-Montes et al. 2013; Jensen et al. 2016; Swan 2008; Swan et al. 2015) reported an approximate 4% decrease in AGD per log-increase in maternal DEHP urinary metabolite concentration (Summary estimate of -4.07, 95% CI: -6.49, -1.66) (NAS 2017). Based on this meta-analysis and a systematic review of available epidemiological data, NAS (2017) concluded that there is a moderate level of evidence that fetal exposure to DEHP is associated with a reduction in AGD in humans; confidence in the body of evidence was also moderate.

In studies examining the effects of DEHP exposure on infant penile dimensions (Bustamante-Montes et al. 2013; Jensen et al. 2016; Martino-Andrade et al. 2016; Swan 2008), results were not consistent. An association (β -0.782; p=0.005) between decreased penile width and log-transformed prenatal MEHP (but not other metabolites) was seen in 1-year-old boys (n=106) in the United States (Swan 2008). However, no association between penile width and DEHP metabolites was observed in newborns (n=73) in Mexico (Bustamante-Montes et al. 2013) or infants (n=273) at 3 months of age (Jensen et al. 2016). Bustamante-Montes et al. (2013) reported an association between reduced penile length in newborn boys and maternal MEHP levels (β -0.2604; p=0.05); however, no other studies are available to corroborate this finding.

Two studies (Su et al. 2015; Ferguson et al. 2014c) examined the relationship between timing of puberty in boys and maternal DEHP exposure, with inconsistent results. In 115 boys 8–14 years old, Ferguson et al. (2014c) observed a decrease in the OR (0.12; p=0.05) for presence of pubic hair with an interquartile range increase in prenatal MEHHP, but the OR for development of genitalia was not associated with prenatal exposure levels. Testicular volume was not associated with DEHP exposure measures in this study or in the study by Su et al. (2015) of 122 boys that were 8 and 11 years old.

In a cross-sectional study using NHANES (2011–-2012) data, Meeker and Ferguson (2014) observed decreased serum testosterone associated with increased urinary levels of DEHP metabolites in a group of

134 boys ages 6–12 years (percent change -29.3; 95% CI -46.8, -6.10 for ∑DEHP). No other data on serum testosterone in prepubertal boys were located.

Animal Studies—Male Reproductive Development. Only one study evaluated male reproductive development following inhalation exposure. Kurahashi et al. (2005) reported a 2- to 4-fold increase in plasma testosterone in weanling male Wistar rats intermittently exposed to DEHP at concentrations of 0.3–1.6 ppm for 4 or 8 weeks immediately following weaning. No exposure-related changes were observed in serum LH or follicle stimulating hormone (FSH). Though increased relative seminal vesicle weights were observed after exposure for 8 weeks, no histopathological lesions in the testes were observed. Neither timing of sexual maturation nor sexual performance were evaluated.

In nonhuman primates, no changes in testes/epididymides weights or testicular histology occurred in sexually immature 2-year-old Cynomolgus monkeys that were treated with 500 mg DEHP/kg/day by gavage for 14 consecutive days (Pugh et al. 2000). Similarly, exposure to doses up to 2,500 mg/kg/day for 65 weeks from weaning at 3 months to sexual maturity at 18 months did not result in changes in serum testosterone, male reproductive organ weight or histology, or sperm parameters in marmoset monkeys (Tomonari et al. 2006).

Permanent reproductive tract malformations and lesions have been observed in rat offspring following gestational plus lactational exposure to DEHP at doses of 3 mg/kg/day or higher. In Wistar rats, an increased incidence of male offspring with mild external genital dysgenesis was observed following maternal exposure to DEHP at doses ≥3 mg/kg/day from GD 7 to PND 16 (lowest dose tested) (Christiansen et al. 2010). In addition, nipple retention was observed at ≥10 mg/kg/day and decreased seminiferous tubule diameter with fewer germ cells and focal Leydig cell hyperplasia occurred at ≥300 mg/kg/day (Christiansen et al. 2010). Testicular lesions were also observed at maternal doses ≥3 mg/kg/day in Long-Evans rat offspring exposed to DEHP during gestation and lactation (Arcadi et al. 1998). In Sprague-Dawley rats, when all reproductive malformations were pooled for analysis, a significant increase in malformed male offspring was observed at maternal exposure levels of ≥11 mg/kg/day during gestation and lactation (a subset of the offspring also received direct DEHP exposure on PNDs 18–64) (Gray et al. 2009). When malformations were evaluated separately, significant findings included abnormal testes histology at 33 and 300 mg/kg/day, malformed coagulating gland at ≥100 mg/kg/day, and permanent nipples and gross testicular and epididymal abnormalities at 300 mg/kg/day. In a systematic review of available rodent data evaluating hypospadias following oral *in*

utero exposure, NAS (2017) concluded that there is a moderate level of evidence that fetal exposure to DEHP is associated with hypospadias in rats; confidence in the body of evidence was also moderate.

Histopathological alterations were also observed in PND 1 and 22 male offspring of Sprague-Dawley rats exposed to doses ≥135 mg/kg/day from GD 6 to PND 21, but not ≤45 mg/kg/day; the changes included enlarged, bi- and multinucleated gonocytes; gonocyte degeneration; acute interstitial hemorrhage and loosening of connective tissue; reduced germ cell differentiation; and hyperemia (Andrade et al. 2006c). By adulthood, abnormal testicular histological findings were largely limited to grossly abnormal testes in male offspring at 405 mg/kg/day (3/20 "small" scrotal testes, 1/20 undescended testes), along with slight focal Leydig cell hyperplasia in 1/20 males and massive reduction of germ cell layers in 2/20 males at 405 mg/kg/day (Andrade et al. 2006a). However, the majority of seminiferous tubules were unaffected by treatment, and no major malformations were observed at maternal doses up to 405 mg/kg/day (although increased nipple retention was observed at this dose) (Andrade et al. 2006a, 2006c).

In gestational exposure-only studies, increased nipple retention on PND 13 and increased hypospadias and cryptorchidism on PND 63 were observed in Sprague-Dawley rats at 500 mg/kg/day, but not ≤100 mg/kg/day (Vo et al. 2009a). Increased nipple retention was also observed in F1 and F2 pups at ≥1,040 mg/kg/day, but not ≤380 mg/kg/day, in 2-generation studies in Wistar rats (Schilling et al. 1999, 2001). In mice, an increased incidence of hypospadias was observed in C57BL/6 mouse fetuses at GD 19 following maternal exposure to doses ≥100 mg/kg/day (lowest dose tested) from GD 12 to 17 (Liu et al. 2008). Decreased anterior urethra length in male fetuses was observed at ≥200 mg/kg/day.

Changes in fetal testicular histopathology were also observed following gestational exposure to DEHP. In Sprague-Dawley and Long-Evans rats, gestational exposure to maternal doses ≥10 mg/kg/day (lowest dose tested) resulted in Leydig cell clustering in fetal testes (Klinefelter et al. 2012; Lin et al. 2008, 2009). At maternal doses ≥100 mg/kg/day, dysgenic seminiferous cords were also observed. In Wistar rats, Leydig cell clustering was also observed in GD 21 offspring after maternal exposure to ≥100 mg/kg/day from GD 7 to 21, but not ≤30 mg/kg/day (Borch et al. 2006). Additional effects observed at maternal doses ≥100 mg/kg/day included multinucleated gonocytes, increased gonocyte number, and centralized gonocytes, and Sertoli cell vacuolization (Borch et al. 2006).

Alterations in male reproductive organ histology have also been reported in neonatal and weanling rats exposed directly to DEHP. Loss of spermatocytes and decreased number of Sertoli cells have been observed in Sprague-Dawley rats exposed to DEHP for 5 days during early postnatal development

(PNDs 6–10 or 14–18) or post-weaning (PNDs 21–25 or 42–46) at doses ≥1,000 mg/kg/day, but not ≤100 mg/kg/day; rats were sacrificed 24 hours after the final dose (Dostal et al. 1988). However, Li et al. (2000) reported altered morphology of germ cells (gonocytes were enlarged and multinucleated) and reduced Sertoli cell proliferation in male Sprague-Dawley rats 24 hours after a single exposure to DEHP on PND 3 at ≥100 mg/kg/day, but not 20 mg/kg/day. In weanling Sprague-Dawley rats, exposure to ≥10 mg/kg/day from PND 21 to 35 resulted in degeneration of the Leydig cells and "disorders of germ cells" in the testes of young Sprague-Dawley rats (Vo et al. 2009b). Dilatation of the tubular lumen and stratification of germ cells was also observed at ≥100 mg/kg/day. Noriega et al. (2009) also reported hypospermia and testicular and epididymal degeneration in weanling Sprague-Dawley rats, but only at exposure levels ≥300 mg/kg/day, and not ≤100 mg/kg/day. These effects were only observed in similarly exposed Long-Evans rats at 900 mg/kg/day (Noriega et al. 2009). In Wistar weanling rats, however, testicular germ cell damage was observed after exposure to 250 mg/kg/day on PNDs 25–54, but not doses ≤100 mg/kg/day (Parmar et al. 1995). In other studies of weanling rats, no changes in testicular or seminal vesicle histology were observed in Long-Evans rats exposed to doses up to 200 mg/kg/day for 14–28 days (Akingbemi et al. 2001).

Numerous studies have also reported decreased testicular weights following gestational and/or lactational exposure to DEHP, although results were not consistent between species, strains, and studies. In Long-Evans rats, significant decreases in testes weight were observed in offspring following maternal exposure to doses ≥100 mg/kg/day during gestation (Lin et al. 2008) or ≥3 mg/kg/day during gestation and lactation (Arcadi et al. 1998). Some gestational and lactational studies in Sprague-Dawley rats reported no changes in offspring testes weights at doses up to 405 mg/kg/day (Andrade et al. 2006a, 2006c; Kobayashi et al. 2006), while Gray et al. (2009) reported significant decreases at 300 mg/kg/day, but not 33 mg/kg/day. Following postnatal exposure in Sprague-Dawley rats for 5 days starting on PND 6, 14, 21, or 42, doses ≥1,000 mg/kg/day resulted in decreased testes weights, but doses ≤100 mg/kg/day did not (Dostal et al. 1988). When Christiansen et al. (2010) conducted two separate experiments in Wistar rats, decreased testes weight was observed in one study at maternal doses ≥10 mg/kg/day, but not at doses up to 100 mg/kg/day in the second study. Decreased testes weight was observed in Wistar rat offspring at 30 mg/kg/day in two additional gestation plus lactation exposure studies (Carbone et al. 2010, 2012), but not at doses up to 500 mg/kg/day in another (Dalsenter et al. 2006). No changes in testicular weights were observed in F1 or F2 weanlings in a 2-generation study in Wistar rats at doses up to 1,088 mg/kg/day (Schilling et al. 2001). Only two mouse developmental studies evaluated testicular weight in offspring. Pocar et al. (2012) observed that testicular weights were significantly decreased by 13% in CD-1 mouse offspring following maternal exposure to 0.05 mg/kg/day during gestation and

lactation, but were comparable to controls at 5 mg/kg/day (highest dose evaluated). Following gestation-only exposure, testicular weights were decreased in CD-1 mouse offspring at maternal doses ≥50 mg/kg/day (Do et al. 2012).

Decreased organ weights have also been observed in other male reproductive organs following gestational and/or lactational exposure. Decreased organ weights were observed in offspring of rats and mice exposed to DEHP during gestation and lactation, including ventral prostate and LABC muscles in Wistar rats at ≥10 mg/kg/day (Christiansen et al. 2010); ventral prostate and seminal vesicles in Wistar rats at 500 mg/kg/day (Dalsenter et al. 2006); glans penis, ventral prostate, seminal vesicles, LABC muscles, Cowper's glands, and epididymides at 300 mg/kg/day (Gray et al. 2009); and seminal vesicles at ≥0.05 mg/kg/day (Pocar et al. 2012). In other studies, no changes in other male reproductive organs were observed in Sprague-Dawley rats exposed during gestation and lactation to maternal doses up to 405 mg/kg/day (Andrade et al. 2006a, 2006c; Kobayashi et al. 2006) or in F1 or F2 weanlings in a 2-generation study in Wistar rats at doses up to 1,088 mg/kg/day (Schilling et al. 2001).

Altered male reproductive organ weights have also been reported in young rats following exposure to DEHP after weaning. The lowest level observed for decreased testes weight was 10 mg/kg/day when Sprague-Dawley rats were exposed for 15 days post-weaning (Vo et al. 2009b). Other studies indicated decreased reproductive organ weight in young Sprague-Dawley, Long-Evans, or Wistar rats exposed to ≥100 mg/kg/day for 14–76 days post-weaning (Noriega et al. 2009; Parmar et al. 1995). In other Long-Evans rat studies, decreased testicular weights were observed from exposure to 500 mg/kg/day from PND 21 to 34, but not after exposure to doses ≤200 mg/kg/day for 28–100 days starting at PND 21 or 35 (Akingbemi et al. 2001, 2004; Ge et al. 2007). Another study in young Long-Evans rats showed a non-monotonic response to DEHP exposure from PND 21 to 48, with increased weight of the seminal vesicles at 10 mg/kg/day, but decreased weight of the seminal vesicles, prostate, and testes at 750 mg/kg/day (Ge et al. 2007). The significance of this non-monotonic response is unclear.

Decreased AGD, suggesting demasculinization, has been reported in male offspring following exposure to DEHP. AGD was significantly decreased in PND 0 male offspring of Long-Evans rat dams exposed to DEHP from GD 2 to 20 at 750 mg/kg/day, but not doses up to 100 mg/kg/day (Lin et al. 2008). Similarly, AGD was significantly decreased in PND 21 male offspring of Long-Evans rat dams exposed to DEHP from GD 12.5 to PND 21.5 at 750 mg/kg/day, but not doses up to 10 mg/kg/day (Lin et al. 2009). In Sprague-Dawley rats, AGD was significantly decreased at PND 2 following gestational and lactational exposure to ≥300 mg/kg/day, but not at doses up to 135 mg/kg/day (Andrade et al. 2006c;

Gray et al. 2009). Decreased AGD was observed in PND 63 male offspring of Sprague-Dawley rat dams exposed to DEHP from GD 11 to 21 at ≥100 mg/kg/day. In 2-generation studies in Wistar rats, both AGD and the anogenital index (AGI; corrected for body weight) were significantly decreased on PND 1 or 2 in both F1 and F2 males at doses ≥340 mg/kg/day in one study (Schilling et al. 2001), but not until doses of 1,040 mg/kg/day in another (Schilling et al. 1999). In a 3-generation study in Wistar rats, AGD, but not AGI, was decreased in F1, F2, and F3 male pups on PND 1 at 447 mg/kg/day, but not ≤57 mg/kg/day (Blystone et al. 2010; NTP 2005). However, a gestation/lactation exposure study in Wistar rats reported decreased AGD in male pups at PND 1 at doses ≥10 mg/kg/day (Christiansen et al. 2010). Decreased AGD was observed in C57BL/6 mouse fetuses at GD 19 following maternal exposure to doses ≥100 mg/kg/day (lowest dose tested) from GD 12 to 17 (Liu et al. 2008). However, no exposure-related changes in AGD were observed in CD-1 fetuses on GD 18 following maternal exposure to doses up to 500 mg/kg/day from GD 9 to 18 (Do et al. 2012). No changes in PND 42 AGD were observed in CD-1 mice following maternal exposure to low doses of DEHP (≤5 mg/kg/day) during gestation and lactation (Pocar et al. 2012).

A meta-analysis of 13 gestational oral studies in rats reported a statistically significant overall effect reduction in AGD with DEHP exposure (-3.96; 95% CI -5.07, -2.85) (NAS 2017). A meta-analysis of three gestational oral studies in mice was also conducted, but an overall significant effect was not observed. However, linear regression analyses showed statistically significant decreases in AGD of ~2% per unit DEHP dose or log-transformed dose in both rats and mice. BMD_5 values of 270 and 110 mg/kg/day were identified for rats and mice, respectively. Based on these meta-analyses and a systematic review of available rodent data evaluating AGD following oral in utero exposure, NAS (2017) concluded that there is evidence that fetal exposure to DEHP is associated with a reduction in AGD in rats; confidence in the body of evidence was high.

In multigenerational studies in rats, delayed preputial separation (PPS) was observed in male offspring exposed to doses ≥447 mg/kg/day, but not ≤380 mg/kg/day (Blystone et al. 2010; NTP 2005; Schilling et al. 1999, 2001). Delayed puberty may be due to developmental exposure, peripubertal exposure, or a combination of the two; it may also be secondary to decreased body weights observed at the same doses. However, PPS was also significantly delayed in male offspring of Sprague-Dawley rats exposed to doses ≥15 mg/kg/day from GD 6 to PND 21 in the absence of decreased body weights (Andrade et al. 2006c). Delayed PPS was also reported in Sprague-Dawley and Long-Evans rats exposed to ≥300 mg/kg/day for 22–76 days immediately following weaning, but not ≤100 mg/kg/day (Noriega et al. 2009). Another study in young Long-Evans rats showed a non-monotonic response to DEHP exposure from PND 21 to

48, with decreased age of PPS at 10 mg/kg/day, but increased age of PPS at 750 mg/kg/day (Ge et al. 2007). The significance of this non-monotonic response is unclear. Other studies did not observe any exposure-related changes in the age at PPS in male offspring following maternal exposure to doses up to 500 mg/kg/day during gestation and lactation (Dalsenter et al. 2006; Gray et al. 2009). A subset of the offspring also received direct DEHP exposure from PND 18 to 64; PPS was not delayed in these rats either (Gray et al. 2009).

In a 2-generation study in Wistar rats, loss of spermatocytes was observed in 2/10 weanling F1 rats at 360 mg/kg/day and 7/9 weanling F1 rats at 1,040 mg/kg/day; no changes in spermatocytes were observed at 130 mg/kg/day (Schilling et al. 1999). Changes in sperm parameters have also been observed in adult rat offspring following gestational exposure to doses ≥10 mg/kg/day (Vo et al. 2009a) and gestational plus lactational exposure to doses ≥3 mg/kg/day (Andrade et al. 2006a; Arcadi et al. 1998). Sperm effects included decreased sperm concentration, viability, and motility; decreased daily sperm production; and altered morphology (elongated or round spermatids). Whole sperm count was also decreased in adult rat offspring following gestational, lactational, and post-lactational exposure to DEHP at 300 mg/kg/day through PND 65, but not at doses ≤100 mg/kg/day (Gray et al. 2009). Sperm count and viability were decreased approximately 50 and 20%, respectively, in PND 42 offspring of CD-1 mouse dams exposed to 0.05 or 5 mg/kg/day during gestation and lactation (Pocar et al. 2012). Sperm from exposed offspring were capable of fertilizing unexposed oocytes *in vitro* (no change in cleavage rate); however, blastocyst rate was significantly reduced at maternal doses ≥0.05 mg/kg/day (Pocar et al. 2012). Consistent with these *in vitro* fertilization data, no changes in male mating behavior or fertility were observed in adult offspring of Sprague-Dawley rats exposed to DEHP at doses up to 405 mg/kg/day from GD 6 to PND 21 (Andrade et al. 2006a). Similarly, no change in reproductive performance was observed in CD-1 mouse offspring exposed to doses up to 95 mg/kg/day from GD 0 to 17 (Price et al. 1988b). At higher doses, sexual behavior was significantly altered in adult male offspring of Wistar rats exposed to 500 mg/kg/day during gestation and lactation, but not at doses ≤100 mg/kg/day (Dalsenter et al. 2006). Observed effects included decreased ejaculation, increased intromission latency, and increased numbers of intromissions until ejaculation. These alterations were accompanied by decreased sperm number and daily sperm production at puberty and adulthood (Dalsenter et al. 2006). No changes in sperm morphology were observed.

Decreased serum testosterone and LH were observed in GD 21 Sprague-Dawley rat offspring following maternal exposure to 500 mg/kg/day during gestation (Vo et al. 2009a) and in PND 15 Wistar rat offspring following maternal exposure to 30 mg/kg/day during gestation and lactation (Carbone et al.

2012). Serum testosterone was significantly decreased by >50% in PND 60 male offspring of Sprague-Dawley rat dams exposed to DEHP from GD 14 to PND 0 at doses ≥100 mg/kg/day (Culty et al. 2008; Martinez-Arguelles et al. 2011). No exposure-related changes were observed in serum estradiol in PND 60 male offspring at maternal doses up to 1,250 mg/kg/day (Culty et al. 2008; Martinez-Arguelles et al. 2011). Following gestational and lactational exposure, serum testosterone was significantly decreased by >30% in male PND 21 Long-Evans rats or adult Wistar rats at maternal doses ≥10 or 100 mg/kg/day, respectively (Dalsenter et al. 2006; Lin et al. 2009). No exposure-related changes in serum testosterone or estradiol were observed in adult male offspring following maternal exposure to doses up to 300 mg/kg/day during gestation and lactation in Sprague-Dawley rats (a subset of the offspring also received direct DEHP exposure from PND 18 to 64); serum hormone changes were not observed in these rats either (Gray et al. 2009). In Wistar rats, serum FSH was significantly decreased by 33% in PND 30 male offspring following maternal exposure to 30 mg/kg/day during gestation and lactation; this was not observed at 3 mg/kg/day (Carbone et al. 2010). No exposure-related changes in serum LH were observed at maternal doses up to 30 mg/kg/day (Carbone et al. 2010).

Observed alterations in male reproductive hormones following exposure to DEHP in weanlings are inconsistent. One study in weanling Long-Evans rats showed a non-monotonic response to DEHP exposure from PND 21 to 48, with increased serum testosterone at 10 mg/kg/day, but decreased serum testosterone at 750 mg/kg/day (Ge et al. 2007). The significance of this non-monotonic response is unclear without further study of the pituitary-testes axis. Similarly, serum LH was increased in Sprague-Dawley rats exposed to 900 mg/kg/day for 22, 42, or 76 days post-weaning, but decreased in weanling Sprague-Dawley rats exposed to 900 mg/kg/day for 35 days (Noriega et al. 2009). No exposure-related changes were observed in similarly exposed Long-Evans rats (Noriega et al. 2009). However, other studies in Long-Evans rats reported that exposure to gavage doses ≥10 mg/kg/day for 28–100 days starting at weaning resulted in increased serum LH and testosterone levels and decreased basal and LH-stimulated Leydig cell testosterone production (Akingbemi et al. 2001, 2004). Reduced testosterone production in Leydig cells was also observed following 14-day exposures to ≥10 or 100 mg/kg/day starting on PND 21 or 35, respectively, but no changes in serum hormone levels were observed (Akingbemi et al. 2001). In Sprague-Dawley rats, serum testosterone was significantly decreased following exposure to ≥10 mg/kg/day for 15 days immediately after weaning, but no changes in serum LH were observed at doses up to 500 mg/kg/day (Vo et al. 2009b).

Fetal serum testosterone was significantly elevated, compared with control, in CD-1 mouse offspring following maternal exposure to 0.0005, 0.005, and 0.5 mg/kg/day from GD 9 to 18; however, serum

testosterone in male fetuses at maternal doses of 50 and 500 mg/kg/day were comparable to control (Do et al. 2012). The biological relevance of the non-monotonic dose response relationship for fetal testosterone is also unclear without further study of the pituitary-testes axis.

Decreased levels of fetal testicular testosterone (FTT) were observed in offspring of Wistar rat dams exposed to 300 mg/kg/day from GD 7 to 21 (Borch et al. 2006). In Long-Evans rats exposed from GD 2 to 20, decreased FTT was observed at maternal doses of 10 mg/kg/day, but increased FTT was observed at maternal doses of 750 mg/kg/day (Lin et al. 2008). Intratesticular testosterone levels were not altered on PND 1 in Sprague-Dawley rats exposed from GD 6 to PND 1 to doses up to 405 mg/kg/day (Andrade et al. 2006c). In Sprague-Dawley weanling rats, testicular testosterone production was decreased following exposure to doses ≥300 mg/kg/day for 22–76 days post-weaning (Noriega et al. 2009). *Ex vivo* FTT production was decreased by >20% following maternal exposure to DEHP for 5–15 days during gestation at doses ≥50 mg/kg/day in Sprague-Dawley rats (lowest dose tested) and ≥300 mg/kg/day in Wistar rats (Borch et al. 2006; Furr et al. 2014; Hannas et al. 2011; Howdeshell et al. 2008; Klinefelter et al. 2012; Saillenfait et al. 2013). FTT production was decreased by >90% at 900 mg/kg/day. No changes in FTT production were observed in GD 18 fetuses of CD-1 mouse dams exposed to doses up to 500 mg/kg/day from GD 9 to 18 (Do et al. 2012).

A meta-analysis of seven gestational oral studies in rats reported a statistically significant overall effect for reduced fetal testicular testosterone and DEHP exposure (-110.14; 95% CI -136.73, -83.54) (NAS 2017). Linear regression analyses also showed statistically significant associations. A BMD_5 value of 15 mg/kg/day was calculated. In addition, an alternate BMD_{40} value of 160 mg/kg/day was calculated. An alternate of benchmark response (BMR) of 40% was selected because this level is assumed to be biologically relevant based on previous studies showing reproductive tract malformations in male rats when fetal testosterone production was reduced by about 40%. Based on this meta-analysis and a systematic review of available rodent data evaluating fetal testosterone levels following oral *in utero* exposure, NAS (2017) concluded that there is a high level of evidence that fetal exposure to DEHP is associated with a reduction in fetal testosterone in rats; confidence in the body of evidence was high.

Altered hormone levels may be due to Leydig cell toxicity. Sex hormone production (testosterone, estradiol) by Leydig cells, measured *ex vivo*, was significantly altered in cells harvested from young rats exposed at doses ≥10 mg/kg/day for 14–100 days after weaning. Across time, the direction of alteration (reduced or increased) for hormone production was not consistent, suggesting different potential reproductive effects dependent on exposure timing (e.g., PND 21 or 62) (Akingbemi et al. 2001, 2004).

Inhibition of steroidogenic enzyme activities was also observed in rats exposed for 28 days, including reduced 17β-hydroxysteroid dehydrogenase (17β-HSD) at ≥10 mg/kg/day, reduced P450scc and 3β-HSD at ≥100 mg/kg/day, and reduced P45017α at 200 mg/kg/day (Akingbemi et al. 2001). In another study, young rats exposed from PND 21 to 34 also showed decreased testosterone production by Leydig cells cultured *in vitro,* but only in cells from animals exposed to 500 mg/kg/day, not 10 mg/kg/day (Ge et al. 2007).

Mechanisms of Altered Male Reproductive Development. The anti-androgenic effects of DEHP do not appear to be mediated by the androgen receptor (AR), because neither DEHP nor MEHP bind the human AR *in vitro* (Parks et al. 2000). Alterations in the hypothalamic-pituitary axis may underlie some of the observed effects in the developing male reproductive system. Carbone et al. (2010, 2012) reported decreased aspartate and increased GABA in the hypothalamus of male offspring of Wistar rats exposed to 30 mg/kg/day during gestation and lactation. These changes could account for observed decreases in serum testosterone, LH, and FSH levels (via decreased release of gonadotropin releasing hormone) in male offspring at this exposure level.

Numerous studies have reported alterations in gene expression related to testicular functions including testicular descent (insulin-like factor 3 or *Insl3*), cholesterol transport (*Scarb1*, *Star*), steroid biosynthesis (*CYP11a1, Hsd3b1, CYP17a1*), and Sertoli-gonocyte interaction (*c-kit*) (Albert and Jugou 2014). Time course experiments using fetal and neonatal rat testes cultures exposed to MEHP showed that Leydig cells were affected first, resulting in a decrease in the germ cell pool, followed by decreased Sertoli cell proliferation and function (i.e., decreased secretion of anti-Mullerian hormone) (Albert and Jugou 2014).

MEHP-induced effects in *in vitro* test systems using cultured testes, Sertoli cell cultures, or mixed Sertoli cell and germ cell cultures include altered morphology of testes and seminiferous tubules (Chauvigné et al. 2009), decreased gonocyte numbers and increased numbers of apoptotic gonocytes (Chauvigné et al. 2009), increased germ cell detachment from Sertoli cell surfaces (Gray and Beamand 1984; Gray and Gangolli 1986; Sjöberg et al. 1986), decreased germ cell viability (Gray and Beamand 1984), elongation of Sertoli cells without evidence of decreased viability (Gray and Beamand 1984), decreased FSH binding to Sertoli cells (Grasso et al. 1993), decreased Sertoli cell proliferation (Li and Kim 2003; Li et al. 1998), decreased anti-Müllerian hormone production by Sertoli cells (Chauvigné et al. 2009), decreased testosterone production (Chauvigné et al. 2009; Jones et al. 1993), increased lactate/pyruvate ratio and decreased cellular ATP levels (Heindel and Powell 1992; Moss et al. 1988), decreased expression of

selected Sertoli cell proteins (Li and Kim 2003), and destruction of Sertoli cell tight junctional structure (Zhang et al. 2008).

Epidemiology Studies—Female Reproductive Development. AGD in female infants has been assessed in two pregnancy cohorts (Adibi et al. 2015; Barrett et al. 2016; Swan et al. 2015; Wenzel et al. 2018). No clear associations between maternal urinary DEHP metabolites and female infant anoclitoral or anofourchette distance were observed in either cohort (Table 2-16).

The timing of puberty has been examined in two studies using urinary biomarkers of DEHP exposure measured prior to outcome evaluation; results were mixed (Watkins et al. 2014; Wolff et al. 2014). In a Mexican birth cohort, evaluation of pubertal development in 129 girls aged 8–13 years showed an association between early development of puberty and third-trimester maternal levels of MEHP (Watkins et al. 2014). The OR for pubic hair development associated with an IQR increase in ln-MEHP in maternal urine was 5.30 (95% CI 1.13, 24.95, after adjustment for age, BMI Z-score, and specific gravity). In contrast, a study that examined childhood urinary metabolite levels and subsequent pubertal onset over 7 years of follow-up observed a relationship between *delayed* puberty and DEHP exposure (Wolff et al. 2014). In this cohort of 1,239 girls in New York, Ohio, and California, urinary levels of DEHP metabolites at ages 6–8 years were associated with reduced hazard ratios (HRs) for age at first pubic hair development (HR 0.79, 95% CI 0.64, 0.98 comparing highest quintile of total DEHP metabolites, after adjustment for covariates), especially among normal weight girls (HR 0.70, 95% CI 0.53, 0.93). Associations were not observed between DEHP metabolites and menarche (Watkins et al. 2014) or breast development (Watkins et al. 2014; Wolff et al. 2014). The use of a single urine sample to estimate exposure is a significant limitation in these studies.

Animal Studies –Female Reproductive Development. Only one study evaluated female reproductive development following inhalation exposure. Ma et al. (2006) reported accelerated vaginal opening and first estrus in weanling female Wistar intermittently exposed to DEHP at concentrations of 0.3–1.6 ppm for 3 or 9 weeks immediately following weaning. Increased serum estradiol and LH were observed at 1.6 ppm following exposure for 3 weeks, and irregular estrous cycles were observed following exposure for 9 weeks. No exposure-related changes in reproductive organ weights were observed. Sexual performance was not evaluated.

In nonhuman primates, exposure to doses ≥500 mg/kg/day for 65 weeks from weaning at 3 months to sexual maturity at 18 months resulted in evidence for accelerated maturation in female marmoset

monkeys, including increased serum estradiol, elevated ovary weights, and enlarged corpora lutea (Tomonari et al. 2006).

In Sprague-Dawley rats, significant increases in AGD were observed at PNDs 7 and 21 in female offspring following maternal exposure to doses ≥37.5 mg/kg/day from GD 6 to 21 (lowest dose tested) (Piepenbrink et al. 2005); however, Grande et al. (2006) did not observe any changes in female AGD at PND 22 following gestational and lactational exposure to doses up to 405 mg/kg/day. In a 2-generation study in Wistar rats, no exposure-related changes were observed in AGD or AGI in F1 or F2 females at doses up to approximately 1,088 mg/kg/day (Schilling et al. 1999, 2001). In CD-1 mice, AGD was not altered following gestational and lactational exposure to doses up to 5 mg/kg/day (Pocar et al. 2012).

In multigenerational studies in rats, delayed vaginal opening was observed in female offspring exposed to doses ≥447 mg/kg/day, but not ≤380 mg/kg/day (Blystone et al. 2010; NTP 2005; Schilling et al. 1999, 2001). Delayed puberty may be due to developmental exposure, peripubertal exposure, or a combination of the two; it may also be secondary to decreased body weights observed at the same doses. However, a nonsignificant trend for an approximate 2-day delay in vaginal opening was observed in female offspring of Sprague-Dawley rats exposed to doses ≥135 mg/kg/day from GD 6 to PND 21 in the absence of decreased body weight (Grande et al. 2006). In adult female offspring similarly exposed, a significant 2-fold increase (over control values) in the number of tertiary atretic ovarian follicles was observed at 405 mg/kg/day; no changes were observed in the numbers of primordial/primary, secondary, or tertiary (healthy) follicles (Grande et al. 2007). A “tendency for dilated interstitial spaces” was reported in the ovaries of female offspring at 405 mg/kg/day (no further details or incidence data provided). No exposure-related changes in the thickness of the uterine or vaginal epithelium were observed. Additionally, no exposure-related changes in estrous cyclicity, serum hormone levels, or reproductive organ weights were observed at maternal doses up to 405 mg/kg/day (Grande et al. 2007). In a 2-generation study in Wistar rats, no exposure-related changes were observed in female reproductive organ weights in F1 or F2 female weanlings at doses up to approximately 1,088 mg/kg/day (Schilling et al. 2001). In another study, serum estradiol was significantly decreased by >50% in PND 60 female offspring of Sprague-Dawley rat dams exposed to DEHP from GD 14 to PND 0 at doses ≥300 mg/kg/day (Martinez-Arguelles et al. 2011).

In CD-1 mice, ovary weight was significantly elevated by 35–45% in PND 42 offspring at maternal exposure to ≥0.05 mg/kg/day during gestation and lactation (Pocar et al. 2012). When oocytes from female offspring of exposed dams were evaluated for *in vitro* fertilization using unexposed sperm,

significantly decreased cleavage and blastocyst rates were observed at maternal doses of 0.05 mg/kg/day; however, this effect was not observed at 5 mg/kg/day (Pocar et al. 2012). The significance of this non-monotonic response is unclear. However, no changes in F1 female fertility were observed at doses up to 500 mg/kg/day in a 1-generation study in C3H/N mice (Schmidt et al. 2012).

In a study that evaluated the estrogenic activity of DEHP and other phthalate esters, DEHP induced no reproducible significant increases in uterine wet weight in immature ovariectomized rats following exposure to doses up to 2,000 mg/kg/day for 4 days (Zacharewski et al. 1998).

Mechanisms of Altered Female Reproductive Development. As discussed in Section 2.16 (Mechanisms of Female Reproductive Toxicity), DEHP has been shown to affect mammalian folliculogenesis following exposure during gestation or early life stages (Li et al. 2016; Mu et al. 2015; Zhang et al. 2013b, 2015). In addition to interaction with ERs (Mu et al. 2015; Zhang et al. 2015), DEHP may alter female reproductive development through interference with estrogen metabolism. Andrade et al. (2006b) observed increased brain aromatase activity in PND 22 female offspring of Sprague-Dawley rats exposed to doses ranging from 0.015 to 405 mg/kg/day during gestation and lactation (Andrade et al. 2006b). As discussed above, altered reproductive development in these female offspring included delayed vaginal opening and increased number of tertiary atretic ovarian follicles at doses ≥15 mg/kg/day (Grande et al. 2006, 2007).

Alterations in ovarian cell proliferation and apoptosis have also been associated with early life exposure to DEHP. Reduced proliferation of pregranulosa precursor cells was observed during the process of primordial folliculogenesis following neonatal exposure via injection (Mu et al. 2015). Similarly, Li et al. (2016) observed significant increases in the number of apoptotic somatic ovarian cells following early postnatal exposure to DEHP via intraperitoneal injections. Gene expression analysis of ovarian tissue from these animals showed upregulation of mRNA levels of apoptosis and antiproliferation. Li et al. (2016) also observed accumulation of ROS in the ovary and evidence of increased oxidative stress in somatic ovarian cells following *in vitro* exposure.

DEHP may cause heritable epigenetic alterations in germ cells, which may contribute to altered ovarian development (Li et al. 2014; Zhang et al. 2013b, 2016). Specifically, reduced DNA methylation patterns of genes has been observed in both F1 and F2 offspring oocytes following maternal DEHP exposure to 0.04 mg/kg/day from GD 0.5 to 18.5, including the maternal imprinted genes for insulin like growth factor 2 receptor (*Igf2r*) and paternally expressed 3 (*Peg3*) (Li et al. 2014).

Animal Studies—Other Noncancer (Glucose/Insulin Homeostasis). Altered glucose homeostasis has been observed in Wistar rats following developmental exposure to DEHP during gestation, gestation plus lactation, or lactation only at doses ≥1 mg/kg/day (Lin et al. 2011; Mangala Priya et al. 2014; Rajesh and Balsubramanian 2014a). Insulin sensitivity, but not altered glucose tolerance, was observed in mice exposed to DEHP during gestation plus lactation at a maternal dose of 500 mg/kg/day (Hunt et al. 2017). Findings from these studies are discussed below. A NOAEL for altered glucose homeostasis following developmental DEHP exposure has not been identified. This endpoint has not been assessed in other strains or species.

Adult offspring of Wistar rats exposed to DEHP at doses ≥1 mg/kg/day (lowest dose tested) during gestation (GDs 9–21) showed numerous alterations in glucose homeostasis, including a 16–49% increase in fasting blood glucose, a 21–70% decrease in serum insulin, and a 13–36% decrease in insulin binding protein levels; elevated serum glucose levels were observed in both the glucose and insulin tolerance tests (Rajesh and Balsubramanian 2014a). Additional significant findings observed in adult offspring included decreased glycogen content and decreased insulin binding, glucose uptake, and glucose oxidation in skeletal muscle. Several genes or gene products involved in insulin signaling were dysregulated in adult offspring, including decreased glucose transporter 4 (*GLU4*) gene expression, increased *GLU4* phosphorylation (posttranslational modification that decreases activity), and epigenetic silencing of *GLU4* (Rajesh and Balsubramanian 2014a).

Altered glucose homeostasis, along with pancreatic dysfunction, was also observed in weanling and adult offspring of Wistar rats exposed to DEHP at 1.25 or 6.25 mg/kg/day during gestation and lactation (GD 0–PND 21) (Lin et al. 2011). Effects observed at weaning included decreased fasting blood glucose and serum insulin levels, and lower blood glucose levels and insulin secretion in glucose and insulin tolerance testing at both exposure levels. By PNW 15, blood glucose levels were comparable among all groups, and serum insulin levels were elevated in female offspring only. No significant differences were observed in glucose levels in females during the glucose challenge test; however, elevated insulin levels were persistent. In exposed males, enhanced glucose tolerance was observed. However, at PNW 27, exposure-related changes in female offspring resumed, including elevated fasting blood glucose and decreased serum insulin; significantly elevated glucose levels and significantly reduced insulin levels were also observed with glucose tolerance tests. In male offspring, no changes were observed in blood glucose, but serum insulin levels were elevated and greater insulin levels were required for glucose clearance. No exposure-related changes in fasting glucagon levels were observed at any time point. In

insulin tolerance tests, glucose lowering effects were increased in all exposed groups at PNW 3, but results were comparable to controls at PNWs 15 and 27. In the pancreas, decreased β-cell mass and pancreatic insulin content were observed in exposed offspring at PND 21, but there were no significant changes in pancreas weight or β-cell area. At PNW 17, pancreatic weights were elevated in female offspring, but β-cell area and mass and pancreatic insulin content were decreased. In DEHP-exposed male offspring, β-cell area was increased and a trend toward increased mass was observed; pancreatic weight and insulin content were comparable to controls. With glucose-stimulation, islets from exposed female offspring had lower insulin secretion compared with controls. Alterations in mRNA expression of genes essential for pancreatic β-cell function were observed, including downregulation of *Pdx-1* and upregulation of *Atf4*, *Atf6*, *Bip*, and *Ucp2*. In this study, no changes in maternal serum insulin or blood glucose levels were observed at doses up to 6.25 mg/kg/day (Lin et al. 2011), indicating that developing offspring may be more susceptible to pancreatic toxicity than adult animals.

Lactational exposure to DEHP from PND 1 to 21 via maternal doses ≥1 mg/kg/day also resulted in altered glucose homeostasis in adult female Wistar rat offspring (male offspring were not assessed) (Mangala Priya et al. 2014). Fasting blood glucose was significantly elevated by ~15–20% (data presented graphically) in PND 59 female offspring. Glucose uptake and oxidation were also significantly decreased in cardiac tissue, and protein expression analysis showed altered expression of insulin signaling molecules that could account for decreased glucose uptake into cardiac tissue.

Insulin sensitivity was observed in PNW 16 wild-type mouse offspring following maternal exposure to 500 mg/kg/day throughout gestation and lactation followed by high-fat diet consumption for 13 weeks (Hunt et al. 2017). Following injection with insulin, all DEHP-exposed wild-type mice became lethargic and 5/6 entered hypoglycemic shock. All high-fat diet control animals were insulin tolerant. Insulin sensitivity was dependent on PCNA, as both control and DEHP-exposed transgenic mice without functional PCNA were insulin tolerant. No changes in glucose tolerance at PNW 15 were observed in control or exposed mice of either genotype. Due to use of a high-fat diet and use of only one high-dose exposure group, this study was not included in the LSE table. However, this study suggests that DEHP-induced changes in insulin tolerance may be mediated via PCNA.

Animal Studies—Other Developmental Effects. Other animal studies have evaluated development and function of the lungs, cardiovascular system, endocrine glands (adrenal, pituitary, thyroid), and immune system following developmental DEHP exposure (Chen et al. 2010; Christiansen et al. 2010; Kobayashi et al. 2006; Martinez-Arguelles et al. 2011, 2013; Piepenbrink et al. 2005; Wei et al. 2012), but data are

too limited to draw conclusions. These studies are discussed in Sections 2.4 (Respiratory), 2.5 (Cardiovascular), 2.13 (Endocrine), and 2.14 (Immunological), respectively.

Summary. Human and animal data indicate that the developing male reproductive system is a sensitive target of DEHP toxicity. In a systematic review, NAS (2017) concluded that DEHP is presumed to be a reproductive hazard to humans based on evidence integration of the animal and the human evidence on DEHP and effects on AGD and fetal testosterone and is suspected to be a reproductive hazard to humans based on evidence integration of the animal evidence and the human evidence on DEHP and fetal hypospadias. Data for early puberty and delayed mental and psychomotor development in humans following early life DEHP exposure are mixed. Additional animal studies report some evidence that DEHP exposure can also adversely affect the developing female reproductive system as well as the nervous, hepatic, and renal systems following DEHP exposure prior to sexual maturity. Altered glucose homeostasis has also been reported following developmental exposure. Fetotoxic and teratogenic effects have been observed at higher exposure levels following gestational exposure in animals.

2.18 OTHER NONCANCER

Epidemiology Studies. Several cross-sectional studies that used urinary metabolite levels to assess DEHP exposure (Table 2-17) have reported associations with increased fasting blood glucose (Huang et al. 2014a) or insulin resistance (as assessed by homeostatic model assessment-insulin resistance [HOMA-IR]; Lin et al. 2016; Attina and Trasande 2015; James-Todd et al. 2012; Trasande et al. 2013a). In addition, a panel study in Korea with repeated same-day urine and blood samples showed associations between increased fasting serum glucose (Kim et al. 2013) or insulin resistance (Kim and Hong 2014; Kim et al. 2013) and higher levels of DEHP metabolites in urine. A study in obese subjects (Dirinck et al. 2015) yielded conflicting results, as there was a relationship between decreased insulin sensitivity and DEHP metabolite levels and associations between decreased insulin resistance and DEHP metabolite levels. No association between fasting blood glucose and DEHP metabolite levels in urine was observed in a study of 250 Mexican children aged 8–14 years (Watkins et al. 2016).

Disparate findings in the cross-sectional studies may reflect differing susceptibilities across populations, genders, or ages, or differences in the covariates considered in the studies. Additionally, due to the cross-sectional design, it is not possible to determine if reported changes in glucose homeostasis in some studies are acute reactions to exposure or represent a trend toward increased blood glucose following chronic

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Indices of glucose homeostasis					
Lin et al. 2016, Cross-sectional (Taiwan)	243 male and 550 female students (mean age 21.28 years), including 303 with and 486 without elevated blood pressure in childhood, from the YOTA study (recruited 1992–2000 from schools). Timing of blood and urine samples was not clearly reported.	Linear regression adjusted for age, gender, and smoking status	Association between log-HOMA-IR and log-transformed Cr-adjusted urinary metabolite concentration		
			MEHP	6.1 (5.1–7.32) µg/g Cr (GM [95% CI])	β 0.071* (NR)
			MEHHP	27.90 (26.05–29.96) µg/g Cr	β -0.015 (NR)
			MEOHP	17.48 (16.44–18.54) µg/g Cr	β -0.007 (NR)
Watkins et al. 2016, Cross-sectional (Mexico)	250 children (age 8–14 years) from birth cohort (ELEMENT); mothers recruited 1997–2004 from maternity hospitals. Children provided contemporaneous blood and urine samples during followup.	Linear regression adjusted for age, BMI z-score, and urinary specific gravity	Percent difference in fasting serum glucose (mg/dL) per IQR increase in child's ln-transformed urinary metabolite concentration		
			Prepubertal boys (n=56)		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	3.09–10.3 µmol/L	Difference 3.0 (-1.4, 7.5)
			Prepubertal girls (n=86)		
			ΣDEHP (see above)	3.09–10.3 µmol/L	Difference -0.04 (-4.8, 5.0)
			Pubertal boys (n=58)		
			ΣDEHP (see above)	3.09–10.3 µmol/L	Difference 1.0 (-1.4, 3.5)

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			Pubertal girls (n=45)		
			ΣDEHP (see above)	3.09–10.3 µmol/L	Difference 1.9 (-1.8, 5.6)
Attina and Trasande 2015, Cross-sectional (United States)	356 adolescents (12–19 years); 191 males and 165 females; participants in NHANES 2009–2012. Insulin resistance defined as HOMA-IR >4.39. Urine and blood samples collected contemporaneously. n=350 in adjusted analyses.	Linear regression, Multivariate Logistic regression (considering these covariates: urinary creatinine, age, caloric intake, sex, poverty-income ratio, serum cotinine, BMI, race/ethnicity categories, and physical activity)	OR for insulin resistance (HOMA-IR >4.39) comparing highest and lowest tertiles of log-transformed urinary metabolite concentration		
			ΣDEHP	0.07–0.32 µM	OR 3.85 (1.6, 9.24)*
			Difference in HOMA-IR between highest and lowest tertiles of log-transformed urinary metabolite concentration		
			ΣDEHP	0.07–0.32 µM	Difference 0.16 (-0.005, 0.33)
			OR for insulin resistance (HOMA-IR >4.39) per log-unit increase in urinary metabolite concentration		
			MEHP	NR	OR 1.52 (1.15, 2.00)*
			MEHHP	NR	OR 1.64 (1.25, 2.15)*
			MEOHP	NR	OR 1.68 (1.25, 2.26)*
			MECPP	NR	OR 1.60 (1.19, 2.14)*
Dirinck et al. 2015, Cross-sectional (Belgium)	123 adult obese subjects (38 men, 85 women) without a history of type 2 diabetes recruited from weight management clinic of Antwerp University Hospital between November 2009 and February 2012; mean	Linear regression adjusted for gender, age, physical activity level, current smoking behavior, current medication use, and BMI	Association with log-transformed creatinine-adjusted urinary metabolite concentration		
			MEHP	0.49–181.9 µg/g Cr (min–max)	NR (not significant)
			MEHHP	2.6–135.8 µg/g Cr	Log-Belfiore index β -0.133 (-0.265, 0.00)* Square root-AUC Insulin β 25.199 (-0.736, 51.134) Log-Matsuda index NR (not significant)

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
	age±SD = 41±12.5. Urine samples collected 1 day before blood samples. Belfiore index is an estimate of insulin resistance; higher values indicate increased resistance. Matsuda index is an estimate of insulin sensitivity; lower values indicate increased insulin resistance.		MEOHP	0.82–42.3 µg/g Cr	Log-Belfiore index β -0.143 (-0.275, -0.011)* Square root-AUC Insulin β 26.617 (0.692, 52.541)* Log-Matsuda index β -0.199 (-0.383, -0.014)*
			MECPP	0.1–268.8 µg/g Cr	NR (not significant)
			No significant association between any urinary DEHP metabolites and HbA1c levels, AUC glucose, HOMA-IR, or insulinogenic index.		
Huang et al. 2014a, Cross-sectional (United States)	3,083 non-diabetic, non-pregnant subjects; 1,620 men, 1,463 women; ages 12–<80 years; participants in NHANES 2001–2008	Median regression adjusted age, sex, race, urinary creatinine, fasting time, total caloric intake, triglyceride, education, smoking status, and poverty	Median difference between highest and lowest quartiles of urinary metabolite concentration		
			ΣDEHP (MEHP, MEHHP, MEOHP)	Men: 5.3–19.7 µmol/100 g Cr; Women: 6.5–23.1 µmol/100 g Cr	Median fasting blood glucose Difference = 2.45 (1.29, 3.60)* Median HOMA-IR Difference = 0.68 (0.47, 0.88)*
			No significant change in median fasting blood glucose for middle quartiles; p for trend = 0.0016. Significant changes in median HOMA-IR for 2nd and 3rd quartiles; p for trend <0.0001.		

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Kim and Hong 2014; Kim et al. 2013, Panel study (Korea)	560 subjects (146 men, 414 women; 60–87 years); participants in Korean Elderly Environmental Panel study; recruited from a community elderly welfare center, where they underwent medical examinations up to 5 times, with blood and urine samples collected on the same day at least 3 times. Kim and Hong (2014) analyzed data on women only; Kim et al. (2013) analyzed data on men and women.	Linear regression adjusted for age, BMI, education, exercise, cotinine levels, PM_{10}, O_3, NO_2, outdoor temperature, dew point, total caloric and fat intake, history of diabetes mellitus (in women only analysis), and sex (in analysis of men and women)	Change per log-change in Cr-adjusted urinary metabolite concentration		
			Women only		
			ΣDEHP	NR	Fasting serum glucose β 0.11 (-0.003, 0.22) HOMA-IR β 0.3 (0.04, 0.56)*
			MEHHP	1.71–317.26 (min–max)	NR
			MEOHP	0.212–231.44	NR
			Men and women		
			ΣDEHP	NR	Fasting serum glucose β 0.11 (0.01, 0.22)* HOMA-IR β 0.26 (0.01, 0.51)*
			MEHHP	12.51–39.93	NR
			MEOHP	9.54–33.14	NR
James-Todd et al. 2012, Cross-sectional (United States)	215 female cases of self-reported diabetes (type not specified), 2,135 women without diabetes (ages 20–79 years); participants in NHANES 2001–2008. Urine and blood samples collected at the same time.	Linear regression adjusted for urine creatinine, age, race/ethnicity, education, poverty status, fasting time, total caloric intake, total fat intake, smoking status, physical activity, BMI, and waist circumference	Difference in between highest and lowest quartiles of urinary metabolite concentration.		
			ΣDEHP (MEHP, MEHHP, MEOHP)	1,110 (1,030, 1,200) (units not reported; GM [95% CI])	Median fasting blood glucose (mg/dL) Difference = 0.01 (-2.34, 2.36) Median A1c (%) Difference = -0.02 (-0.07, 0.03) Median ln-HOMA-IR Difference = 0.13 (0.01, 0.25)*

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Trasande et al. 2013a, Cross-sectional (United States)	766 adolescents (424 males and 342 females; 12–19 years of age); participants in NHANES 2003–2008. Urine and blood samples collected at the same time.	Logistic regression adjusted for urinary creatinine, age, BMI, gender, poverty-income ratio, parental education, serum cotinine, and race/ethnicity	OR for HOMA-IR >2 SD above mean per log-unit increase in urinary metabolite concentration		
			ΣDEHP	0.17–0.71 μM	OR 1.44 (1.14, 1.82)*
			MEHP	NR	OR 1.13 (0.91, 1.4)
			MEHHP	NR	OR 1.51 (1.21, 1.88)*
			MEOHP	NR	OR 1.49 (1.19, 1.87)*
			MECPP	NR	OR 1.36 (1.08, 1.73)*
Stahlhut et al. 2007, Cross-sectional (United States)	1,451 adult males >18 years who were not taking insulin, oral hypoglycemic agents, or sex hormone agonists/ antagonists; participants in NHANES 1999–2002.	Linear regression adjusted for age, age, race/ethnicity, total fat and calorie intake, physical activity level, smoking exposure, urinary Cr, GFR, ALT, and GGT	Association between ln-HOMA-IR and log-transformed urinary metabolite concentration		
			MEHP	11±1.3 μg/g Cr (mean±SE)	β 0.016 (NR)
			MEHHP	65.8±7.9 μg/g Cr	β 0.038 (NR)
			MEOHP	38.7±4.5 μg/g Cr	β 0.044 (NR)

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Odds of incident type 2 diabetes					
Sun et al. 2014a, Cohort (United States)	Nurses with type-2 diabetes and matched controls from the NHS of female registered nurses aged 23–79 (394 cases, 393 controls) and the NHSII of female registered nurses aged 32–52 (577 cases, 577 controls); cases and controls were matched for age at urine collection, date and time of day of sample collection, ethnicity, fasting status when blood was drawn, and menopausal status and hormone replacement therapy at sample collection. Urine and samples collected from NHS participants aged 53–79 years during 2000–2002 and from NHSII participants aged 32–52 years during 1996–2001.	Multiple logistic regression adjusted for age at urine sample collection, ethnicity, fasting status, time of sample collection, menopausal status, postmenopausal hormone use (NHS only), smoking status, and use of hormone replacement therapy (NHSII only)	OR for incident type 2 diabetes comparing highest quartile of urinary metabolite concentration with lowest quartile (both studies combined)		
			ΣDEHP	NHS cases: 154.4–545.8 nmol/L NHS controls: 142.8–463.7 nmol/L NHSII cases: 201.4–586.3 nmol/L NHSII controls: 170.8–522.3 nmol/L	NR
			MEHP	NR	OR 0.97 (0.55, 1.69)
			MEHHP	NR	OR 1.54 (0.96, 2.46)
			MEOHP	NR	OR 1.42 (0.95, 2.11)
			MECPP	NR	OR 2.17 (1.40, 3.38)*
			Significant ORs (2.05–2.30) were also observed for MECPP, but not other metabolites, in separate analyses of NHS and NHSII.		

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
Gestational diabetes and insulin resistance					
James-Todd et al. 2016a Cohort (United States [Boston])	298 pregnant women with full term births recruited from a prospective pregnancy cohort at Brigham and Women's Hospital that delivered between 2006 and 2008 (LIFECODES cohort), mean age 31.9 years, 47 with IGT; maternal urine samples collected at median 9.9 and 17.9 weeks of gestation. IGT was determined in the second or third trimester (median 26.1 weeks).	Multivariable logistic regression adjusted for age, race/ethnicity, education, baseline BMI, alcohol drinking, and smoking	Odds of having IGT (glucose levels >140 mg/dL) in the highest quartile of first trimester urinary metabolite concentration with the lowest quartile		
			ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Controls (n=251): 0.2–0.8 µmol/L IGT cases (n=47): 0.2–1.4 µmol/L (GM; SG-adj)	OR 0.25 (0.08,0.85)*
			In other analyses, least geometric mean blood glucose levels were not associated with urine ΣDEHP levels (nonsignificant p for trend).		
Shapiro et al. 2015, Cohort (Canada)	1,274 pregnant women (>18 years), members of birth cohort recruited during first trimester between 2008 and 2011 at 10 sites in 6 Canadian provinces (MIREC); n=47 cases of IGT and n=43 cases of GDM. Urine samples collected during the first trimester. IGT and GDM determined by chart review after delivery.	Multiple logistic regression adjusted for maternal age, race, pre-pregnancy BMI, education, and specific gravity	OR comparing the highest quartile of first-trimester urinary metabolite concentration with the lowest quartile		
			ΣDEHP	NR	GDM OR 0.9 (0.3, 2.9) IGT OR 1.0 (0.3, 3.4) GDM or IGT OR 0.9 (0.4, 2.3)
			MEHP	Controls: 2.6 (2.5) IGT cases: 2.3 (2.4) GDM cases: 2.7 (2.9) (GM [GSD]; SG-adj)	NR
			MEHHP	Controls: 10.6 (2.5) IGT cases: 10.4 (2.4) GDM cases: 11.4 (3.0)	NR
			MEOHP	Controls: 7.4 (2.3) IGT cases: 6.9 (2.2) GDM cases: 7.8 (2.7)	NR

Table 2-17. Selected Epidemiological Studies of DEHP Exposure and Diabetes or Glucose Homeostasis

Reference and study type	Population	Method of analysis	Urinary metabolite levels (IQR in ng/mL unless otherwise specified)		Effect estimate (95% CI)[a]
			No significant OR in any exposure quartile, and no significant trend across exposure quartiles.		
Robledo et al. 2015, Cohort (United States [Oklahoma])	72 pregnant women (18–38 years) without diabetes recruited during first prenatal care visit at the University of Oklahoma Medical Center Women's Clinic between February and June 2008. Oral glucose challenge test administered at median gestational age 26.3 weeks. Urine sample collected at enrollment.	Linear regression adjusted for urinary creatinine, gestational age at enrollment, and race/ethnicity	Difference between blood glucose levels (mg/dL) in highest versus lowest tertiles of urinary metabolite concentration		
			ΣDEHP	36.82–126.00	β -9.97 (-27.11, 7.17)
			MEHP	1.40–7.75	β 9.07 (-6.3, 24.45)
			MEHHP	10.35–40.85	β -5.55 (-21.77, 10.66)
			MEOHP	7.70–24.20	β -9.65 (-27.19, 7.89)
			MECPP	16.90–54.20	β -3.26 (-20.38, 13.86)

[a]Asterisk indicates association with DEHP or DEHP metabolites; unless otherwise specified, values in parenthesis are 95% confidence limits.

ΣDEHP = sum DEHP metabolites; ALT = alanine aminotransferase; AUC = area under the curve; BMI = body mass index; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; GDM = gestational diabetes mellitus; GFR = glomerular filtration rate; GGT = gamma-glutamyl transferase; GM = geometric mean; HOMA-IR = homeostatic model assessment-insulin resistance; IGT = impaired glucose tolerance; IQR = interquartile range; max = maximum; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; min = minimum; MIREC = Maternal-Infant Research on Environmental Chemicals; NHANES = National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; NHSII = Nurses' Health Study II; NR = not reported; OR = odds ratio; SD = standard deviation; SE = standard error; YOTA = Young Taiwanese Cohort

exposure to DEHP. Finally, cross-sectional studies may also be vulnerable to spurious findings due to reverse causality if higher urinary metabolite levels occur as a consequence of higher exposure via medications or personal care products in persons with impaired glucose homeostasis. However, the finding of increased risk of impaired glucose homeostasis is supported by a case-control study nested within the Nurses' Health Study and Nurses' Health Study II (Sun et al. 2014a) that examined incident diabetes and thus, was not confounded by reverse causality. In this study, a pooled analysis of the two nurses' studies showed increased odds of developing type 2 diabetes with increased levels of mono-2-ethyl-5-carboxypentylphthalate (MECPP) in urine (OR 2.17; 95% CI 1.40, 3.38). No association was observed between type 2 diabetes and urinary levels of other DEHP metabolites or the sum of all DEHP metabolites.

Little information was located on the association between DEHP exposure and gestational diabetes (Table 2-17). In two cohort studies (Robledo et al. 2015; Shapiro et al. 2015), no association between DEHP exposure and impaired glucose tolerance or gestational diabetes was observed (Table 2-17). A third cohort study reported reduced odds of having impaired glucose tolerance during pregnancy with increased DEHP concentration in maternal urine (James-Todd et al. 2016a).

Animal Studies. Glucose homeostasis may be impaired in animals following exposure to DEHP. Rajesh et al. (2013) reported altered glucose metabolism and homeostasis in Wistar rats exposed to doses ≥10 mg/kg/day via gavage for 30 days (lowest dose tested). Altered endpoints included decreased glycogen levels and glucose uptake in visceral adipose tissue, and elevated serum glucose levels. Oxidative stress and lipid peroxidation markers were also elevated in adipose tissue of treated rats from both groups. Gene expression analysis showed altered expression of insulin signaling molecules that could account for decreased glucose uptake into adipose tissue, and therefore increased serum glucose (Rajesh et al. 2013). However, no changes in serum glucose were observed in male Wistar rats exposed to gavage doses up to 10,000 mg/kg/day for 4 weeks or 1,000 mg/kg/day for 9 weeks (Dalgaard et al. 2000). In F344 rats, increased serum glucose was observed in males exposed to doses ≥850.1 mg/kg/day for 13 weeks; this effect was not observed in males at doses ≤261.2 mg/kg/day or females at doses up to 1,857.6 mg/kg/day (Myers 1992b). Serum glucose changes were not observed in mice exposed to doses up to 7,899 mg/kg/day for 28 days (Myers 1992a).

Several developmental studies have also reported altered glucose homeostasis and impaired pancreatic β-cell function in rats following prenatal and/or early postnatal exposure to oral doses of 1–10 mg/kg/day (Lin et al. 2011; Mangala Priya et al. 2014; Rajesh and Balsubramanian 2014a). In these studies, no

changes in maternal serum insulin or blood glucose levels were observed at doses up to 6.25 mg/kg/day, indicating that developing offspring may be more susceptible to pancreatic toxicity (Lin et al. 2011). See Section 2.17 (Developmental) for more details on these studies.

There is limited evidence of metabolic syndrome in laboratory animals following oral exposure to DEHP. Increases in visceral adipose tissue and adipocyte hypertrophy were observed in female mice following exposure to dietary doses ≥0.05 mg/kg/day for 8 weeks; this finding was accompanied by significant increases in body weight and food intake (Schmidt et al. 2012). Significant increases in leptin, an appetite-controlling hormone, were also observed at 500 mg/kg/day. Similarly, significant increases in visceral adipose tissue were observed in F0 mouse dams exposed to dietary doses ≥0.05 mg/kg/day from 1-week premating through PND 21 (Schmidt et al. 2012). Visceral adipose tissue was also elevated in F1 adult female offspring at maternal doses ≥0.05 mg/kg/day (Schmidt et al. 2012). Rajesh and Balasubramanian (2014a) also reported significant increases in adipose tissue in adult rat offspring following maternal exposure to ≥1 mg/kg/day via gavage from GD 9 to 21 (Rajesh and Balasubramanian 2014a). However, a significant *decrease* in adipose tissue was reported in PND 42 female mouse offspring at maternal dietary doses ≥0.05 mg/kg/day from GD 0 to PND 21 (Pocar et al. 2012) and in PND 21 rat offspring following maternal gavage exposure to ≥1.25 mg/kg/day from GD 9 to 21 (Lin et al. 2011).

Extensive fur loss was reported in rats exposed to dietary DEHP at doses ≥1,414 mg/kg/day for 17 weeks (Gray et al. 1977). Rats showing fur loss were also described as “emaciated” by study authors, with decreases in food consumption and body weight of >25%. Therefore, it is unclear if fur loss is a primary health effect or secondary to overall poor health.

Summary. A limited number of epidemiological studies found potential associations between DEHP exposure and diabetes-related outcomes (e.g., impaired glucose homeostasis) in humans (Attina and Trasande 2015; Huang et al. 2014a; James-Todd et al. 2012; Kim and Hong 2014; Kim et al. 2013; Lin et al. 2016; Trasande et al. 2013a). A limited number of animal studies report altered glucose homeostasis and metabolic syndrome.

2.19 CANCER

Epidemiological Studies—Cancer. Available epidemiological studies of the association between cancer and DEHP exposure in humans are limited to three case-control studies (Lopez-Carillo et al. 2010;

Martinez-Nava et al. 2013; Holmes et al. 2014) in which exposure (as urinary metabolite levels) was measured after the outcome (breast cancer) was observed. There is no information (qualitative or quantitative) on exposures prior to incidence/diagnosis that could have been involved in tumor induction. Furthermore, cancer treatments could increase exposure to, and excretion of, phthalates from medical equipment. Thus, these studies are not useful for evaluating the carcinogenicity of DEHP.

Animal Studies—Cancer. Lifetime exposure of hamsters to 0.001 ppm DEHP did not result in any significant increase in the incidence of tumors (Schmezer et al. 1988). Because the concentration in this study was very low, it is not possible to reach conclusions concerning whether or not higher concentrations might produce different results.

Hepatic Cancer. Several chronic exposure studies in rodents indicate that DEHP can cause liver tumors in rats and mice. Hepatocellular adenomas and carcinomas have consistently been reported following chronic oral exposure in F344 rats at doses ≥394 mg/kg/day (Cattley et al. 1987; David et al. 1999, 2000a; Hayashi et al. 1994; Kluwe et al. 1982a, 1982b, 1985; NTP 1982; Rao et al. 1987, 1990) and in B6C3F1 mice at doses ≥354.2 mg/kg/day (David et al. 1999, 2000b; Kluwe et al. 1982a, 1982b, 1985; NTP 1982). Only David et al. (1999, 2000) reported an increased incidence of hepatocellular tumors in male F344 rats at lower doses, observing a dose-related increase in tumors at dietary doses ≥147 mg/kg/day, but not ≤29 mg/kg/day (David et al. 1999, 2000a). A nonsignificant increase in hepatocellular adenomas and carcinomas was observed in male Sprague-Dawley rats following lifetime exposure to 300 mg/kg/day (Voss et al. 2005). In contrast, Ganning et al. (1991) did not observe any liver tumors in male Sprague-Dawley rats following exposure to doses up 1,400 mg/kg/day for 102 weeks; however, only 7–18 animals were included in each dose group. In Sherman rats, hepatocellular tumors were not significantly increased following chronic exposure to DEHP, but the maximum tested dose was only 200 mg/kg/day (Carpenter et al. 1953). In other species, liver tumors were not elevated following 1-year exposure of dogs at doses up to 56.6 mg/kg/day or guinea pigs at doses up to 64 mg/kg/day (Carpenter et al. 1953). Due to study design deficiencies (low animal number and/or low doses), it is unclear if the studies by Ganning et al. (1991) or Carpenter et al. (1953) were adequate to assess potential carcinogenicity.

Mechanisms of Hepatic Cancer. The mechanistic events associated with DEHP liver toxicity are described briefly in Section 2.9 (Mechanisms of Liver Toxicity). The exact mechanism(s) by which DEHP induces hepatic cancer in rodents are not precisely known; however, the available data suggest that multiple molecular targets and pathways are affected in multiple liver cell types (Guyton et al. 2009; Melnick 2001; Rusyn and Corton 2012).

As discussed in Section 2.9, DEHP activates PPARα in rats and mice (Rusyn and Corton 2012). Therefore, it follows that observed liver tumors in rodents may be PPARα-dependent. Key events identified in this mode of action are: (1) PPARα activation; (2) alterations in cell growth pathways; (3) perturbation of hepatocyte growth and survival; (4) selective clonal expansion of preneoplastic foci cells; and (5) increases in hepatocellular adenomas and carcinomas (apical event) (Corton et al. 2018). Isenberg et al. (2000, 2001) proposed that increased peroxisomal proliferation, increased replicative DNA synthesis, and inhibition of GJIC observed in rat and mouse livers following oral exposure to DEHP may contribute to PPARα-dependent hepatic tumor formation. Observed losses in GJIC following oral exposure to DEHP may permit unchecked proliferation of transformed cells. Inhibition of GJIC was not observed in exposed hamsters, a species that is refractory to PPARα-dependent tumors (Isenberg et al. 2000).

It is generally accepted that the PPARα mode of action is not relevant to humans due to differences observed in key events downstream of PPARα activation (Corton et al. 2018; Klaunig et al. 2003; Maloney and Waxman 1999). Guyton et al. (2009) reported that PPARα activation may not be essential to rodent liver tumor formation since liver tumors have been observed in some studies using PPARα-null mice; however, the validity of this argument has been questioned by Corton et al. (2018). Concerns regarding conclusions reached by Guyton et al. (2009) include: (1) all liver tumor types, including hepatoblastomas, which originate from a different cell population compared with adenomas and carcinomas, were combined for statistical analysis; (2) use of DEHP doses that did not cause liver tumors in wild-type mice in studies reporting tumors in PPARα-null mice; (3) comparison of findings in PPARα-null mice to non-concurrent controls of a different strain; and (4) different molecular environments in PPARα-null mice compared with wild-type mice (e.g., increased levels of background and DEHP-inducible levels of oxidative stress).

The genotoxicity data for DEHP are presented in Section 2.20. DEHP has been shown to induce DNA damage, chromosomal effects, and cell transformation (Caldwell et al. 2012).

Endocrine Cancer. There is limited evidence of pancreatic adenomas following chronic exposure to DEHP; however, these tumors have only been observed in male F344 rats at high dose levels (789–1,600 mg/kg/day). Pancreatic acinar cell adenomas were reported in male F344 rats following chronic exposure to 789 mg/kg/day; incidences were not increased at doses ≥147 mg/kg/day in males or at doses up to 939 mg/kg/day in females (David et al. 2000a). Rao et al. (1990) also reported an increased

incidence of pancreatic islet cell adenomas in male F344 rats exposed to 1,600 mg/kg/day for 108 weeks. Pancreatic tumors were not elevated in another chronic-duration study in F344 rats; however, the maximal tested dose in male F344 rats was 674 mg/kg/day (Kluwe et al. 1982a, 1982b, 1985; NTP 1982). In other species, pancreatic tumors were not elevated compared to controls following chronic exposure in dogs at doses up to 56.6 mg/kg/day (Carpenter et al. 1953), guinea pigs at doses up to 64 mg/kg/day (Carpenter et al. 1953), or mice at doses up to 1,821 mg/kg/day (David et al. 1999, 2000b; Kluwe et al. 1982a, 1982b, 1985; NTP 1982).

Reproductive Cancer. One study reported an increased incidence of Leydig cell tumors in male rats following chronic oral exposure to DEHP. Voss et al. (2005) reported a significant increase in the incidence of Sprague-Dawley rats with any Leydig cell tumor (unilateral, bilateral, or multifocal) following lifetime exposure to DEHP at doses of 300 mg/kg/day. In contrast, Ganning et al. (1991) did not observe any testicular tumors in male Sprague-Dawley rats following exposure to doses up 1,400 mg/kg/day for 102 weeks; however, only 7–18 animals were included in each dose group. Due to low animal number, it is unclear if the study design was adequate to assess potential carcinogenicity. Increased incidences of testicular tumors were not observed in other rat species following chronic exposure to doses up to 789 mg/kg/day (Carpenter et al. 1952; David et al. 1999, 2000a; Kluwe et al. 1982a, 1982b, 1985; NTP 1982), in male B6C3F1 mice at doses up to 1,325 mg/kg/day (David et al. 1999, 2000b; Kluwe et al. 1982a, 1982b, 1985; NTP 1982), in guinea pigs at doses up to 64 mg/kg/day (Carpenter et al. 1953), or in dogs at doses up to 56.6 mg/kg/day (Carpenter et al. 1953).

2.20 GENOTOXICITY

As discussed below and shown in Tables 2-18, 2-19, 2-20, and 2-21, DEHP has been extensively tested in a variety of genotoxicity assays. Evidence suggests that DEHP is not mutagenic to bacterial or mammalian cells; however, there is limited evidence that it may damage DNA and/or result in chromosomal abnormalities (either directly or indirectly via oxidative stress mechanisms), and it has been shown to induce morphological transformation. The weight of evidence from these assays indicates that DEHP is not a potent genotoxin, but may lead to genotoxic effects secondary to oxidative stress.

Table 2-18. Genotoxicity of DEHP *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms				
Salmonella typhimurium (TA98, TA100, TA1535, TA1538)	Gene mutation	–	–	Agarwal et al. 1985
S. typhimurium (NS)	Gene mutation	–	–	Astill et al. 1986
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Kirby et al. 1983
S. typhimurium (TA100)	Gene mutation	–	+	Kozumbo et al. 1982
S. typhimurium (TA98)	Gene mutation	–	–	Sato et al. 1994
S. typhimurium (TA102)	Gene mutation	–	–	Schmezer et al. 1988
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Simmon et al. 1977
S. typhimurium (TA100)	Gene mutation	–	–	Seed 1982
S. typhimurium (TA100)	Gene mutation	+	NS	Tomita et al. 1982b
S. typhimurium (TA98, TA100)	Gene mutation	–	–	Yoshikawa et al. 1983
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1985
Escherichia coli PQ37	Gene mutation	–	–	Sato et al. 1994
E. coli WP2UVRA$^+$	Gene mutation	–	–	Yoshikawa et al. 1983
E. coli WP2UVRA	Gene mutation	–	–	Yoshikawa et al. 1983
S. typhimurium (TA1535/psk 1002)	DNA damage	+	–	Okai and Higashi-Okai 2000
Bacillus subtilis (rec assay)	DNA damage	+	–	Tomita et al. 1982b
S. typhimurium (TA100)	Azaguanine resistance	–	–	Seed 1982
Eukaryotic organisms				
Saccharomyces cerevisae (XV185-14C, D7, RM52, D6, D5, D6-1)	Gene mutation	–	–	Parry et al. 1985
Saccharomyces cerevisiae (JD1, D7-144, D7)	Gene conversion	–	–	Parry et al. 1985
S. cerevisiae (D61M, D6)	Mitotic aneuploidy	+	+	Parry et al. 1985
S. cerevisiae (D61M, D6)	Mitotic segregation	–	–	Parry et al. 1985
Schizosaccharomyces pombe (P1)	Gene mutation	–	–	Parry et al. 1985
Aspergillus niger (P1)	Mitotic segregation	–	NS	Parry et al. 1985
Mammalian cells				
Mouse lymphoma cells	Mutagenicity	–	–	Astill et al. 1986
Mouse lymphoma cells	Mutagenicity	–	–	Kirby et al. 1983

Table 2-18. Genotoxicity of DEHP *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mouse lymphoma cells	Mutagenicity	±[a]	–	Oberly et al. 1985
Mouse lymphoma cells	Mutagenicity	–	–	Tennant et al. 1987
Human leukocytes	DNA damage	–	+	Anderson et al. 1999
Human lymphocytes	DNA damage	–	+	Anderson et al. 1999
Human HeLa cells	DNA damage	NS	+	Park and Choi 2007
Human HepG2 cells	DNA damage	NS	+	Choi et al. 2010
Human LNCaP prostate adenocarcinoma cells	DNA damage	NS	+	Erkekoglue et al. 2010a
Human HepaRG cells	DNA damage	–	NA	Le Hegarat et al. 2014
Mouse MA-10 Leydig tumor cells	DNA damage	NS	+	Erkekoglu et al. 2010b
Mouse lung cells	DNA damage	NS	+	Wang et al. 2014
Rat hepatocytes	DNA damage	–	NA	Schmezer et al. 1988
Hamster hepatocytes	DNA damage	–	NA	Schmezer et al. 1988
CHO cells	DNA damage	–	–	Douglas et al. 1986
Human hepatocytes	DNA repair	–	NA	Butterworth et al. 1984
Mouse hepatocytes	DNA repair	–	NA	Smith-Oliver and Butterworth 1987
Rat hepatocytes	DNA repair	–	NA	Astill et al. 1986
Rat hepatocytes	DNA repair	–	NA	Butterworth 1984
Rat hepatocytes	DNA repair	–	NA	Hodgson et al. 1982
Rat hepatocytes	DNA repair	–	NA	Kornbrust et al. 1984
Rat hepatocytes	DNA repair	–	NA	Probst and Hill 1985
Chinese hamster V79 fibroblasts	DNA repair	–	NA	Kornbrust et al. 1984
Human HepaRG cells	Micronuclei	–	NA	Le Hegarat et al. 2014
Human TK6 lymphoblastoid cells	Micronuclei	NS	–	Sobol et al. 2012
Rat RL4 liver cells	Sister chromatid exchange	–	NA	Priston and Dean 1985
CHO cells	Sister chromatid exchange	NS	–	Abe and Sasaki 1977
CHO cells	Sister chromatid exchange	–	–	Douglas et al. 1986
CHO cells	Sister chromatid exchange	NS	–	Phillips et al. 1982
CHO cells	Sister chromatid exchange	NS	+	Tennant et al. 1987
Human hepatocytes	Chromosomal aberrations	–	NA	Turner et al. 1974
Human leucocytes	Chromosomal aberrations	–	NA	Stenchever et al. 1976
Rat RL4 liver cells	Chromosomal aberrations	–	NA	Priston and Dean 1985
CHO cells	Chromosomal aberrations	NS	–	Phillips et al. 1982
CHO cells	Chromosomal aberrations	NS	–	Tennant et al. 1987
SHE cells	Chromosomal aberrations	–	–	Tsutsui et al. 1993

Table 2-18. Genotoxicity of DEHP *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
CH SV40-transformed liver cells	Selective DNA amplification	–	NA	Schmezer et al. 1988
Mouse JB6 epidermal cells	Cell transformation	+	NA	Diwan et al. 1985
Mouse C3H/10T1/2 fibroblasts	Cell transformation	NS	–	Sanchez et al. 1987
Mouse BALB 3T3 cells	Cell transformation	–	–	Astill et al. 1986
SHE cells	Cell transformation	NS	+	LeBoeuf et al. 1996; Mauthe et al. 2001
SHE cells	Cell transformation	NS	+	Mikalsen et al. 1990
SHE cells	Cell transformation	NS	+	Pant et al. 2010
SHE cells	Cell transformation	NS	+	Sanner and Rivedal 1985
SHE cells	Cell transformation	+	±	Tsutsui et al. 1993
Rat hepatocytes	DNA binding	–	NA	Gupta et al. 1985
Human fetal pulmonary cells	Aneuploidy	–	NA	Stenchever et al. 1976
Rat RL4 liver cells	Polyploidy	–	NA	Priston and Dean 1985

[a]Mutagenic effect coincident with cytotoxicity.

– = negative result; + = positive result; ± = equivocal result; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable to mammalian cell cultures with endogenous metabolic activity; NS = not specified; SHE = Syrian hamster embryo

Table 2-19. Genotoxicity of MEHP *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms				
Salmonella typhimurium (TA98, TA100, TA1535, TA1538)	Gene mutation	−	−	Agarwal et al. 1985
S. typhimurium (NS)	Gene mutation	−	−	Astill et al. 1986
S. typhimurium (TA97, TA98, TA100, TA102)	Gene mutation	−	−	Dirven et al. 1991
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	−	−	Kirby et al. 1983
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	−	−	Ruddick et al. 1981

Table 2-19. Genotoxicity of MEHP *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
S. typhimurium (TA100, TA102)	Gene mutation	−	−	Schmezer et al. 1988
S. typhimurium (TA100)	Gene mutation	−	±	Tomita et al. 1982b
S. typhimurium (TA98, TA100)	Gene mutation	−	−	Yoshikawa et al. 1983
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	−	−	Zeiger et al. 1985
Escherichia coli (WP2 B/r)	Gene mutation	NS	±[a]	Tomita et al. 1982b
E. coli (WP2 *try*$^-$ [*UvrA*$^+$ *and UvrA*$^-$])	Gene mutation	−	−	Yoshikawa et al. 1983
Bacillus subtilis (H17, M45)	DNA damage (Rec assay)	NS	+	Tomita et al. 1982b
Mammalian cells				
Mouse lymphoma cells L5178Y (tk$^+$/tk$^-$)	Mutagenicity	−	−	Kirby et al. 1983
CHO cells	Mutagenicity	NS	−	Phillips et al. 1982
Human leukocytes	DNA damage	NS	+	Anderson et al. 1999
Human LNCaP prostatic cancer cells	DNA damage	NS	+	Erkekoglu et al. 2010a
Mouse MA-10 Leydig tumor cells	DNA damage	NS	+	Erkekoglu et al. 2010b
Human peripheral lymphocytes	DNA damage	NS	+	Kleinsasser et al. 2004
Human nasal mucosa cells	DNA damage	NS	+	Kleinsasser et al. 2004
Human HepG2 cells	Oxidative DNA damage	NS	+	Yang et al. 2012
Human primary hepatocytes	DNA repair	−	NA	Butterworth et al. 1984
Rat primary hepatocytes	DNA repair	−	NA	Cattley et al. 1986
Mouse primary hepatocytes	DNA repair	−	NA	Smith-Oliver and Butterworth 1987
Hamster SV40 transformed cells	DNA amplification	NS	−	Schmezer et al. 1988
Chinese hamster V79 fibroblasts	Sister chromatid exchange	NS	+	Tomita et al. 1982b
Rat RL4 liver cells	Chromosomal aberrations	NS	+	Phillips et al. 1986
CHO cells	Chromosomal aberrations	+	+	Phillips et al. 1986
CHO cells	Chromosomal aberrations	NS	+	Phillips et al. 1982

Table 2-19. Genotoxicity of MEHP *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
SHE cells	Chromosomal aberrations	+	−	Tsutsui et al. 1993
Mouse BALB 3T3 cells	Cell transformation	–	–	Astill et al. 1986
Mouse C3H/10T1/2 fibroblasts	Cell transformation	NS	–	Sanchez et al. 1987
SHE cells	Cell transformation	NS	+	Mikalsen et al. 1990
SHE cells	Cell transformation	+	−	Tsutsui et al. 1993

[a]Mutagenic effect coincident with cytotoxicity.

– = negative result; + = positive result; ± = equivocal result; DNA = deoxyribonucleic acid; NA = not applicable to mammalian cell cultures with endogenous metabolic activity; NS = not specified

Table 2-20. Genotoxicity of DEHP *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Mouse (subcutaneous)	Dominant lethal test	+	Autian 1982
Mouse (gavage)	Dominant lethal test	–	Rushbrook et al. 1982
Mouse (intraperitoneal)	Dominant lethal test	+	Singh et al. 1974
Rat (*gpt* delta transgenic) (diet)	Gene mutation in liver	–	Kanki et al. 2005
Mouse (lacZ transgenic) (NS)	Gene mutation in liver	+	Boerrigter 2004
Mouse (lacZ transgenic) (NS)	Gene mutation in kidney or spleen	–	Boerrigter 2004
Hamster embryo (gavage; via placenta)	8AG/6TG-resistant mutation	+	Tomita et al. 1982b
Mouse (NS)	Micronuclei in bone marrow	–	Astill et al. 1986
Mouse (intraperitoneal)	Micronuclei in bone marrow	–	Douglas et al. 1986
Rat (gavage, diet)	DNA damage in liver	–	Butterworth et al. 1984
Rat (diet)	DNA damage in liver	–	Tamura et al. 1991
Rat (diet)	DNA damage in liver	−	Pogribny et al. 2008
Rat (diet)	DNA base modification in liver	–	Cattley and Glover 1993
Rat (diet)	DNA base modification in liver	+	Takagi et al. 1990
Rat (gavage, diet)	DNA repair in liver	–	Butterworth et al. 1984
Rat (diet)	DNA repair in liver	–	Cattley et al. 1988
Rat (gavage, diet)	DNA repair in liver	–	Kornbrust et al. 1984
Rat (gavage)	DNA repair in liver	+	Hayashi et al. 1998

Table 2-20. Genotoxicity of DEHP *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse (gavage, diet)	DNA repair in liver	–	Smith-Oliver and Butterworth 1987
Rat (diet)	DNA binding in liver	+	Albro et al. 1982a
Rat (gavage)	DNA binding in liver	–	Gupta et al. 1985
Rat (gavage, diet)	DNA binding in liver	–	Lutz 1986; Von Däniken et al. 1984
Human (occupational)	Chromosomal aberrations in leucocytes	–	Thiess and Fleig 1978
Rat (gavage)	Chromosomal aberrations in bone marrow	–	Putman et al. 1983
Hamster embryo (gavage; via placenta)	Chromosomal aberrations	+	Tomita et al. 1982b
Hamster embryo (gavage; via placenta)	Cell transformation	+	Tomita et al. 1982b
Rat embryo (intraperitoneal; via placenta)	Mitotic recombination	+	Fahrig and Steinkamp-Zucht 1996
Rat (diet)	Tetraploid nuclei in liver	+	Ahmed et al. 1989
Host-meditated assay			
Salmonella typhimurium (TA100); (rat host-meditated)	Gene mutation	–	Kozumbo et al. 1982
Eukaryotic organisms			
Drosophila melanogaster (feeding)	Mitotic recombination	–	Vogel and Nivard 1993
D. melanogaster (injection)	Sex linked recessive lethal	–	Yoon et al. 1985

– = negative result; + = positive result; DNA = deoxyribonucleic acid; *gpt* = guanine phosphoribosyltransferase; NS = not specified

Table 2-21. Genotoxicity of MEHP *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Rat (gavage)	DNA damage in liver	−	Elliott and Elcombe 1987
Rat (gavage)	Chromosomal aberrations in bone marrow	−	Putman et al. 1983
Hamster embryo (gavage; via placenta)	Chromosomal aberrations	+	Tomita et al. 1982b
Hamster embryo (gavage; via placenta)	Cell transformation	+	Tomita et al. 1982b
Hamster embryo (gavage; via placenta	8AG/6TG-resistant mutation	+	Tomita et al. 1982b

– = negative result; + = positive result

As shown in Tables 2-18 and 2-19, 27 *in vitro* assays indicate that neither DEHP nor its metabolite, MEHP, is mutagenic to bacteria, eukaryotic organisms, or mammalian cells, either with or without metabolic activation. The few isolated positive results have not been replicated, were borderline responses, and/or were accompanied by cytotoxicity (Kozumbo et al. 1982; Oberly et al. 1985; Tomita et al. 1982b). In a host-mediated assay, urine from rats injected with DEHP was not mutagenic to bacterial cells (Kozumbo et al. 1982). Additionally, DEHP did not induce sexed-linked recessive lethal mutations in *Drosophila melanogaster* (Yoon et al. 1985).

In vivo mammalian assays are limited and reported mixed results. 8AG/6TG-resistant mutations were observed in embryonic DNA collected from hamster dams exposed to a single gavage dose up to 15,000 mg/kg DEHP or MEHP during gestation (Tomita et al. 1982b). In transgenic animal lines, exposure to DEHP resulted in gene mutations in the liver of *lacZ* transgenic mice, but not in the kidney or spleen (Boerrigter 2004), and not in the liver of guanine phosphoribosyltransferase (*gpt)* delta transgenic rats (Kanki et al. 2005). Dominant lethal mutations were increased in mice that were exposed to DEHP by injection at dose levels that also resulted in decreased fertility, but not when exposure was by oral administration (Autian 1982; Rushbrook et al. 1982; Singh et al. 1974). The results of these studies are not necessarily indicative of genotoxicity because DEHP has not been shown to induce DNA lesions in most studies, and positive findings can be interpreted in different ways. For example, dominant lethal tests can be interpreted as indicating that the test chemical altered gene expression (i.e., by epigenetically shutting off the marker gene) rather than by mutation.

Spot tests were conducted in which mouse embryos heterozygous for recessive coat color mutations were exposed *in utero* to the direct monofunctional alkylating mutagen ethylnitrosourea (ENU), either alone or followed by intraperitoneal injection of the pregnant dam with DEHP (Fahrig and Steinkamp-Zucht 1996). DEHP, in combination with ENU, resulted in an increase in the number of spots indicative of reciprocal recombination, compared to ENU treatment alone. Conversely, DEHP alone resulted in a reduction in the number of spots that arose from ENU-induced gene mutations. These findings are not necessarily indicative of interference with DNA repair processes because DEHP could have induced altered spots epigenetically rather than by mutagenic means. As discussed by Trosko (1997, 2001), mutation assays are often misinterpreted to give false positives results for epigenetic (nonmutagenic) agents.

Binding of DEHP to DNA in rat liver was reported by Albro et al. (1982a, 1982b) following *in vivo* exposure, but was not observed by other investigators (Gupta et al. 1985; Lutz 1986; Von Däniken et al. 1984). *In vitro,* DEHP did not bind to DNA in rat hepatocytes (Gupta et al. 1985). However, several studies reported DNA damage (strand breakage) in cultured human, mouse, or bacterial cells exposed to DEHP or MEHP without metabolic activation (Anderson et al. 1999; Choi et al. 2010; Erkekoglue et al. 2010a, 2010b; Kleinsasser et al. 2004; Okai and Higashi-Okai 2000; Park and Choi 2007; Tomita et al. 1982b; Wang et al. 2014). Yang et al. (2012) specifically reported oxidative DNA damage in human HepG2 cells exposed to MEHP without metabolic activation. As shown in Tables 2-18 and 2-19, 14 studies reported that DEHP and MEHP did not cause DNA damage or repair in human, rat, mouse, or hamster cells with metabolic capacity or cultured cells with exogenous metabolic activation. Hayashi et al. (1998) reported evidence of DNA repair (increased expression of the post-translational modifying enzyme poly[ADP-ribose] polymerase) in the livers of rats exposed to 2,000 mg/kg/day DEHP via gavage for 7 days or 1,800 mg/kg/day DEHP in feed for up to 97 weeks. However, eight *in vivo* studies did not observe DNA damage or repair in rat livers following exposure to DEHP or MEHP (Tables 2-20 and 2-21). 8-Hydroxydeoxyguanosine was detected in hepatic DNA in rats exposed to 1,200 mg/kg/day DEHP for 2 weeks, indicating a potential for DNA damage secondary to oxidative stress (Takagi et al. 1990); however, Cattley and Glover (1993) did not confirm this finding in similarly treated rats exposed for up to 22 weeks.

Chromosomal aberrations were observed in embryonic DNA collected from hamster dams exposed to a single gavage dose up to 15,000 mg/kg DEHP or MEHP during gestation (Tomita et al. 1982b). However, increased frequencies of chromosomal aberrations were not observed in peripheral leukocytes collected from 10 workers occupationally exposed to DEHP at air concentrations of 0.0006–0.01 ppm for

10–30 years, compared with 20 control workers (Thiess and Fleig 1978). Additionally, chromosomal aberrations were not induced in rat bone marrow following oral exposure to DEHP or MEHP (Putman et al. 1983). Six *in vitro* mammalian studies reported a lack of chromosomal aberrations following exposure to DEHP (Table 2-18). However, findings following *in vitro* MEHP exposure were mixed, with evidence of chromosomal aberrations in 1/1 rat RL4 liver cell assay (without activation), 2/4 CHO cells assays (with and without metabolic activation), and 1/1 SHE cell assays (with activation) (Phillips et al. 1982, 1986; Tsutsui et al. 1993).

No clear evidence of micronucleus induction was observed following exposure to DEHP or MEHP in mouse bone marrow assays *in vivo* (Astill et al. 1986; Douglas et al. 1986) or in human cells exposed *in vitro* (Le Hegarat et al. 2014; Sobol et al. 2012). Similarly, the majority of *in vitro* studies did not observe increases in sister chromatid exchanges in mammalian cells exposed to DEHP, with or without metabolic activation (Abe and Sasaki 1977; Douglas et al. 1986; Phillips et al. 1982; Priston and Dean 1985), although a few studies reported equivocal or positive results in mammalian cells exposed to DEHP or MEHP without metabolic activation (Tennant et al. 1987; Tomita et al. 1982b).

Cell transformation was observed in embryonic DNA collected from hamster dams exposed to a single gavage dose up to 15,000 mg/kg DEHP or MEHP during gestation (Tomita et al. 1982b). Cell transformation was observed in all seven *in vitro* Syrian hamster embryo (SHE) cell assays with DEHP or MEHP, both with and without metabolic activation (Tables 2-18 and 2-19). Cell transformation was not observed in *in vitro* assays with mouse fibroblasts or 3T3 cell lines exposed to DEHP or MEHP (Astill et al. 1986; Sanchez et al. 1987); however, DEHP induced cell transformation in mouse epidermal cells exposed to DEHP with (but not without) metabolic activation (Diwan et al. 1985).

Rats that were exposed to 1,000 mg/kg/day DEHP for periods of 3 or 7 days alternating with 7-day withdrawal periods had increased liver cell division and numbers of tetraploid nuclei during the exposure periods (Ahmed et al. 1989). During the withdrawal periods in the latter study, the cell number declined and degenerated cells appeared to be those containing the tetraploid nuclei. Cells are more vulnerable to irreversible mutagenic alterations during a period of rapid cell division (Marx 1990), and it has been postulated that the carcinogenicity of DEHP might be a consequence of its induction of cell division in the liver in the presence of other mutagens (Smith-Oliver and Butterworth 1987). The available evidence supports the interpretation that DEHP is mitogenic, not mutagenic, because mutagens, by inducing DNA lesions, would inhibit DNA synthesis and cell proliferation. In general, evidence for DNA amplification and aneu/polyploidy has not been observed in mammalian cells exposed to DEHP or MEHP *in vitro*

(Priston and Dean 1985; Schmezer et al. 1988; Stenchever et al. 1976); however, mitotic aneuploidy was observed in *Saccharomyces cerevisiae* following exposure to DEHP both with and without metabolic activation (Parry et al. 1985). Gene conversion and/or mitotic segregation were not observed in *S. cerevisiae* or *Aspergillus niger* (Parry et al. 1985). Additionally, mitotic recombination was not observed in *D. melanogaster* fed DEHP (Vogel and Nivard 1993).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Human studies of DEHP provide primarily qualitative information on absorption and distribution and limited quantitative data on metabolite profiles and urinary excretion kinetics. DEHP toxicokinetics have been extensively studied in nonhuman primates (e.g., marmosets) and rodents, with most quantitative information derived from studies conducted in rats. An overview of these data is summarized below.

- At least 98% of inhaled radiolabeled DEHP is absorbed by the male rat. Based on volunteer studies, the expectation is that >70% of an oral dose is absorbed. Other experimental animals absorb a minimum of 30%. DEHP can be absorbed through skin. Approximately 2% of a dermal dose is absorbed in humans (6% in rats and 19–>50% in hairless guinea pigs).
- DEHP can saturate the enzymes responsible for metabolite absorption.
- No studies have been identified that provide reliable information about the distribution of DEHP in tissues (other than blood) in humans.
- DEHP has been detected in human adipose tissue collected at autopsy.
- Animal studies indicate that for all routes of exposure, the initial distribution is to liver, intestine, muscle, kidney, and fat (and lung during inhalation exposure).
- DEHP has been detected in placenta, amniotic fluid, fetal liver, and other fetal tissues in exposed rats. Mammary milk contains and transfers DEHP and MEHP to nursing rat pups.
- Tissue lipases hydrolyze DEHP. DEHP metabolites are further metabolized by cytochrome P450s, alcohol dehydrogenase, and aldehyde dehydrogenase.
- Most elimination of DEHP metabolites occurs by excretion in urine and feces (biliary secretion).
- Metabolite excretion profiles observed in humans are similar to those that have been observed in monkeys, rats, mice, hamsters, and guinea pigs, although species differences in relative abundance of metabolites and glucuronide conjugates have been reported.

3.1.1 Absorption

Inhalation Exposure. No quantitative data regarding absorption after inhalation exposures of humans to DEHP were located. However, absorption was confirmed to occur through the lungs of humans as evidenced by identification of DEHP in the urine of infants exposed to DEHP during respiration therapy (Roth et al. 1988). Up to 98% of inhaled [^{14}C]-DEHP was recovered from urine,

feces, and tissues of exposed male Sprague-Dawley rats (n=3) within 72 hours of exposure (Pegg 1982). Inhalation absorption of DEHP is also suggested by reported non-respiratory health effects observed following inhalation exposure (Table 2-1).

Oral Exposure. Oral absorption was demonstrated in four male volunteers (21–61 years old) who ingested a single dose (645±20 μg/kg) of full ring-deuterated DEHP (DEHP-D_4) (Kessler et al. 2012). The concentration-time courses of DEHP-D_4, free MEHP-D_4, and total MEHP-D_4 in blood varied widely among the volunteers. Peak blood concentrations of DEHP-D_4 generally occurred 3–4 hours after dosing. Free and total MEHP-D_4 blood concentrations each exhibited two spikes at 3–4 and 5–10 hours after exposure. Mean area under the concentration-time course (AUC) values for 24 hours after dosing indicated that the blood burden of free MEHP-D_4 was 2-fold higher than the blood burden of DEHP-D_4. Total MEHP-D_4 in the blood consisted of 64% free MEHP-D_4 and 36% MEHP-D_4-β-glucuronide (Kessler et al. 2012). Measurement of DEHP urinary metabolites after ingestion of a single oral dose in humans (0.35, 2.15, or 48.5 mg) indicated that at least 70% of the oral dose was systemically absorbed (Koch et al. 2005a). Other human studies reported lower oral absorption (11–47%); however, these studies have methodological limitations, including analysis of a smaller number of urinary metabolites and use of unlabeled DEHP (Anderson et al. 2001; Koch et al. 2004; Schmid and Schlatter 1985). In all cases, the oral absorption is expected to be higher than reported due to the biliary excretion of orally absorbed DEHP, which is not accounted for in these studies.

Studies conducted in several different experimental animal models (cynomolgus monkey, marmoset, rats, mice, hamsters) have suggested that at least 30% of a single oral dose of [^{14}C] administered as [^{14}C]-DEHP is systemically absorbed (Astill 1989; Astill et al. 1986; Daniel and Bratt 1974; Lake et al. 1984; Rhodes et al. 1986; Short et al. 1987; Sjöberg et al. 1985a; Williams and Blanchfield 1974). Absorption in rodents and monkeys has been underestimated because studies do not account for fecal excretion nor tissue storage of DEHP metabolites (Daniel and Bratt 1974; Rhodes et al. 1986).

In marmosets, 54–78% of a single oral dose of 100 mg/kg [^{14}C]-DEHP was excreted in urine and feces over 7 days (Kurata et al. 2012b). Oral absorption of DEHP appears to be lower in marmosets compared to rats based on blood and tissue levels of [^{14}C] observed in the two species following oral dosing with [^{14}C]-DEHP (Kurata et al. 2012b; Rhodes et al. 1986) or measurements of plasma C_{max} and AUC at comparable doses (Kessler et al. 2004). Oral absorption of DEHP also appears to be greater in immature rats compared to mature rats. Plasma AUC for [^{14}C] following a single oral dose of 1,000 mg/kg [^{14}C]-DEHP administered to rats at age 20 days was approximately twice that of rats that received the

same dose at age 40 or 60 days (Sjöberg et al. 1985a). Plasma concentration data for 3- or 18-month-old marmosets, however, did not show an age-related change in oral absorption of radiolabel following administration of a single dose of 100 or 2,500 mg/kg ^{14}[C]-DEHP (Kurata et al. 2012b). Plasma AUC data (all radiolabel) for 3-month-old marmosets suggest a saturation of absorption at higher doses (AUC/dose ratios were 0.374 and 0.108 for administered doses of 100 and 2,500 mg/kg, respectively) (Kurata et al. 2012b).

Hydrolysis of DEHP appears to be the rate-limiting step in the absorption of MEHP in the small intestine. In an *in vitro* preparation of rat small intestine, exposure of the intestinal mucosa to DEHP resulted in an absorptive flux of MEHP with no flux of DEHP, and MEHP was absorbed 7–8 times more rapidly when the intestinal mucosa was exposed to MEHP than when exposed to DEHP (White et al. 1980). Chang-Liao et al. (2013) estimated the bioavailability of DEHP following a single gavage dose of 100 mg/kg to be approximately 7% in male Sprague-Dawley rats based on comparison to a 10 mg/kg intravenous dose.

The appearance of DEHP in liver shortly after (e.g., 4 hours) an oral dose of DEHP has been used as an indirect measure of absorption of unhydrolyzed DEHP from the gastrointestinal tract (transport to the liver in the hepatic-portal blood). Gavage and intravenous studies have reported an apparent dose threshold for the appearance of DEHP in liver soon after dosing in rats and certain mouse strains (Albro 1986; Albro et al. 1982b). However, Astill (1989) found that no such absorption threshold existed when rats were fed DEHP in the diet at comparable doses and for prolonged feeding periods, indicating that the gavage and intravenous methods could influence absorption assessments. DEHP was not detected in the liver of rats 6 hours following intravenous administration of doses ≤500 mg/kg; however, over the dose range 500–1,000 mg/kg, DEHP concentration in the liver increased with increasing dose, suggesting an intravenous threshold for absorption of DEHP at approximately 500 mg/kg (Albro et al. 1982b). A similar dose-dependency in liver DEHP concentration was observed in CD-1 mice, with DEHP detected in the liver following gavage doses in excess of approximately 500 mg/kg (Albro 1986). No threshold for DEHP absorption was detected in B6C3F1 mice following oral doses of ranging from 20 to 575 mg/kg, as indicated by liver DEHP concentrations (Albro 1986). The observations of apparent thresholds for DEHP gavage absorption are consistent with either exposure methodology effects or saturation of DEHP hydrolysis in the gastrointestinal tract, leading to increased absorption of unhydrolyzed DEHP. *In vitro* studies have shown that hydrolysis of DEHP to MEHP in contents of rat caecum and small intestine is saturable (Rowland 1974). Albro and Thomas (1973) suggested that there is little chance that DEHP would be absorbed as an intact molecule following oral exposure.

Dermal Exposure. DEHP applied dermally penetrates skin and can be absorbed into the systemic circulation (Chu et al. 1996; Deisinger et al. 1998; Elsisi et al. 1989; Wester et al. 1998). Wester et al. (1998) observed, in humans, that approximately 1% of a [^{14}C] dose applied as [^{14}C]-DEHP (18.5 µg/cm^2 dissolved in ethanol) was excreted in urine in 7 days. The dose was applied to the forearm of five to six adults and washed 24 hours after application. The urinary excretion of [^{14}C]-DEHP was also measured following intravenous injection in Rhesus monkeys to account for fecal excretion and tissue storage. From these data, Wester et al. (1998) estimated the total human dermal dose absorbed to be 1.8±0.5%. In rats, approximately 6% of an applied dose of [^{14}C]-DEHP (5–8 mg/cm^2, dissolved in ethanol) was excreted (urine plus feces) in 7 days (Elsisi et al. 1989). The dose was applied to the shaved back, covered with a perforated plastic bandage, and left in place for 7 days. Absorption, as measured by [^{14}C] in excreta and carcass, was much lower in rats when the DEHP dose was applied as a polyvinyl carbonate film containing [^{14}C]-DEHP (Deisinger et al. 1998). A 24-hour exposure to approximately 400 mg DEHP resulted in 0.01% of the applied dose appearing in the excreta (urine plus feces) and carcass after 7 days (Deisinger et al. 1998).

Dermal absorption of DEHP was higher in hairless guinea pigs than in rats (Chu et al. 1996; Ng et al. 1992). A dermal dose (13 µg/cm^2) of [^{14}C]-DEHP (dissolved in acetone, applied to the back, covered with a non-occlusive bandage, and left in place for 24 hours) resulted in excretion (urine plus feces) of approximately 21% of the applied dose in hairless guinea pigs (Ng et al. 1992). The estimated dermal absorption was approximately 53% of the applied dose (calculated from the cumulative 7-day excretion of [^{14}C] following a single intramuscular dose of [^{14}C]-DEHP).

Chu et al. (1996) applied a 442 µg/cm^2 (dissolved in acetone) dose of radiolabeled DEHP to the backs of hairless guinea pigs. A non-occlusive bandage covered the application site and for 7 days, and feces and urine were collected. Chu et al. (1996) determined that 19% of the applied dose was dermally absorbed and either excreted or stored within the body.

In vitro studies have provided estimates of transdermal flux rates of [^{14}C] when [^{14}C]-DEHP is applied to the epidermal surface (Barber et al. 1992; Hopf et al. 2014; Ng et al. 1992; Scott et al. 1987; Wester et al. 1998). Experiments using fresh dermatomed human abdominal skin demonstrated that an aqueous solution of DEHP-D_4 readily permeated the skin (K_p of 15.1x10^{-5} cm/hour), while the permeability of neat DEHP was much lower (K_p of 0.13x10^{-5} cm/hour) (Hopf et al. 2014). Two studies have measured and compared permeability coefficients for [^{14}C] in skin preparations from humans and rats exposed to [^{14}C]-DEHP; both studies found human skin to be approximately 4-fold more permeable than rat skin

(Barber et al. 1992; Scott et al. 1987). Barber et al. (1992) estimated permeability coefficients to be $1.05\pm0.21x10^{-7}$ cm/hour for isolated human epidermal membranes and $4.31\pm1.34x10^{-7}$ cm/hour for isolated rat skin (whole skin). Scott et al. (1987) estimated coefficients to be $0.57\pm0.12x10^{-5}$ cm/hour for human epidermal membranes and $2.28\pm0.23x10^{-5}$ cm/hour for rat epidermis.

In vitro studies have also been conducted with preparations of hairless guinea pig skin and in perfused pig skin flaps (Ng et al. 1992; Wester et al. 1998). These studies did not derive permeability coefficients; however, they do provide [^{14}C] flux rates for similar initial doses applied to the epidermal surfaces. The flux rate in the perfused pig skin was approximately 10-fold lower; 0.003 µg/cm^2/hour at a starting dose of 18.5 µg/cm^2 (Wester et al. 1998) in the pig epidermal membranes, compared to 0.035 µg/cm^2/hour at a starting dose of 14 µg/cm^2 in the guinea pig skin (Ng et al. 1992). In the Ng et al. (1992) study, [^{14}C] recovered in the receptor fluid was analyzed to determine whether the [^{14}C] that was transferred across the skin preparation was [^{14}C]-DEHP or [^{14}C]-MEHP. Approximately 70% of the transdermal flux of [^{14}C] across the hairless guinea pig skin was attributed to MEHP. Treatment of the preparation with an esterase inhibitor (phenylmethylsulfonyl fluoride) decreased the MEHP contribution to the flux rate from 70 to 45%; however, total [^{14}C] flux was not significantly affected (3.36±0.37%/24 hours versus 2.67±0.42%/24 hours). These results suggest that, while hydrolysis of DEHP to MEHP occurred in the skin, it was not a rate-limiting step for *in vitro* dermal absorption.

3.1.2 Distribution

No studies were identified that provide reliable information about the distribution of DEHP in tissues (other than blood) in humans. While DEHP has been detected in human adipose tissues collected at autopsy (Mes et al. 1974), contamination from plastics used in the handling and storage of the tissues may have contributed to the levels of DEHP detected in this study.

Inhalation Exposure. More direct measurements of tissue distribution are available from studies conducted in animals that received doses of labeled DEHP (e.g., [^{14}C]-DEHP). The tissue distribution of [^{14}C] following intravenous, oral, inhalation, and dermal dosing with [^{14}C]-DEHP has been studied in rodents, dogs, pigs, and nonhuman primates (Ikeda et al. 1980; Kurata et al. 2012b; Pegg 1982; Rhodes et al. 1986; Tanaka et al. 1975). In general, for all of the above routes of exposure, the initial distribution (within 4 hours of dosing) is dominated by uptake of [^{14}C] in liver, intestine, muscle, kidney, and fat (and in lung during inhalation exposure) (Pegg 1982). Concentrations in liver, spleen, intestine, lung, kidney, heart, and adipose can exceed that of blood (Rhodes et al. 1986; Tanaka et al. 1975). Distribution to the

intestine occurs following intravenous dosing, indicating transport of absorbed [^{14}C] to the intestine (Tanaka et al. 1975; Wallin et al. 1974). The elimination from fat is slower than from other tissues and, as a result, the contribution of fat to [^{14}C] body burden increases over time following a single dose of [^{14}C]-DEHP, as [^{14}C] is eliminated from other tissues (Ikeda et al. 1980; Tanaka et al. 1975). In male Sprague-Dawley rats exposed to an aerosol (0.24–0.61 µm particle size range) of [^{14}C]-DEHP (83 mg/m^3) for 6 hours, approximately 50% of the inhaled [^{14}C] was excreted in urine, 40% was excreted in feces within 72 hours, and approximately 5–7% remained in the carcass (Pegg 1982).

Oral Exposure. Although numerous studies have measured tissue levels of [^{14}C] following dosing with [^{14}C]-DEHP, Tanaka et al. (1975) reported time-course observations for [^{14}C] in various tissues (male Wistar rats) following a single intravenous or oral dose of [^{14}C]-DEHP. Tissue [^{14}C] levels were expressed as percent of dose and as dose-adjusted tissue [^{14}C] concentrations. The latter metric allows comparisons of tissue [^{14}C] concentrations and tissue [^{14}C] kinetics for the two exposure routes (Tables 3-1 and 3-2). Following an intravenous dose (50 mg/kg), the highest concentrations of [^{14}C] were observed in liver, and tissue:blood concentration ratios 1 hour following the intravenous dose were >1 for liver (53), spleen (20), intestine (tissue and contents, 7.8), lung (4.7), kidney (3.0), and heart (1.9). Seven days following the intravenous dose, the total body burden of [^{14}C] was <1% of the administered dose and the highest [^{14}C] concentration was in adipose. Tissue:blood concentration ratios were ≥1 in adipose (7.5), lung (2.2), liver (2.0), kidney (1.5), and intestine (1.1). A similar pattern of distribution was observed following the oral dose of [^{14}C]-DEHP (500 mg/kg) (Tanaka et al. 1975). The highest concentrations (excluding the gastrointestinal tract) were observed in liver 3 hours following the oral dose. At that time, tissue:blood concentrations were ≥1 in liver (6.9), kidney (4.8), lung (2.8), spleen (2.4), heart (1.8), and muscle (1.2). Twenty-four hours following the oral dose, the body burden of [^{14}C] (excluding the gastrointestinal tract) was <3% of the administered dose.

Table 3-1. Tissue Distribution of [14C] Following an Intravenous Dose of 50 mg/kg [14C]-DEHP in Male Wistar Rats[a]

	Time following dose (hours)						
Tissue	1	2	3	6	12	24	168
Liver	15	12	10	7.3	5.6	1.5	0.04
Spleen	5.7	2.1	0.63	0.4	3.8	0.4	0.015
Intestine	2.2	3.0	3.7	3.7	1.7	1.9	0.022
Lung	1.3	0.76	0.64	0.47	0.23	0.07	0.045
Kidney	0.83	0.48	0.54	0.43	0.18	0.12	0.03
Heart	0.54	0.45	0.38	0.33	0.18	0.06	0.015
Blood	0.28	0.16	0.19	0.15	0.09	0.08	0.02

Table 3-1. Tissue Distribution of [14C] Following an Intravenous Dose of 50 mg/kg [14C]-DEHP in Male Wistar Rats[a]

	Time following dose (hours)						
Tissue	1	2	3	6	12	24	168
Adipose	0.25	0.20	0.09	0.10	0.21	0.18	0.15
Stomach	0.15	0.16	0.13	0.25	0.14	0.07	0.015
Muscle	0.12	0.13	0.13	0.15	0.07	0.22	0.015
Testicle	0.035	0.030	0.028	0.036	0.026	0.011	0.005
Brain	0.020	0.026	0.031	0.028	0.034	0.012	0.006

[a]Values are [^{14}C] activity (dpm) per g tissue per dose/kg body weight (dpm/g per mg/kg).

Source: Tanaka et al. 1975

Table 3-2. Tissue Distribution of [14C] Following an Oral Dose of 500 mg/kg [^{14}C]-DEHP in Male Wistar Rats[a]

	Time following dose (hours)					
Tissue	1	2	3	6	12	24
Stomach	33	17	8.1	5.3	1.4	0.29
Intestine	3.7	5.5	6.5	3.6	5.7	6.9
Liver	0.43	0.44	0.69	0.66	0.36	0.18
Kidney	0.42	0.36	0.48	0.61	0.32	0.090
Lung	0.10	0.32	0.28	0.23	0.13	0.020
Spleen	0.070	0.12	0.24	0.13	0.030	0.0060
Heart	0.096	0.14	0.19	0.27	0.11	0.030
Muscle	0.080	0.10	0.12	0.11	0.04	0.008
Blood	0.060	0.07	0.10	0.11	0.06	0.030
Testicle	0.020	0.05	0.09	0.09	0.03	0.006
Adipose	0.42	0.10	0.08	0.11	0.05	0.020
Brain	0.010	0.025	0.036	0.018	0.05	0.00030

[a]Values are [^{14}C] activity (dpm) per g tissue per dose/kg body weight (dpm/g per mg/kg).

Source: Tanaka et al. 1975

Following oral doses of [^{14}C]-DEHP administered to pregnant rats, [^{14}C] has been detected in placenta, amniotic fluid, and fetal liver and other fetal tissues (Calafat et al. 2006; Clewell et al. 2010; Singh et al. 1975; Stroheker et al. 2006). Plasma DEHP and MEHP kinetics have been compared in pregnant and nonpregnant rats and marmosets. These studies indicate that plasma C_{max} and dose-adjusted plasma AUC are not markedly affected by pregnancy in these species (Kessler et al. 2004). The amniotic fluid:maternal plasma concentration ratio was approximately 0.2–0.3 following oral doses (750 mg/kg/day) administered to rats on GDs 14–21 (Stroheker et al. 2006). A major fraction of the [^{14}C]

that is transferred to the fetus appears in the liver. Liver [^{14}C] was approximately 30% of total fetal [^{14}C] burden following an oral dose of [^{14}C]-DEHP (750 mg/kg) administered on GDs 14–21 (Stroheker et al. 2006). When dosing was extended to PND 4, [^{14}C] was detected in the livers of pups (3–5% of pup [^{14}C] burden). Lactational exposure, as well as residual [^{14}C] from *in utero* exposure, could have contributed to the [^{14}C] observed in the pups. Kurata et al. (2012b) compared the distribution of [^{14}C] in fetal blood, liver, kidney, and testes 24 hours after administration of a single gavage dose of 100 mg/kg [^{14}C]-DEHP on GD 20 in rats and GD 130 in marmosets. Radioactivity was highest in all tissues of fetal rats compared to fetal marmosets. MEHP was detected in the livers of mouse offspring (fetuses and PND 2 pups) following DEHP administration in the diet (0.01 and 0.05%) of pregnant dams (dosed throughout gestation) (Hayashi et al. 2012). DEHP lipase activity and MEHP concentrations were higher in pregnant dams compared to postpartum dams or nonpregnant mice.

DEHP and MEHP transfer to mammary milk. Milk concentrations of DEHP and MEHP were approximately 216 and 25 µg/mL, respectively, following oral doses of DEHP (2,000 mg/kg) administered to rats on days 15–17 of lactation (Dostal et al. 1987). Milk:maternal plasma concentration ratios in this study were >200 for DEHP and 0.3 for MEHP. DEHP and MEHP were not detected in pup plasma, which may reflect low bioavailability of DEHP and MEHP from milk, or rapid clearance of DEHP and MEHP from the pup plasma (the pups were analyzed 3–4 hours after the last maternal dose). DEHP was detected in livers of rat pups that nursed from dams that received oral doses of DEHP (2,000 mg/kg/day) from PND 1 through 21, indicating that DEHP in milk is bioavailable (Parmar et al. 1985). Supporting this are studies in which pups received oral doses of [^{14}C]-DEHP (in lipid emulsion). Liver [^{14}C] was approximately 27% of the administered oral dose 24 hours following an oral dose of DEHP (0.7 mg/kg) administered on PND 3. Liver levels decreased to approximately 8% of the dose when administered on PND 10 and approximately 2% of the dose when administered on PND 20 (Eriksson and Darnerud 1985).

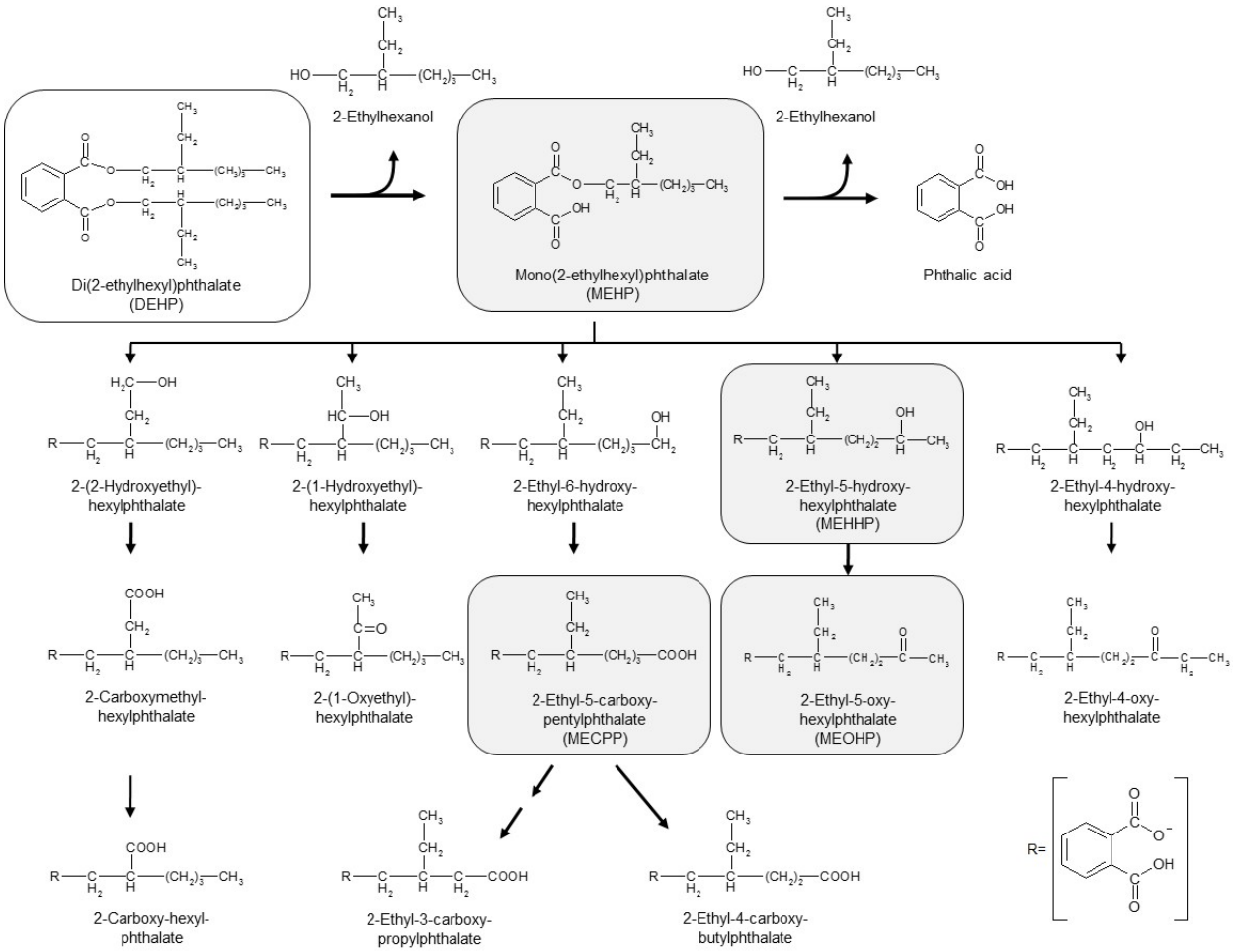
3.1.3 Metabolism

The metabolism of DEHP has been studied in humans and various animal models, including nonhuman primates and rodents (Albro 1986; Albro et al. 1981, 1982a, 1982b, 1983; Anderson et al. 2011; Astill 1989; Choi et al. 2012, 2013; Hayashi et al. 2012; Ito et al. 2014; Koch et al. 2005a, 2005b; Kurata et al. 2012a, 2012b; Lhuguenot et al. 1985; Schmid and Schlatter 1985; Silva et al. 2006). Figure 3-1 depicts the metabolic pathways for DEHP.

The first step in the metabolism of DEHP is hydrolytic cleavage to yield MEHP and 2-EH. The hydrolysis reaction is catalyzed by "DEHP hydrolases," which may include several different carboxyesterases, including lipases. DEHP hydrolase activity has been detected in a variety of tissues including pancreas, intestinal mucosa, liver, kidneys, lungs, skin, testes, and plasma (Albro 1986; Choi et al. 2012; Hopf et al. 2013). The pancreatic tissue is the richest source of DEHP hydrolase activity, whereas adipose has a relatively low activity. Pancreatic lipases secreted into the small intestine contribute DEHP hydrolase activity to the intestinal contents (White et al. 1980). This activity, along with esterases in the intestinal mucosa, results in substantial hydrolysis of ingested DEHP (to MEHP) at the gastrointestinal portal of entry (Barber et al. 1994; Rowland 1974; Rowland et al. 1977). Enzymes in gut microflora and gut contents can also convert DEHP to MEHP before absorption occurs (Rowland et al. 1977). Hydrolysis of DEHP in the gastrointestinal tract is saturable (Albro 1986; Albro et al. 1982b; Rowland 1974). This contributes to a dose-dependence in the bioavailability of DEHP, with increasing bioavailability of DEHP as dose approaches the saturating level in the gastrointestinal tract.

Although absorption of DEHP occurred in rats following oral doses >500 mg/kg (Albro et al. 1982a), DEHP was not detected in plasma following oral DEHP doses of 500–1,000 mg/kg/day for 7 days in rats (Sjöberg et al. 1986). These studies suggest that esterase activity in plasma, liver, and other tissues was sufficient to completely hydrolyze absorbed DEHP before it appears in plasma, even after oral doses of DEHP that would saturate hydrolysis in the gastrointestinal tract. Pollack et al. (1985b) estimated that approximately 80% of a 2,000 mg/kg oral dose of [^{14}C]-DEHP had been hydrolyzed prior to the appearance of [^{14}C] in plasma in rats. Other studies conducted in rats and marmosets have shown that following an oral dose of DEHP, most of the phthalate that appears in plasma is MEHP and not DEHP (Kessler et al. 2004; Koo and Lee 2007). These studies suggest that as a result of the rapid hydrolysis of DEHP during and following absorption; the [^{14}C] in plasma primarily reflects that of MEHP and MEHP metabolites rather than DEHP.

Figure 3-1. Metabolic Pathway of DEHP*



*Highlighted metabolites are measured in CDC's National Biomonitoring Program, (https://www.cdc.gov/biomonitoring/DEHP_BiomonitoringSummary.html).

Source: Adapted by permission from Macmillan Publishers Ltd: Lorber et al. (2010)

Species differences in DEHP hydrolase activity have been reported. Ito et al. (2005) compared activities in tissues (kidney, liver, lung, and small intestine) of mice, rats, and marmosets. The highest activities were observed in mice and the lowest activities were observed in marmosets. DEHP hydrolase observed in marmoset liver homogenates was approximately 5–10% of that of the mouse and rat. Ito et al. (2005) also measured the K_m and V_{max} for DEHP hydrolase activity in liver microsomes, a source of lipase and DEHP hydrolase activity (Table 3-3). Relative to rats and mice, marmosets had a higher K_m and lower V_{max}, with a V_{max}/K_m ratio that was <1% of that of rats and mice (i.e., lower intrinsic clearance). Relatively low activities of DEHP hydrolase in marmosets may at least partially explain the lower oral bioavailability of DEHP metabolites in marmosets compared to rats—see further discussion in Section 3.1.1. Ito et al. (2014) compared DEHP hydrolase activity in liver microsomes from mice and 38 human subjects (liver samples obtained from deceased donors). Mean DEHP hydrolase activity in human liver microsomes was 5-fold lower than the activity measured using mouse microsomes. Similar to marmosets, human hydrolase kinetics were characterized by a higher K_m and a lower V_{max} than mice, resulting in a 6.7-fold lower V_{max}/K_m ratio (Ito et al. 2014; Table 3-3). The inter-individual variation in DEHP hydrolase activity was approximately 10-fold among the 38 donors (primarily Caucasian males between the ages of 16 and 80 years).

Table 3-3. Michaelis-Menten Constants for DEHP Hydrolase Activity in Liver Microsomes[a]

	Ito et al. (2005)			Ito et al. (2014)	
Reaction parameters	Mouse	Rat	Marmoset	Mouse	Human
K_m (mmol/L)	0.012	0.006	1.357	0.0076	0.0144
V_{max} (nmol/minute/mg protein)	3.91	1.32	0.49	5.45	1.52
V_{max}/K_m ratio	333	227	1.38	714	106

[a]Values represent the mean of triplicate analyses for each group.

Sources: Ito et al. 2005, 2014

Hydrolysis of the second ester bond of DEHP to convert MEHP to phthalic acid is a relatively minor pathway. The major pathways of metabolism of MEHP are ω- and ω-1-oxidation of the aliphatic side chain, which forms side-chain hydroxyl products, followed by α- or β-oxidation and formation of side-chain carboxylic acid and ketone products. The ω- and ω-1-oxidation reactions are mediated by CYP isozymes, specifically human recombinant CYP2C9*1, CYP2C9*2, and CYP2C19 and rat recombinant CYP2C6 (Choi et al. 2012, 2013). Secondary α- or β-oxidation reactions have been attributed to alcohol dehydrogenase or aldehyde dehydrogenase (Albro and Lavenhar 1989; Ito et al. 2005). The oxidized

phthalate metabolites of MEHP can be conjugated with glucuronic acid to form acyl-glucuronides (Albro 1986; Astill 1989; Silva et al. 2003; Sjöberg et al. 1991). Conjugation of MEHP and MEHP metabolites with glucose to form β-glucosides has also been detected in mouse urine; however, it appears to be a minor conjugation pathway relative to the glucuronide pathway (Egestad and Sjöberg 1992; Egestad et al. 1996). No other conjugation products of DEHP metabolites have been detected (e.g., sulfate, glutathione, taurine). Metabolites of the aromatic moiety of DEHP have not been reported. The 2-EH product of hydrolysis of DEHP is metabolized through oxidative pathways that include 2-ethylhexanoic acid keto acid derivatives, which appear to be products of β-oxidation (Albro and Corbett 1978).

The primary urinary metabolites of DEHP in humans include MEHP, MEHHP, 2-ethyl-5-oxyhexyl-phthalate; MEOHP, MECPP, and the corresponding acyl-glucuronides (Albro et al. 1982a; Anderson et al. 2011; Ito et al. 2014; Koch et al. 2005a, 2005b; Kurata et al. 2012b; Schmid and Schlatter 1985). Metabolite excretion profiles observed in humans are similar to those that have been observed in monkeys, rats, mice, hamsters, and guinea pigs, although species differences in relative abundance of metabolites and glucuronide conjugates have been reported (Albro et al. 1981, 1982a, 1982b; Astill 1989; Kurata et al. 2012a, 2012b; Lhuguenot et al. 1985, 1988; Rhodes et al. 1986; Short et al. 1987). Relative abundances of DEHP metabolites excreted in urine of various animal species are presented in Table 3-4 (based on Albro et al. 1982a). Guinea pigs excreted relatively few MEHP oxidation products, suggesting low rates of oxidative metabolism of MEHP in this species. By contrast, rats excreted MEHP oxidation products but only trace levels of MEHP, indicating extensive oxidative metabolism of MEHP in this species. Species differences in conjugation patterns have also been observed. Phthalate metabolites of DEHP were excreted predominantly as glucuronide conjugates in humans and in monkeys, whereas glucuronide conjugates were not observed in rats (Albro et al. 1982a). Based on studies in which urine was treated with aryl sulfatase, acylase I, and carboxypeptidase A, conjugation of DEHP metabolites with glutathione, sulfates, or amino acids (e.g., taurine) does not occur in rats, mice, guinea pigs, or hamsters (Albro et al. 1982a). More recent studies confirm that urinary metabolites of DEHP are highly conjugated to glucuronide in humans and marmosets compared to rats (Kurata et al. 2012a, 2012b).

Table 3-4. Comparison of Phthalate Metabolites in Urine Following Dosing with DEHP

	Percentage of total metabolites in urine[a]					
Metabolite	Rat	Mouse	Guinea pig	Green monkey	Man	Hamster
Residual DEHP	–	0.5	–	2.2	–	0.3
MEHP	Trace	18.6	71.2	28.9	18.3	4.5
MECPP	51.3	1.1	6.9	4.2	5.3	14.0
MEOHP	2.6	14.9	1.1	5.9	12.1	10.2
MEHPP	13.3	12.3	3.4	38.2	36.2	32.7
Free[b]	100[c]	36[d]	35	20	20	85
Conjugated[b]	0[d]	64[d]	65	80	80	15

[a]Urine containing 90% of administered [^{14}C] following a single oral (rat, mouse, guinea pig, hamster) or intravenous (monkey, human) dose of [^{14}C]-DEHP were pooled. Data for rat, mouse, guinea pig, and hamster represent pooled urines from three animals; data for monkeys and humans represent two pooled urine samples.
[b]Percent of total ^{14}C not conjugated or conjugated with glucuronic acid (based on comparisons of urine treated or not treated with β-glucuronidase).
[c]Three rat strains.
[d]CD strain.

MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEOHP = mono-2-ethyl-5-oxyhexylphthalate

Source: Albro et al. 1982a

3.1.4 Excretion

DEHP is mostly metabolized to MEHP and other DEHP metabolites. Elimination of these metabolites occurs by excretion in urine and feces (Daniel and Bratt 1974; Koch et al. 2004, 2005a; Kurata et al. 2012a, 2012b). Studies conducted in several different experimental animal models (Cynomolgus monkey, marmoset, rats, mice, hamsters) have shown that approximately 30–50% of a single oral dose of [^{14}C] administered as [^{14}C]-DEHP is excreted in urine (Astill 1989; Astill et al. 1986; Daniel and Bratt 1974; Lake et al. 1984; Rhodes et al. 1986; Short et al. 1987; Sjöberg et al. 1985a; Williams and Blanchfield 1974). Doses utilized in these studies ranged from 85 to 2,000 mg/kg. DEHP and MEHP were detected by high-performance liquid chromatography (HPLC) in rat urine following doses of 40 to 1,000 mg/kg DEHP (Koo and Lee 2007); however, DEHP was not detected by ultra performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS) in urine from rats exposed to 100 mg/kg (Chang-Liao et al. 2013). DEHP was not detected in human urine following single oral doses of DEHP-D_4 (3 mg or ~0.04 mg/kg from Kurata et al. [2012b]; 0.005–0.65 mg/kg from Koch et al. [2005a, 2004]). MEHP has also been detected in human sweat, which suggests that perspiration may also contribute to the elimination of DEHP (Genuis et al. 2012).

Fecal excretion results from biliary secretion of DEHP metabolites. [^{14}C]-MEHP, but not [^{14}C]-DEHP, was detected in bile of rats following an oral dose of [^{14}C]-DEHP (2.6 mg/kg) (Daniel and Bratt 1974). Metabolites delivered into the small intestine from biliary secretion may be reabsorbed, resulting in an enterohepatic circulation of DEHP-derived phthalates (Keys et al. 1999). Following oral or intravascular dosing with DEHP, serum concentrations of MEHP exhibit an oscillation in some reports that has been interpreted as indirect evidence for enterohepatic circulation (Kessler et al. 2004; Ljungvall et al. 2004; Pollack et al. 1985b; Sjöberg et al. 1985b); however, such a pattern was not observed in rats orally exposed to 100 mg/kg (Chang-Liao et al. 2013). Enterohepatic circulation is discussed further in context with physiologically-based toxicokinetic models of DEHP (Section 3.1.5).

Estimates of the relative contribution of the urinary and biliary routes vary widely. Estimates of urinary excretion following an oral dose of isotopically-labeled DEHP in humans range from 11 to 74% (Anderson et al. 2001; Koch et al. 2004, 2005a; Schmid and Schlatter 1985). Daniel and Bratt (1974) measured urinary and biliary [^{14}C] following an oral dose of [^{14}C]-DEHP (2.6 mg/kg) in rats and estimated the urinary:biliary excretion ratio to be approximately 3:1. Other studies conducted in animals found urinary:fecal excretion ratios to be 2:1 in marmosets following an intravenous dose of 100 mg/kg DEHP (Rhodes et al. 1986), approximately 1–3:1 in rats following a dermal dose (Deisinger et al. 1998), and 4–5:1 in hairless guinea pigs following a dermal dose (Ng et al. 1992). The urinary:fecal excretion ratio in marmosets given a single oral dose of [^{14}C]-DEHP (100 or 2,500 mg/kg) was approximately 1:2–5 (cumulative excretion over 7 days postdosing) (Kurata et al. 2012b).

Elimination half-life ($t_{1/2}$) values for DEHP and MEHP have been estimated in humans, marmosets, pigs, and rats. Estimates of the blood, serum, or plasma elimination $t_{1/2}$ for MEHP following exposure to DEHP range from 2 to 4 hours in humans and marmosets and from 1.1 to 9.4 hours in rats (Table 3-5) (Kaun-Yu et al. 2014; Kessler et al. 2004, 2012; Koch et al. 2004, 2005a; Koo and Lee 2007; Ljungvall et al. 2004; Oishi 1989, 1990; Pollack et al. 1985b; Sjöberg et al. 1985b; Teirlynck and Belpaire 1985). After DEHP administration in rats, the range of elimination values for DEHP from blood or plasma is wider than observed for MEHP, with reported values for $t_{1/2}$ ranging from 0.5 to 19 hours (Chang-Liao et al. 2013; Kaun-Yu et al. 2014; Kessler et al. 2004; Koo and Lee 2007; Oishi 1989, 1990; Pollack et al. 1985b; Sjöberg et al. 1985b). After direct exposure to MEHP, reported blood and plasma elimination $t_{1/2}$ for MEHP range from 2.8 to 5.5 hours in rats (Pollack et al. 1985b; Teirlynck and Belpaire 1985).

Table 3-5. Blood, Serum, or Plasma Elimination Half-Lives ($t_{1/2}$) for DEHP and MEHP

Species	Route of administration[a]	Dose (mg/kg)	Measured chemical	Measured medium	Elimination $t_{1/2}$ (hour)	Clearance (mL/hour/kg)	Reference
After administration of DEHP							
Human	Oral	0.645	DEHP	Blood	4.3	NA	Kessler et al. 2012
Human	Oral	0.645	MEHP	Blood	1.9 and 4.4 (biphasic[c])	NA	Kessler et al. 2012
Human	Oral	0.65	MEHP	Serum	2.0	NA	Koch et al. 2004, 2005a
Marmoset	Oral	30	MEHP	Blood	2.2[d]	NA	Kessler et al. 2004
Rat	Oral	1,000	DEHP	Blood	3.3	NA	Kessler et al. 2004
Rat	Oral	1,000	DEHP	Blood	17	NA	Oishi 1989
Rat	Oral	2,000	DEHP	Blood	16	NA	Pollack et al. 1985b
Rat	Oral	30	MEHP	Blood	2.8[d]	NA	Kessler et al. 2004
Rat	Oral	500	MEHP	Blood	3.1[d]	NA	Kessler et al. 2004
Rat	Oral	1,000	MEHP	Blood	3.9[d]	NA	Kessler et al. 2004
Rat	Oral	1,000	MEHP	Blood	5.8	NA	Oishi 1989
Rat	Oral	2,000	MEHP	Blood	6.7	NA	Pollack et al. 1985b
Rat	Oral	2,000	MEHP	Blood	7.4	NA	Oishi 1990
Rat	Oral	500	[$^{14}CO_2$][e]	Blood	11[d]	NA	Tanaka et al. 1975
Rat	Oral	40	DEHP	Plasma	19	552	Koo and Lee 2007
Rat	Oral	100	DEHP	Plasma	0.5	NA	Chang-Liao et al. 2013
Rat	Oral	200	DEHP	Plasma	15	2,116	Koo and Lee 2007
Rat	Oral	400	DEHP	Plasma	ND	NA	Teirlynck and Belpaire 1985
Rat	Oral	500	DEHP	Plasma	1.1	NA	Kaun-Yu et al. 2014
Rat	Oral	1,000	DEHP	Plasma	13	5,493	Koo and Lee 2007
Rat	Oral	2,800	DEHP	Plasma	ND	NA	Teirlynck and Belpaire 1985
Rat	Oral	40	MEHP	Plasma	9.4	NA	Koo and Lee 2007
Rat	Oral	200	MEHP	Plasma	8.8	NA	Koo and Lee 2007
Rat	Oral	500	MEHP	Plasma	1.1	NA	Kaun-Yu et al. 2014
Rat	Oral	1,000	MEHP	Plasma	7.4	NA	Koo and Lee 2007

Table 3-5. Blood, Serum, or Plasma Elimination Half-Lives ($t_{1/2}$) for DEHP and MEHP

Species	Route of administration[a]	Dose (mg/kg)	Measured chemical	Measured medium	Elimination $t_{1/2}$ (hour)	Clearance (mL/hour/kg)	Reference
Rat	Oral	2,800	MEHP	Plasma	5.2	NA	Teirlynck and Belpaire 1985
Rat	Arterial	100	DEHP	Blood	15	1,290	Pollack et al. 1985b
Rat	Venous	50	[$^{14}CO_2$]	Blood	17[d]	NA	Tanaka et al. 1975
Rat	Venous	5	DEHP	Plasma	1.6[b]	571	Sjöberg et al. 1985b
Rat	Venous	10	DEHP	Plasma	3.2	NA	Chang-Liao et al. 2013
Rat	Venous	50	DEHP	Plasma	2.0[b]	514	Sjöberg et al. 1985b
Rat	Venous	500	DEHP	Plasma	3.8[b]	126	Sjöberg et al. 1985b
Pig	Oral	1,000	MEHP	Blood	6.3	NA	Ljungvall et al. 2004
After administration of MEHP							
Rat	Oral	400	MEHP	Plasma	5.5	NA	Teirlynck and Belpaire 1985
Rat	Oral	100	MEHP	Blood	2.8	NA	Pollack et al. 1985b
Rat	Venous	50	MEHP	Blood	3.2	690	Pollack et al. 1985b

[a]Single administration of compound.
[b]Effective $t_{1/2}$ calculated from mean residence time (MRT): ln[2] × MRT.
[c]MEHP elimination was quantified for two distinct phases: an initial fast elimination phase and a secondary slow elimination phase.
[d]Based on fitting blood-time data to a first-order exponential model.
[e][$^{14}CO_2$] represents the total for DEHP and its metabolites.

DEHP = di(2-ethylhexyl)phthalate; MEHP = mono(2-ethylhexyl)phthalate; NA = not available

Estimates of the urinary elimination $t_{1/2}$ for MEHP range from 2 to 8 hours in humans and from 6 to 18 hours in rats (Table 3-6) (Anderson et al. 2011; Kessler et al. 2012; Koch et al. 2004, 2005a; Koo and Lee 2007; Mittermeier et al. 2016). Koch et al. (2004, 2005a) estimated that the urinary $t_{1/2}$ in an adult human who received a single oral dose of 0.65 or 3.7 mg/kg DEHP was somewhat shorter for MEHP (2–5 hours) compared to its secondary metabolites (2–15 hours; see Table 3-6).

Table 3-6. Urinary Elimination Half-Lives ($t_{1/2}$) for DEHP, MEHP, and Metabolites

Species	Route of Administration[a]	DEHP dose (mg/kg)	Measured chemical	Elimination $t_{1/2}$ (hours)	Reference
Human	Oral	0.00052 or 0.047	MEHP MECPP MEHHP MEOPP	4–8[b]	Anderson et al. 2011
Human	Oral	0.645	MEHP MEHHP MEOHP	4.6 6.6 6.2	Kessler et al. 2012
Human	Oral	3.7	MEHP MEHHP MEOHP	2–5 2–10 2–10	Koch et al. 2004
Human	Oral	0.65	MEHP MECPP MEOHP MEHPP	5 12–15 10 10	Koch et al. 2005a
Human	Oral	0.05 (MEHP)	MEHP MECPP MEOHP MEHPP	2.2–5.9 7.9–9.9 4.8–7.8 5.3–7.3	Mittermeier et al. 2016
Rat	Oral	200 1,000 5,000 200 1,000 5,000 40 200 1,000	MEHP MEHP MEHP DEHP DEHP DEHP [^{14}C][c] [^{14}C][c] [^{14}C][c]	18 6.0 6.4 ND 13 8.9 9.1 6.9 9.1	Koo and Lee 2007

[a]Single administration of compound.
[a]Reported as a single range for all metabolites.
[b][^{14}C] represents the total for DEHP and its metabolites.

DEHP = di(2-ethylhexyl)phthalate; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHP = mono(2-ethylhexyl) phthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEOHP = mono-2-ethyl-5-oxyhexylphthalate; ND = not detected

DEHP is measurable in blood and urine only after relatively higher doses of DEHP are administered (Kessler et al. 2004; Koo and Lee 2007; Pollack et al. 1985b; Sjöberg et al. 1986). Slower elimination $t_{1/2}$

values for DEHP relative to MEHP may reflect saturation of DEHP hydrolysis. Studies conducted in rats have demonstrated a dose-dependence of the kinetics of DEHP elimination. This was observed as a decrease in clearance and an increase in mean residence time and effective $t_{1/2}$ associated with increasing oral doses (4–2,000 mg/kg) (Koo and Lee 2007; Oishi 1989, 1990) or intravenous doses of DEHP (5–500 mg/kg) (Sjöberg et al. 1985b). Although the urinary elimination $t_{1/2}$ for MEHP remains relatively constant over dose ranges that begin to saturate DEHP elimination (Koo and Lee 2007), the dose-adjusted blood AUC for MEHP increases with increasing dose (Kessler et al. 2004). Contributing mechanisms for the higher plasma AUC may include saturation of pre-absorption hydrolysis of DEHP resulting in a larger and slower absorbed dose of DEHP, as well as possible saturation of systemic hydrolysis of DEHP. Both outcomes would contribute to a slowing of the time course for the elimination of MEHP from plasma.

Tanaka et al. (1975) reported data on the time course for [^{14}C] in various tissues (male Wistar rats) following single intravenous (50 mg/kg) or oral (500 mg/kg) doses of [^{14}C]-DEHP (Tables 3-1 and 3-2). Based on these data, elimination $t_{1/2}$ values for blood and liver were approximately 17 and 8 hours, respectively, following the intravenous dose (predicted for this report from reported observations made 3–168 hours following the dose), and 11 and 10 hours following the oral dose (predicted for the observations made 3–24 hours following the dose; data for 168 hours were not reported). The $t_{1/2}$ for adipose following the oral dose was <10 hours; however, it could not be estimated following the intravenous dose because concentrations in adipose tended to remain the same or increase over time. Differences in the blood and tissue elimination rates of [^{14}C] following intravenous and oral doses may reflect differences in the composition of the [^{14}C]-labeled compounds in the systemic circulation. Following intravenous injection, a larger fraction of the systemic [^{14}C] would have been comprised of [^{14}C]-DEHP, since pre-absorption hydrolysis would not have occurred. The more highly lipophilic DEHP may have a longer residence time in adipose, which has a relatively low activity of DEHP hydrolase. See Section 3.1.2 for discussion of tissue distribution of DEHP hydrolase.

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

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 endpoints.

Several PBPK models of DEHP have been reported. These include a rat PBPK model that simulates the kinetics of orally administered DEHP and MEHP (Keyes et al. 1999), a generic PBPK model and reported chemical parameter values for DEHP in rats (along with styrene, trichloroethene, and dibutylphthalate) (Cahill et al. 2003), an empirical model for predicting serum concentrations and urinary excretion of DEHP metabolites in humans (Lorber et al. 2010), and a simplified humanized mouse model (Adachi et al. 2015).

Keys et al. (1999)

Keys et al. (1999) developed a rat PBPK model that simulates the kinetics of orally administered DEHP and its metabolite, MEHP. Tissue compartments represented in the model include blood, fat, liver, small intestine, testes, slowly perfused tissues, and rapidly perfused tissues. The model simulates absorption of DEHP and MEHP in the small intestine as first-order transfer to liver. DEHP that is not absorbed is eliminated from the small intestine by a first-order loss parameter that represents fecal excretion. Hydrolysis of DEHP to MEHP in the small intestine is assumed to be capacity-limited and elimination of absorbed DEHP is assumed to be entirely by metabolism in liver and blood. Other viable elimination mechanisms for DEHP, including urinary excretion and biliary secretion, are not explicitly represented in the model, although they would have been at least partially represented in the metabolism parameters, since these were optimized against blood DEHP elimination kinetics. Elimination of absorbed MEHP is assumed to be entirely by metabolism in the liver. As with DEHP, other elimination mechanisms for MEHP, including urinary excretion, are not simulated and would have been at least partially represented with the metabolism parameters for MEHP. Metabolites of MEHP are not simulated in the model.

Keys et al. (1999) explored three approaches to modeling the blood-tissue exchange of DEHP and MEHP: (1) flow-limited (with or without enterohepatic circulation); (2) diffusion-limited; and (3) intracellular pH trapping. Model performance was evaluated against observations of blood and tissue (liver, testes) MEHP concentrations in rats following single intravascular doses of DEHP or MEHP or repeated oral doses of DEHP (Oishi 1989, 1990; Pollack et al. 1985b; Sjöberg et al. 1985a; Teirlynck and Belpaire 1985). Simulation code was developed for Advanced Continuous Simulation Language (ACSLTOX, Pharsight) and parameter values were estimated using ACSLopt.

Keys et al. (1999) compared the performance of the various models using a log-likelihood ratio test with the flow-limited model as the reference. Significant improvement in the log-likelihood ratio was achieved for each alternative to the flow-limited model. The pH-trapping model was statistically better than all models and was selected for further evaluation. The model that assumed pH trapping without diffusion limitation consistently underpredicted observed blood concentration profiles. The diffusion-limited and enterohepatic flow-limited models gave comparable log-likelihood values. The enterohepatic circulation model was explored because delayed peaks in blood MEHP concentrations were evident in observations made in rats that received oral doses of DEHP (Kessler et al. 2004; Ljungvall et al. 2004; Pollack et al. 1985b; Sjöberg et al. 1985b). One contributor to a delayed peak in blood MEHP concentration could be the absorption of MEHP secreted in bile into the small intestine. Biliary secretion of MEHP has also been observed in rats following oral administration of DEHP (Daniel and Bratt 1974). Although the enterohepatic circulation model did produce a series of delayed peaks in blood MEHP concentration, the simulation did not offer an improved fit to the observed blood MEHP profile compared to the pH-trapping model.

Cahill et al. (2003)

Cahill et al. (2003) proposed a generic PBPK model and reported chemical parameter values for DEHP (along with styrene, trichloroethene, and dibutylphthalate). Parameter values were not optimized. Predictions from DEHP model are reported; however, evaluations of the model are limited to comparisons of predicted and observed mass balance (e.g., percentage of dose retained in body and excreted in urine and feces) based on single-dose studies conducted in cynomolgus monkeys (Astill 1989) and rats (Daniel and Bratt 1974; Lake et al. 1984; Tanaka et al. 1978).

Lorber et al. (2010)

Lorber et al. (2010) reported a single-compartment model for simulating serum concentrations and urinary excretion of DEHP and metabolites in humans. The Lorber et al. (2010) model is not a PBPK model; however, it includes metabolism rates that could be useful for the development of PBPK models of MEHP metabolism. The model consists of two compartments, serum and urine, and one physiological parameter, volume of distribution in the serum compartment. Chemical parameters include first-order rate constants for each metabolic conversion of DEHP and MEHP, and deposition fractions of each metabolite representing the fraction of chemical mass transferred to bladder urine. Rates of change of the

amount of chemical in the serum compartment are the sum of the products of the metabolism rates and deposition fractions.

Values for rate constants and deposition fractions were "optimized" against measurements made in a single adult subject who ingested 48.5 mg (0.65 mg/kg) DEHP-D_4 (Koch et al. 2005a), using a "trial and error" approach and not statistical goodness-of-fit evaluations. The model was evaluated against observations of DEHP metabolites excreted in urine of human platelet donors who received intravascular doses of DEHP from disposable PVC medical devices used in the donation process (Koch et al. 2005b). Dose reconstruction exercises were performed using this model and urinary biomarker data for DEHP metabolites collected from individuals in the general population (Lorber and Calafat 2012).

Adachi et al. (2015)

Adachi et al. (2015) developed a three-compartment model for simulating MEHP and its metabolite, MEHP-O-glucuronide (MEHP-O-G), in chimeric TK-NOG mice with humanized liver. The TK-NOG mouse strain expresses an inducible herpes simplex type 1 thymidine kinase, which destroys native hepatocytes. Immunosuppression of the mice allows human hepatocyte xenografts to establish liver function, with expression of human hepatocyte transporters, cytochrome P450, and UDP-glucanosyl-transferases (Hasegawa et al. 2011). Mice with humanized liver exhibited kinetics of plasma and urinary MEHP and MEHP-O-G following an oral dose of DEHP that were distinct from those of control mice: (1) faster clearance of MEHP and MEHP-O-G; (2) larger fraction of dose excreted in urine; and (3) larger fraction of dose converted to MEHP-O-G (Adachi et al. 2015). Control mice also exhibited biphasic elimination from plasma with a delayed peak in plasma MEHP and MEHP-O-G concentrations, indicative of hepatobiliary recirculation that was not evident in mice with humanized livers.

The Adachi et al. (2015) model consists of two submodels, one for MEHP and one for MEHP-O-G, which are linked by the conversion of MEHP to MEHP-O-G in the liver. An oral dose of DEHP is delivered to the liver compartment from the gastrointestinal tract (first-order k_a, $hour^{-1}$) where it is completely metabolized to MEHP and further metabolized to MEHP-O-G (first-order Cl_{int}, L/hour). Conversion of DEHP to MEHP is not simulated and, therefore, is treated as being essentially instantaneous. The central compartment represents blood, which is in equilibrium with plasma (R_b, blood-plasma concentration ratio). Transfers of MEHP and MEHP-O-G between the liver and central compartment are flow-limited (Q_h, L/hour; $K_{p,h}$, liver-plasma concentration ratio). MEHP and MEHP-O-G are eliminated from the central compartment by excretion into urine (first-order, Cl_r, L/hour).

The liver compartment also includes an unspecified elimination pathway for MEHP-O-G (first order, Cl_{int}).

Adachi et al. (2015) estimated initial values for liver-plasma ($K_{p,h}$) and blood-plasma (R_b) concentration ratios and plasma binding ($f_{u,p}$) in mice from physical-chemical properties (Emoto et al. 2009; Poulin and Theil 2002). All other chemical parameter values for mice were estimated by optimization against data from oral dosing of mice with DEHP (Adachi et al. 2015) after initial values were assigned from the literature on studies of other chemicals in mice with humanized liver (Suemizu et al. 2014; Tsukada et al. 2013; Yamashita et al. 2014). In creating the human model, values for liver-plasma and blood-plasma concentration ratios were assumed to be the same in mice and humans. Intrinsic hepatic clearances were estimated for humans based on *in vivo-in vitro* ratios measured in mice (Adachi et al. 2015), with subsequent optimization against excretion data in humans (Kurata et al. 2012b).

Mouse model predictions were compared to observed kinetics of elimination of MEHP and MEHP-O-G from plasma following an oral dose of 250 mg/kg DEHP. Predictions were not significantly different from observations (chi-square, $p<0.001$). Human model predictions were compared to observed kinetics of MEHP and MHEP-O-G in urine, following an oral dose of 0.04 mg/kg DEHP. Predictions appeared to be close to observations (goodness of fit was not reported).

Applications for Dosimetry Extrapolation and Risk Assessment. The most fully advanced PBPK models for DEHP are those reported by Keys et al. (1999); however, these models have several important limitations for use in dosimetry predictions. The models simulate DEHP and MEHP kinetics in rats. An analogous human model has not been proposed, although the Keys et al. (1999) model could be scaled to the human and optimized against observations in humans (Koch et al. 2005a). This precludes the use of the model, as currently developed, for interspecies extrapolation of DEHP dosimetry. All elimination of MEHP is attributed to liver metabolism; this precludes the use of extensive data on urinary excretion for evaluating model performance and would preclude the use of the model for translating urinary excretion data into predictions of DEHP intake (i.e., dose reconstruction). Other reported models are not useful in their current form for interspecies dosimetry predictions. The generic Cahill et al. (2003) model with metabolism parameters for DEHP is a rat model that has not been fully optimized or evaluated for performance. The largely empirical model proposed by Lorber et al. (2010) may be useful for predicting internal dosimetry of DEHP metabolites in humans; however, its structure will not support scaling to other animal species.

Adachi et al. (2015) used the human model to predict DEHP intakes that corresponded to observed urinary levels of MEHP in human populations (reverse dosimetry). Confidence in reverse dosimetry could be improved with more extensive evaluations of model predictions of dose-excretion relationships for MEHP in humans. Data used to evaluate predictions were from a single study of 20 subjects who received a single dose of DEHP (0.04 mg/kg). Another potential application of the model is for internal dose-response analysis using plasma MEHP as the dosimeter. The model provides predictions of plasma MEHP concentrations; however, model predictions of plasma concentrations in humans have not been evaluated against observations in humans.

3.1.6 Animal-to-Human Extrapolations

The toxicokinetics of DEHP in humans are generally similar to those that have been observed in monkeys, rats, mice, hamsters, and guinea pigs. As discussed in Section 3.1.1, oral absorption data indicate absorption of 11–70% in humans and 30–78% in laboratory animals. No reliable data are available regarding distribution in humans. Metabolic pathways are similar between species (Figure 3-1), although species differences in relative abundance of metabolites and glucuronide conjugates have been reported. Extensive oxidative metabolism of MEHP was demonstrated to occur in rats compared to humans, and metabolites were primarily unconjugated in rat urine, whereas conjugation with glucuronide was extensive in humans (Albro et al. 1982a); see Section 3.1.3 for additional details. Species differences in DEHP hydrolase activities have been reported, with much lower activities in human and marmoset liver tissue compared with rodent liver tissue (Ito et al. 2005, 2014). In both humans and laboratory animals, elimination is primarily via excretion in urine and feces (Daniel and Bratt 1974; Koch et al. 2004, 2005a; Kurata et al. 2012a, 2012b). Elimination half-lives for DEHP and MEHP did not differ widely between species (Table 3-5).

Some DEHP-induced effects in rats and mice are thought to be mediated through the peroxisome proliferator-activated receptor-alpha (PPARα) (e.g., liver effects) and it is generally agreed that humans and nonhuman primates are refractory, or at least less responsive than rodents, to PPARα-mediated effects (Corton et al. 2018; Klaunig et al. 2003; Maloney and Waxman 1999). However, many of the health effects associated with DEHP and its metabolites in rodents (e.g., reproductive effects) are believed to act through other mechanisms that are independent of PPARα activation, which may be also relevant for exposed human populations.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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 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. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to DEHP are discussed in Section 5.7, Populations with Potentially High Exposures.

Age-Related Exposure and Pharmacokinetic Differences. Efforts to reduce and/or regulate the use of DEHP in cosmetics, food contact materials, and toys, have reduced all exposures to DEHP in the United States and Europe, including children's exposure (Johns et al. 2016). In 2008, the U.S. Consumer Product Safety Improvement Act restricted the amount of DEHP in children's toys and childcare products to ≤0.1% (Johns et al. 2016). Coupled with earlier actions by the European Union to prohibit the use of DEHP in other consumer products and public awareness of the issue, this action has led to the reformulation of many consumer products to limit or eliminate DEHP, sometimes substituting other phthalate esters (Johns et al. 2016). Thus, infant and toddler exposures have likely decreased, although biomonitoring data over time for these age groups are limited. However, mouthing behaviors of infants and toddlers may still lead to higher DEHP exposures than experienced by older children or adults.

No specific information was located regarding the comparative absorption of DEHP in children and adults. In rats, oral absorption of DEHP appears to be greater in immature animals compared with mature animals (Sjöberg et al. 1985a), but no age-related differences in oral absorption were seen in marmosets (Kurata et al. 2012a). Age-related differences in metabolism may also contribute to variations in susceptibility. The metabolism of DEHP to MEHP is mediated by lipases that are mainly in the gastrointestinal tract. Gastric lipase activity is high in infants to aid in the digestion of fats in milk,

peaking in children at 28–33 weeks of age (FDA 2001; Lee et al. 1993). Consequently, young children might convert DEHP to MEHP more efficiently than older children or adults (FDA 2001). In addition, compared to adults, children generally have a reduced capacity to metabolize compounds via glucuronidation (FDA 2001). Since approximately 60% of an administered dose of DEHP is excreted as the glucuronide conjugate in humans (Albro et al. 1982a, 1982b), a reduced glucuronidation capacity could result in delayed excretion of DEHP or its metabolites. The MEHP metabolite of DEHP also undergoes glucuronidation, and has been shown to interfere with bilirubin conjugation (Sjöberg et al. 1991), possibly as a competitive inhibitor of glucuronidase (FDA 2001).

Age-Related Differences in Susceptibility. As detailed in Chapter 2, epidemiological and/or animal studies have suggested that exposure to DEHP may lead to numerous developmental effects, including preterm birth, fetotoxicity, teratogenicity, effects on the male reproductive system, early puberty, and altered development of the nervous, endocrine, hepatic, and renal systems. The developing male reproductive system appears to be a particularly sensitive target for DEHP.

Studies directly comparing the effects of DEHP exposure in humans or animals of different ages are few, but confirm the greater susceptibility of younger organisms. For example, acute DEHP doses associated with lethality are lower in younger rats (Dostal et al. 1987; Tonk et al. 2012). Two oral doses of 2,000 mg/kg/day DEHP caused nearly 100% mortality in ≤21-day-old rats, but no mortality in ≥42-day-old rats (Dostal et al. 1987). In addition, five daily doses of 1,000 mg/kg DEHP resulted in 66–70% mortality in rats exposed on PNDs 6–10, 16–20, or 21–25, but not in those exposed at ages ≥PND 42. Similarly, several PND 10 pups died within 1 day receiving a dose of 1,000 mg/kg DEHP, while no mortality was seen in PND 50 animals receiving the same dose for 40 consecutive days (Tonk et al. 2012).

Studies in male rats of different ages demonstrate the increased susceptibility of younger (≤PND 35) rats to DEHP-induced effects on the male reproductive system (Murphy et al. 2014; Sjöberg et al. 1985b; Tonk et al. 2012). For example, Tonk et al. (2012) exposed male Wistar rats exposed to DEHP by gavage for 40 days, beginning at either PND 10 or 50. A broad range of doses from 1 to 1,000 mg/kg/day was administered to both groups. The juvenile rats exhibited significantly decreased androgen-dependent organ weights (testes, epididymides, and ventral prostate) at lower doses than adult rats, while effects on liver and kidney weights occurred at the same dose for both juveniles and adults. In addition, serum LH and FSH levels were markedly increased in juvenile rats, but not adult rats, while serum testosterone changes occurred at the same dose and magnitude of response at both ages (Tonk et al. 2012). Similar

findings were reported by Sjöberg et al. (1985b), who observed testicular damage in rats exposed to DEHP at 1,000 mg/kg/day for 14 days beginning at PND 24, but not when exposure was begun at PND 40 or 60.

Age-dependent susceptibility to testicular effects was also seen in rats after exposure to the DEHP metabolite, MEHP (Murphy et al. 2014; Teirlynck et al. 1988). Murphy et al. (2014) compared effects of oral exposure to MEHP (1 g/kg) in mouse and rat testes after single exposures on PNDs 21, 28, 35, or 56. In rat testes, increased infiltration of immunoreactive interstitial cells (mediated by increased production of monocyte chemoattractant protein-1) and increased apoptosis were seen after dosing in juvenile rats, but not adult (PND 56) rats. Effects occurred earlier in younger (PND 21 and 28) juveniles (e.g., within 12 hours after dosing, compared with 48 hours) than in older (PND 35) juveniles (Murphy et al. 2014). Similarly, testicular damage was observed in rats given a single dose of 800 mg/kg MEHP on PND 25, but not when MEHP was administered on PND 44 or 71 (Teirlynck et al. 1988).

Age-dependent sensitivity to DEHP-induced effects on the hypothalamic-pituitary-adrenal (HPA) axis and steroidogenesis has also been demonstrated. When male rats were exposed to DEHP on 4 consecutive days beginning on PND 16, 36, or 56, significant increases in adrenocorticotropic hormone (ACTH) and cortisone were seen in the younger rats, but not in the rats exposed as adults (PND 56) (Supornsilchai et al. 2007). In addition, adrenocortical cells from rats exposed at PNDs 16 and 36 showed increased steroidogenesis compared with cells from rats exposed as adults, as shown by greater corticosterone production in response to stimulation by ACTH, dibutyryl cAMP, and 22R-hydroxy-cholesterol, and greater transportation of cholesterol into mitochondria (Supornsilchai et al. 2007).

In addition to increased susceptibility to male reproductive and adrenal effects, juvenile rats exhibit greater sensitivity to immune system perturbations induced by DEHP. In male Wistar rats exposed to DEHP by gavage from PND 10 to 50 or from PND 50 to 90, immune system endpoints were affected at a lower dose in juvenile rats than adults (Tonk et al. 2012). Effects seen in juvenile rats included decreases in white blood cells, neutrophils, lymphocytes, and monocytes, and increases in KLH-stimulated cytokine production. Adult rats exhibited some, but not all, of these effects at higher doses (Tonk et al. 2012).

Transgenerational Effects. There is no information regarding possible transgenerational effects of DEHP in humans. However, studies in animals showed transgenerational effects on gonad development in both male and female descendants, possibly resulting from epigenetic changes in the germ cells.

In male descendants of rats exposed to DEHP, effects included cryptorchidism, impaired fertility, and effects on testicular structure and function (Chen et al. 2015; Doyle et al. 2013; Quinnies et al. 2015). Chen et al. (2015) observed increased incidences of cryptorchidism, decreased AGD, and decreased testes and epididymides weights in both F1 and F2 (but not F3 or F4) generation Sprague-Dawley rats, after DEHP exposure limited to the F0 generation dams (750 mg/kg/day from GD 7 to 19). Testes from both F1 and F2 rats in the DEHP-exposed line exhibited significantly increased expression of mRNA for three DNA methyltransferases compared with controls, while no treatment-related changes were seen in the F3 and F4 generations. It was suggested that DNA methylation changes might be responsible for the transgenerational effects on rat testes (Chen et al. 2015). Further evidence for transgenerational effects of DEHP exposure on testicular structure and function comes from a study in CD-1 mice (Doyle et al. 2013). F0 mice were exposed to 500 mg/kg/day DEHP by gavage from GD 7 to 14. The F1 mice were used in three experiments examining maternal (F1 females bred with untreated males), paternal (F1 males bred with untreated females), and double-cross (F1 males and females bred within exposure group) inheritance patterns. Male F2 and F3 offspring of paternal and double-cross groups from the DEHP exposure line exhibited significantly delayed pubertal onset; offspring of the maternal DEHP exposure inheritance line did not show a change in onset of puberty. In addition, F2, F3, and F4 offspring of all three exposure inheritance lines displayed increased numbers of abnormal seminiferous tubules and decreased epididymal sperm counts and sperm motility. The authors also conducted experiments in which germ cells from F3 offspring were transplanted into recipient testes; these experiments showed markedly reduced germ-cell recovery of spermatogenesis in the DEHP-exposed inheritance group compared with offspring of the control group. In addition, the testes of animals receiving germ cells from the exposure line exhibited morphology that resembled that of DEHP-exposed F1 offspring (i.e., tubules were disorganized, lacked layers of germ cells, and contained vacuoles and/or multinucleated cells), while testes of animals receiving germ cells from the control line exhibited normal morphology. Based on this observation, Doyle et al. (2013) postulated that the testicular phenotype has its origin in the F3 offspring stem cells.

Transgenerational effects of DEHP exposure on ovarian development were observed in mice (Zhang et al. 2015). When pregnant CD-1 mice (F0 generation) were given oral doses of DEHP at 0.04 mg/kg/day throughout gestation, effects on ovarian development were seen not only in the F1 offspring, but also in F2 generation females; the numbers of primordial follicles were significantly decreased, and numbers of secondary follicles increased, compared with control mice with ancestors that were not exposed to DEHP (Zhang et al. 2015). After observing that F1 females exhibited significantly increased methylation of the *Stra8* gene (stimulated by retinoic acid gene 8, *Stra8* is expressed in the embryonic mouse germ cells and

is important to the initiation of meiosis), along with decreased levels of *Stra8* mRNA, the authors suggested that modification of DNA methylation patterns may play a role in the transgenerational effects of DEHP on ovarian development.

Genetic Polymorphisms Altering Susceptibility. Genetic polymorphisms that may increase susceptibility to the effects of DEHP have been examined in a few epidemiological studies, but most of these studies were cross-sectional in design, providing an inadequate basis with which to draw clear conclusions. Xie et al. (2015) reported that the association between MEHP levels in meconium and low birth weight or short birth length was enhanced in infants exhibiting the paraoxonase-2 148AG/GG (PON-2 A148AG/GG) genotype (PON-2 deficiency is associated with increased ROS levels). DEHP exposure (measured as urinary metabolites) was associated with greater decreases in lung function in elderly Koreans who exhibited certain polymorphisms in oxidative stress-related genes (catalase, myeloperoxidase, and superoxide dismutase 2) (Park et al. 2013)

Park et al. (2014) investigated potential genotype-phthalate interactions between urinary levels of phthalate metabolites (including MEHP and MEOHP) and polymorphisms at major candidate genes for attention-deficit/hyperactivity disorder (ADHD) with regard to neuropsychological performance in 179 Korean children with ADHD. An increased in DEHP urinary metabolites was associated with poor attentional performance in children with the dopamine receptor D4 (DRD4) gene 4/4 variant, but not in children without the DRD4 4/4 genotype. This suggests that the DRD4 4/4 genotype may increase susceptibility to the effects of DEHP.

The potential for increased susceptibility to DEHP in individuals with loss-of-function filaggrin gene (FLG) variants has also been evaluated (filaggrin is an epidermal protein important to maintaining normal skin function, and its loss may enhance absorption of xenobiotics or allergens). No relationship between DEHP and atopic dermatitis was observed in individuals with or without FLG variants (Wang and Karmaus 2015). Additionally, internal body burden of DEHP (as measured by urinary metabolite levels) was not altered in persons with FLG variants (Joensen et al. 2014).

In a case-control study (Martinez-Nava et al. 2013), the associations between urinary DEHP metabolite levels and breast cancer were stronger in individuals with polymorphisms in *PPARγ* (shown previously to modify breast cancer risk) and PPARγ coactivator 1 beta *(PPARGC1B*, a co-activator of estrogen receptor α that amplifies ER signaling). However, since exposure was measured after the individuals developed breast cancer in this study, the findings were not considered to be useful for assessment of cancer hazard

for DEHP, and thus, the potential roles of PPARγ and its coactivator remain unknown. In another case-control study of women with uterine conditions (endometriosis, adenomyosis, or leiomyoma), Huang et al. (2010) observed a significant association between MEHP in urine and odds of leiomyoma or adenomyosis only in individuals with GSTM1 null-type polymorphisms and not in those with wild-type GSTM1.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to DEHP are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (http://www.cdc.gov/exposurereport/). If available, biomonitoring data for DEHP from this report are discussed in Section 5.6, General Population Exposure.

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 effect caused by DEHP are discussed in Section 3.3.2.

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 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

As discussed in Section 3.1, DEHP is rapidly and extensively hydrolyzed to MEHP within the gastrointestinal tract, and both DEHP and MEHP (formed in the gastrointestinal tract) are readily absorbed. Systemically absorbed DEHP may undergo hydrolysis to MEHP by tissue lipases found in many tissues; in addition, MEHP may be oxidized, yielding MEHHP, MEOHP, and MECPP. The oxidized metabolites of MEHP are primarily conjugated with glucuronic acid and excreted in the urine. Hydrolysis of absorbed DEHP to MEHP is sufficiently rapid that, regardless of the route of administration of DEHP, most of the phthalate eliminated from the body is in the form of MEHP and its metabolites. Elimination of MEHP and its oxidative metabolites occurs via urinary and biliary excretion.

It is generally agreed that the preferred biomarkers for exposure to DEHP are its urinary metabolites (Calafat et al. 2015; Johns et al. 2016). While modern analytical techniques permit the detection and quantification of DEHP and its metabolites in serum, amniotic fluid, meconium, breast milk, and semen, there are several advantages to using metabolites in urine over measurement of DEHP or its metabolites in other biological fluids. First, urine samples are the least invasive samples to obtain, improving participation in efforts to assess exposure. Second, urine samples are typically of larger volume than those of other biological fluids, facilitating detection of metabolites. Third, the concentration of DEHP metabolites in urine is higher than that of DEHP or its metabolites in other biological fluids, leading to fewer samples below the limit of detection. Fourth, while DEHP can be detected in these media, enzymes present in blood, milk, amniotic fluid, etc., but not in urine, are known to hydrolyze DEHP to its monoester during sample storage, leading to underestimates of DEHP levels. Further complicating the analysis of DEHP in biological fluids is the significant potential for contamination from materials used to store samples and/or in the laboratories where analyses are performed. The direct measurement of metabolites in urine reduces the potential for sample contamination by the parent diester and subsequent metabolism by enzymes found in blood, milk, and amniotic fluid, but not urine (Johns et al. 2015).

While urinary metabolites are considered the optimal biomarkers for DEHP exposure, these metrics are also subject to uncertainties that should be considered in assessing DEHP exposure (Johns et al. 2016). For example, urinary metabolites of DEHP vary over time, with concentrations increasing over the course of the day as well as between days. In studies assessing temporal variability, intraclass correlation

coefficients (ICCs; reflecting the variance between individuals divided by the sum of the variances between and within individuals) for DEHP metabolites in urine have been relatively low (on the order of 0.1–0.3; Johns et al. 2016) over short time periods (up to 1 month) and lower over longer time periods (1–3 years). Evaluations of ICCs for individual or summed DEHP metabolites during pregnancy have reported values from 0.08 (Braun et al. 2012) to 0.22 (Peck et al. 2010). Despite the temporal variability, single urine samples have been shown to provide reasonable prediction of exposure category (e.g., whether a given person's exposure is above or below the median or quartile of exposure level; Johns et al. 2016). Due to the potential for significant temporal variability, repeated urine samples are recommended to examine long-term exposure.

One study has shown that the intra-individual variability over a week in MEHHP concentrations from repeated spot urine samples is comparable to the intra-individual variability obtained from repeated first morning or 24-hour urine samples, indicating that spot urine samples remain useful for exposure assessment where 24-hour void samples are not feasible (Johns et al. 2016). However, a limitation of spot urine samples as biomarkers of exposure is the issue of urine dilution: the concentration of a given metabolite in urine will depend on the volume of urine, which in turn varies by time of day, water intake, physical activity, and sweating, as well as other factors unrelated to exposure (Johns et al. 2016). Efforts to address this limitation include adjustment for dilution using creatinine levels and specific gravity. Specific gravity adjustment is preferred over creatinine adjustment, because creatinine levels vary by an individual's activity level, time of day, age, gender, muscle mass, and medical conditions, while specific gravity is a more stable measure of dilution (Johns et al. 2016).

DEHP is rapidly metabolized to MEHP, but typically <10% of an oral dose of DEHP is eliminated in the urine as MEHP; most of the dose is excreted as oxidative metabolites including MEHHP, MEOHP, and MECPP (Johns et al. 2016). Thus, the concentration of the monoester MEHP alone is not considered an adequate measure of exposure (Johns et al. 2016). While phthalic acid can be quantified in urine, this is a nonspecific biomarker of DEHP exposure, since other phthalate esters such as butyl benzyl phthalate, dibutyl phthalate, and diethyl phthalate will also result in measurable phthalic acid in the urine. Recently, efforts to identify a single metric of DEHP exposure have focused on either the sum of the primary DEHP metabolites (MEHP, MEHHP, MEOHP, and MECPP), the percent of the sum attributable to MEHP (MEHP%), or the ratio of MECPP to MEHHP as valuable metrics. As reported by Johns et al. (2016), MEHP% may be an indicator of an individual's capacity to further metabolize the monoester, which is believed to be more bioactive than its oxidative metabolites. The ratio of MECPP to MEHHP is thought

to provide a measure of the duration of time since exposure to DEHP, based on the half-lives of each of these metabolites (Johns et al. 2016).

Despite the limitations, urinary concentrations of DEHP metabolites are currently considered the optimal biomarkers for exposure. Based on studies of the sensitivity and specificity of a single sample to correctly classify categories (e.g., highest tertile versus lowest) of exposure. Johns et al. (2016) conducted sensitivity and specificity studies to evaluate the ability of a single urine sample to correctly classify categories (e.g., highest tertile versus lowest) of exposure. Based on the results of these studies, Johns et al. (2016) concluded that a single urine sample provides a reasonable means of categorizing an individual's exposure over several months or possibly up to 1 or 2 years. Little information is available on the identification of biomarkers that more accurately reflect long-term or cumulative exposure to DEHP. Camann et al. (2013) postulated that DEHP metabolite levels in deciduous teeth might serve as a marker for early childhood exposure. MEHP was detected in the molars of 29% of 21 children, and levels were higher in older than younger children, consistent with accumulation with longer exposure. However, the use of DEHP metabolites in teeth as a biomarker of exposure has not been validated.

3.3.2 Biomarkers of Effect

No specific biomarkers of the effects of exposure to DEHP were identified in the available literature.

3.4 INTERACTIONS WITH OTHER CHEMICALS

There are no studies in humans examining interactions between DEHP and other chemicals; however, most available human studies examined members of the general population with potential exposures to other phthalates as well as other ubiquitous chemicals.

Interactions Potentially Influencing Male Reproductive Toxicity. The majority of available interaction studies focused on potential interactions between DEHP and other chemicals with respect to adverse effects on the adult or developing male reproductive system. A number of studies focus specifically on the potential interactions between DEHP and other phthalate esters. Due to the similarities between the different phthalates, NAS recommends a cumulative risk assessment approach to determining the risks posed by phthalates (NAS 2008).

Available evidence from two well-designed oral interaction studies in rats indicates that phthalate esters act in a dose-additive manner with respect to developmental male reproductive toxicity (Hannas et al.

2011; Howdeshell et al. 2008). Both studies were adequately designed to evaluate interactions, including dose-response analyses for individual chemicals as well as the tested mixture. Howedeshell et al. (2008) evaluated the dose-response effects of benzobutyl phthalate (BBP), di(n)butyl phthalate (DBP), DEHP, diisobutyl phthalate (DIBP), and dipentyl phthalate (DPP) on *ex vivo* fetal testicular testosterone (FTT) production in Sprague-Dawley rats following maternal exposure to individual phthalates at various doses from GD 8 to 18. FTT data from these experiments were used to build a dose-addition model, which accurately predicted FTT data following maternal exposure to various doses of the five-phthalate mixture (a set 3:3:3:3:1 mixture ratio for BBP:DBP:DEHP:DIBP:DPP was used for equipotency). Using a similar experimental design, Hannas et al. (2011) also observed that dose-additivity model predictions provided the best fit to FTT data from Sprague-Dawley rats following maternal exposure to a mixture of nine phthalates, including DEHP, DIBP, DBP, BBP, DPP, diisoheptyl phthalate, dicyclohexyl phthalate, diheptyl phthalate, and dihexyl phthalate, from GD 14 to 18.

Findings from other studies also suggest dose additivity between DEHP and DBP for additional reproductive development effects in male rats (malformations, androgen-dependent organ weights, gene expression) (Howdeshell et al. 2007; Martino-Andrade et al. 2009); however, study designs were inadequate to characterize potential interactions (lack of dose-response data for individual phthalates and/or mixture). Taken together, these findings support the hypothesis that phthalates share a common mechanism of action.

With regard to shared mechanisms, several *in vitro* and *in silico* studies have measured phthalate binding to various receptors (androgen, progesterone, glucocorticoid, sex hormone-binding globulin [SHBG], CAR, PXR, PPAR), binding to enzymes in the glucocorticoid biosynthesis pathway, and toxicogenetic signatures in an effort to predict how phthalates may interact with one another and to better inform cumulative risk assessments (Ahmad et al. 2016; Laurenzana et al. 2016; Sarath Josh et al. 2016; Sheikh et al. 2016; Singh and Li et al. 2011). However, none of these studies speak to the potential nature of the interaction between phthalates.

Studies have also been conducted to evaluate potential interactions between DEHP and non-phthalate endocrine disruptors. Christiansen et al. (2009) evaluated several male reproductive endpoints in Wistar rats following maternal exposure from GD 7 to PND 16 to known androgen disruptors with different proposed mechanisms of action, including DEHP, vinclozolin (androgen receptor agonist), prochloraz (androgen receptor antagonist, inhibition of progesterone conversion to testosterone), and finasteride (androgen receptor agonist). Dose-response studies were conducted for individual chemicals as well as

the mixture, and evaluated endpoints included AGD, nipple retention, external malformations, and sex organ weights. The mixture ratio of vinclozolin:finasteride:DEHP:prochloraz was set at 500:1:300:500 for equipotency of chemicals based on NOAELs determined in individual compound studies. Based on statistical analysis, both dose-addition and independent action models underpredicted the incidence of dysgenesis of the external genitalia in male offspring at PND 16 and 47, suggesting a synergistic or greater-than-additive effect (Christiansen et al. 2009). However, dose-additivity models accurately predicted the data for other endpoints (AGD, nipple retention, organ weights). Similarly, Fiandanese et al. (2016) reported a synergistic (or greater-than-additive) effect between DEHP and a mixture of polychlorinated biphenyls (PCBs) in the development of gross and histopathological changes in the testes of male offspring of mouse dams exposed to the mixture during gestation and lactation, and reported "non-interaction" for sperm parameters or testosterone production. However, the study design was not adequate to properly characterize the nature of chemical interactions (single dose only for individual chemicals and mixture). In a cohort of male partners of infertile couples, Hauser et al. (2005) did not find a significant relative excess risk due to interaction (RERI) for below-normal sperm parameters between urinary MEHP levels and various serum PCB levels.

Jarefelt et al. (2006) evaluated potential interactions between DEHP and the proposed substitute chemical, di(2-ethylhexyl)adipate (DEHA), on the developing male reproductive system. Pregnant Wistar rats were exposed to DEHP alone at 300 or 750 mg/kg/day or DEHP (750 mg/kg/day) + DEHA (400 mg/kg/day) from GD 7 to PND 17, and male offspring were examined for AGD, nipple retention, sex organ weights, and testicular histology. The study authors concluded that there was no evidence for interaction between DEHP and DEHA because male reproductive effects were similar in the 750 mg/kg/day DEHP-only group and the DEHP+DEHA group; however, the study design is inadequate to fully characterize potential interactions.

A series of studies evaluated the influence of the phytoestrogen genistein on DEHP-induced male reproductive toxicity (Jones et al. 2014, 2015, 2016; Zhang et al. 2013b, 2014). Results from these studies have been conflicting, and the designs of most studies were inadequate to establish the nature of the potential interactions.

Zhang et al. (2014) examined AGD, sex organ weight, testicular histology, and oxidative stress in adult rats exposed to genistein at 50 mg/kg/day, DEHP at 50, 150, or 450 mg/kg/day, or genestein+DEHP (at each DEHP dose level) from PND 22 to 32 (prepubertal exposure). Genistein alone did not affect any measured parameter; however, it significantly decreased several adverse effects observed with DEHP

exposure, including sex organ weight, testicular oxidative stress, and testicular histopathological changes. The study authors proposed that enhancement of testicular antioxidative enzyme activities by genistein protected against DEHP-induced testicular toxicity.

Jones et al. (2015) also observed partial alleviation of DEHP-induced alterations in testicular gene expression in neonatal male offspring of pregnant rats exposed to 10 mg/kg genistein plus 10 mg/kg/day DEHP from GD 14 through parturition, compared with 10 mg/kg/day DEHP alone. However, when adult offspring were evaluated following the same exposure scenario, long-term alterations in the male reproductive system (increased testicular weights and altered testicular gene expression suggestive of altered testicular function and spermatogenesis) were observed only in the DEHP+genistein group (Jones et al. 2014). Similar effects on steroid production and lipid homeostasis were observed with combined exposure to mouse tumor Leydig cells *in vitro* (Jones et al. 2016).

Zhang et al. (2013b) also reported potential enhancement of DEHP-induced male reproductive effects with coexposure to genistein. While exposure-related changes in offspring AGD, testicular histology, testosterone levels, or testicular gene expression were not observed following maternal exposure to 250 mg DEHP/kg/day, 50 mg genistein/kg/day, or 400 mg genistein/kg/day alone from GD 3 to PND 21 in Sprague-Dawley rats, dose-related changes were observed in these endpoints following exposure to 250 mg DEHP/kg/day plus 50 or 400 mg genistein/kg/day. The study authors concluded that genistein and DEHP acted in a cumulative manner.

The potential effect of acetone on the testicular toxicity of DEHP was evaluated in in male Wistar rats in a 4-week oral study (Dalgaard et al. 2000). Rats were exposed to 0, 1,000, 5,000, or 10,000 mg/kg/day for 4 weeks or 0, 125, 250, 500, or 1,000 mg/kg/day DEHP for 9 weeks with or without 0.5% acetone. Male reproductive endpoints evaluated in the study included male fertility (4-week study only) and sex organ weight and histology. A significant, dose-related decrease in male fertility was observed with DEHP exposure; this effect was not significantly altered by co-exposure to acetone. No significant changes were observed in male reproductive organ weight or histology in the 9-week study following DEHP or DEHP+acetone exposure. In the 4-week study, decreased testes weight and increased incidence of testicular histopathological lesions were observed at ≥5,000 mg DEHP/kg/day, both with and without acetone. Analysis showed no significant interaction between DEHP and acetone with respect to organ weight; however, degeneration of the seminiferous tubules was “apparently” increased by acetone. The study authors did not present statistical analysis of potential interaction between DEHP and acetone with

regard to testicular degeneration. Overall, the study concluded that there was no significant interaction between DEHP and acetone with respect to male reproductive toxicity.

In an *in vitro* study with a full-factorial design (all possible combinations tested at multiple concentrations), no clear evidence of synergism with respect to glucocorticoid-like activity in MDA-kb2 cells was observed using binary, trinary, or quaternary mixtures containing DEHP, propylparaben, butylparaben, and tetramethrin; all individual compounds showed glucocorticoid-like activity (Klopcic et al. 2015).

Interactions Potentially Influencing Developmental Toxicity. In the dose-response study by Howdeshell et al. (2008) described above, phthalates (BBP, DBP, DEHP, DIBP, and DPP) acted in a dose-additive manner for fetal toxicity in Sprague-Dawley rats following maternal exposure from GD 8 to 18. Decreased litter size and postnatal survival were also observed in rats exposed to DEHP+DEHA, compared with DEHP-only groups, in the study by Jarfelt et al. (2006) described above. However, since there was no DEHA-only group, no conclusions regarding interactions can be made.

Interactions between DEHP, trichloroethylene, and heptachlor on developmental toxicity have been investigated (Narotsky et al. 1995). The compounds were administered to pregnant rats from GD 6 to 15 via gavage, singly and in combination, using five dose levels of each in a 5x5x5 factorial design. The dose levels were 0, 24.7, 78, 247, and 780 mg/kg/day for DEHP; 0, 10.1, 32, 101, and 320 mg/kg/day for trichloroethylene; and 0, 0.25, 0.8, 2.5, and 8 mg/kg/day for heptachlor. Endpoints that were analyzed for possible interactions included maternal death, maternal body weight gain on GDs 6–8 and 6–20, full-litter resorption, prenatal loss, postnatal loss, pup body weight on PNDs 1 and 6, and pups/litter with eye defects. Statistical analysis of the three maternal and six developmental endpoints yielded several significant two-way interactions. DEHP and heptachlor showed synergism for maternal death on GDs 6–8 and antagonism for maternal weight gain on GDs 6–8, full-litter resorption, and pup weight on PNDs 1 and 6. DEHP and trichloroethylene were synergistic for maternal weight gain on GDs 6–8, prenatal loss, and pup weight on PND 6. No significant three-way interactions were observed.

A combination of 150 mg/kg caffeine administered by injection to pregnant rats in conjunction with a single dose of 9,756 mg/kg DEHP on GD 12 caused a 5-fold increase in the number of dead and resorbed fetuses and nearly a 4-fold increase in the malformed survivors, as compared to the effects of DEHP alone (Ritter et al. 1987). The mean fetal weight was also depressed. The addition of the caffeine to the treatment using equimolar quantities of 2-ethylhexanol and 2-ethylhexanoic acid at doses half of the

molar quantity used for DEHP resulted in 2- to 30-fold increases in the dead and malformed fetuses and malformed survivors, but only minor decreases in the fetal weights.

Interactions Potentially Influencing Neurotoxicity. Interactions between DEHP, trichloroethylene-, and heptachlor-induced neurotoxicity were investigated in the study by Moser et al. (2003) described earlier. Neurobehavioral endpoints that were analyzed for possible interactions of the three chemicals included automated motor activity analysis in a figure-eight maze and an abbreviated FOB (general appearance, open-field observation, sensorimotor responses to click stimulus, pinch, and penlight stimulation, and grip strength); potential interactions were analyzed using a statistical response-surface analysis. No exposure-related changes in neurobehavior were observed with DEHP exposure alone, while various alterations were associated with trichloroethylene or heptachlor exposure. In two-way analyses, no significant interaction was observed between DEHP and trichloroethylene in any of the measures or DEHP and heptachlor for most measures. The one exception was evidence for a greater-than-additive effect between DEHP and heptachlor for tremors. In the three-way analysis, evidence for an antagonistic interaction was observed for the tail-pinch response; no other significant interactions were observed in neurobehavioral endpoints. Lethality was also assessed in this study, with DEHP exerting a less-than-additive effect on heptachlor-induced lethality. In the three-way analysis, there was evidence for a greater-than-additive effect on lethality.

In the 4-week study by Dalgaard et al. (2000) evaluating potential interactions between DEHP and acetone described in the male reproductive section above, a FOB was conducted. No exposure-related effects were observed in the 9-week study. In the 4-week study, acetone exposure was associated with significant decreases in hind limb grip strength and DEHP exposure was associated with significant decreases in forelimb grip strength; however, there was no significant interaction between the two chemicals.

The potential interactions between DEHP, bisphenol A (BPA), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) on neurodevelopment were evaluated in ICR mouse offspring following maternal exposure to 1 mg DEHP/kg/day, 5 mg BPA/kg/day, 8 ng TCDD/kg/day, or their mixture during gestation (GDs 8–17 for BPA and DEHP, GD 8 only for TCDD) and lactation (GDs 3–7 BPA or DEHP, single exposures, or GDs 3–5 BPA and DEHP, mixture). TCDD exposure was only once due to its extended biological half-life. Endpoints examined were limited to markers of dopamine and neuronal activation in the midbrain. While significant alterations were observed with individual chemical exposures, none were observed

following exposure to the mixture. The study authors suggested that this was presumably due to antagonistic effects; however, the study design was not adequate to rigorously assess interaction.

Interactions Potentially Influencing Liver Toxicity. Data are available suggesting that DEHP might act as an antagonist for the hepatic damage caused by TCDD. DEHP was combined with TCDD to determine if the hypolipidemic effects of DEHP could counteract the hyperlipidemic effects of the TCDD (Tomaszewski et al. 1988). Pretreatment with DEHP mitigated many of the toxic effects of TCDD. There was a 50% decrease in TCDD-related mortality when the rats received DEHP pretreatment. DEHP administered after TCDD administration had considerably less of an effect on TCDD toxicity, but did alleviate the TCDD toxic effects to a slight extent. The authors postulated that the antagonist properties of DEHP could have resulted from either or both of two mechanisms: (1) reduction in TCDD-induced hyperlipidemia by DEHP stimulation of peroxisomal lipid metabolism, and/or (2) DEHP-altered hepatic distribution of the TCDD.

In another study evaluating the effect of DEHP on the peroxisomal system, Perera et al. (1986) reported increased effects in rats kept on a choline-deficient diet. This conclusion was based on an increase in the conjugated dienes (indicators of free radical oxygen modification of cellular lipids) in the microsomes of choline-deficient animals exposed to 500 mg/kg DEHP for 4 weeks.

Other studies have indicated potential additive effects regarding liver toxicity with DEHP and other chemicals. In a full-factorial study evaluating potential interactions between DEHP, trichloroethylene, and heptachlor, with respect to systemic toxicity, the study authors reported a greater-than-additive effect on liver toxicity between DEHP and trichloroethylene (Simmons et al. 2005). However, this study was only available as an abstract, and conclusions cannot be independently reviewed. Another study evaluated hepatic endpoints in male rats following dietary exposure to 10,000 ppm DEHP, 10,000 ppm di-*n*-hexyl phthalate (DnHP), or their combination (Howarth et al. 2001). These study authors indicated that decreases in serum cholesterol “seemed additive” for the mixture, while all other hepatic effects observed in DEHP+DnHP-treated animals were similar to those observed in DEHP-treated animals. However, the study design was inadequate to evaluate interactions due to lack of dose-response data for individual chemicals or mixture.

Several hepatic endpoints were evaluated in male rats in the 4-week study by Dalgaard et al. (2000) evaluating potential interactions between DEHP and acetone described in the male reproductive section

above, including clinical chemistry, liver weight, and liver histology. No significant interactions were observed with respect to any of these endpoints.

Toxicokinetic Interactions. Co-exposure to the food emulsifier, glycerin monostearate, increased the oral absorption of DEHP when co-administered to rats (Gao et al. 2016). This increase in bioavailability resulted in an increase in DEHP-induced male reproductive toxicity (decreased testosterone, sperm damage) in rats co-exposed to DEHP and glycerin monostearate compared with exposure to DEHP alone (Gao et al. 2016).

In studies of the effects of DEHP ingestion on the metabolism of ethanol, there was a distinct difference between the action of single doses of 1,500–7,500 mg/kg DEHP and the same doses given over a 7-day period (Agarwal et al. 1982). The single dose appeared to decrease the metabolism of intraperitoneal ethanol, given 18 hours after DEHP, as reflected by an increase in the ethanol-induced sleeping time of the exposed rats and inhibition of hepatic alcohol dehydrogenase activity. On the other hand, when DEHP was given for 7 days before the ethanol, the ethanol-induced sleeping time was decreased and the activities of both alcohol and aldehyde dehydrogenase were increased. This indicates that the changes in sleeping time were the result of more rapid metabolic removal of the alcohol from the system in the rats treated with repeated doses of DEHP and slower metabolism in the rats given one dose.

Companion *in vitro* studies of the effects of DEHP, MEHP, and 2-ethylhexanol on the activities of alcohol and aldehyde dehydrogenase indicated that it is the metabolites of DEHP that affect the enzymes, rather than unmetabolized DEHP (Agarwal et al. 1982). The authors suggested that 2-ethylhexanol acts as a competitive inhibitor of alcohol dehydrogenase when a single dose of DEHP is administered. When DEHP exposure occurred for several days prior to ethanol exposure, the liver adjusted to the metabolic demands of the 2-ethylhexanol. Thus, at the time of ethanol ingestion, most of the 2-ethylhexanol was metabolized and the capacity of the liver to metabolize the ethanol was expanded due to the induction of the alcohol-metabolizing enzymes.

Other Interactions. In the 4-week study by Dalgaard et al. (2000) evaluating potential interactions between DEHP and acetone described in the male reproductive section above, an apparent increase in DEHP-associated lethality at the highest dose (10,000 mg/kg/day) was observed with co-exposure to acetone for 4 weeks. Observed mortality was 2/10 in the DEHP-only group and 4/10 in the DEHP+acetone group.

One study evaluated potential interactions between DEHP and benzo(a)pyrene (BaP) with respect to female reproductive toxicity (Xu et al. 2010). Female XX rats were exposed to DEHP at 300 or 600 mg/kg/day, BaP at 5 or 10 mg/kg/day, or a combination of the low- or high-doses of each for 60 days via gavage (every other day). Examined endpoints include ovary weight, estrous cycle, serum hormone levels, ovarian follicle populations, granulosa cell apoptosis, and gene and protein expression of aromatase and PPAR. While both chemicals caused exposure-related changes in certain outcomes, there was no qualitative evidence of interaction (no formal statistical interaction analysis was conducted).

Intermediate-duration oral studies in rats have shown that high doses of DEHP can affect thyroid cell structure (e.g., hypertrophy of Golgi apparatus, increases in lysosomes, dilation of the endoplasmic reticula, and increases in colloid droplets) and function (e.g., decreased levels of circulating T4) (Hinton et al. 1986; Poon et al. 1997; Price et al. 1987, 1988a). When large oral doses of 500 and 2,500 mg/kg/day DEHP were combined with dietary exposure to a compound that has similar effects on the thyroid (Aroclor 1254, a polychlorinated biphenyl mixture), there was an apparent additive effect of the two compounds on changes in thyroid cell structure and decreases in serum T3 and T4. At lower doses of DEHP (50 and 100 mg/kg/day) and Aroclor 1254, there were no additive effects apparent with the changes in cell structure or the levels of T3 and T4. In another study, Howarth et al. (2001) did not observe any interaction between DEHP and DnHP with regard to thyroid toxicity in male rats following dietary exposure to 10,000 ppm DEHP, 10,000 ppm DnHP, or their combination for 14 days; however, the study design was inadequate to evaluate interactions due to lack of dose-response data for individual chemicals or mixture.

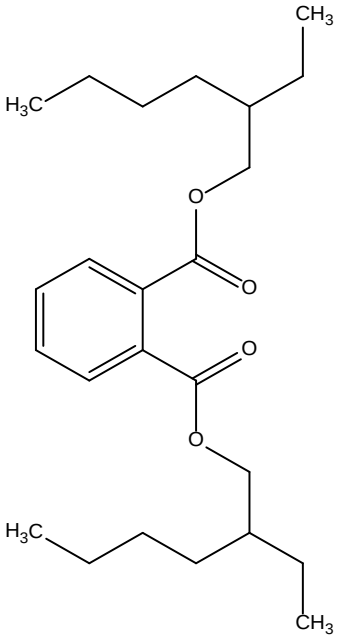
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Di(2-ethylhexyl)phthalate, also known as DEHP, is an organic ester containing an eight-carbon alcohol moiety widely used as a plasticizer in polymers. DEHP is widely used for a variety of standard products due to its overall performance characteristics, including fusion rate, efficiency, and viscosity (Cadogan and Howick 2001; TURI 2006).

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for DEHP.

Table 4-1. Chemical Identity of DEHP

Characteristic	Information	Reference
Chemical name	Di(2-ethylhexyl)phthalate	RTECS 2013
Synonym(s) and Registered trade name(s)	DEHP; dioctylphthalate; DOP; bis(2-ethylhexyl) phathalate; Bisoflex 81; Eviplast 80; Octoil; Plantinol DOP; Staflex DOP; 1,2-benzenedicarboxylic acid, 1,2-bis(2ethylhexyl) ester	EPA 2012; RTECS 2013
Chemical formula	$C_{24}H_{38}O_4$	RTECS 2013
Chemical structure		Howard and Meylan 1997
CAS Registry Number	117-81-7	RTECS 2013

CAS = Chemical Abstracts Services

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of DEHP is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of DEHP

Property	Information	Reference
Molecular weight	390.57	Howard and Meylan 1997
Color	Colorless	NIOSH 2016
Physical state	Liquid	Staples et al. 1997
Melting point	-47 °C	Staples et al. 1997
Boiling point	384 °C	Howard and Meylan 1997
Density at 20 °C	0.984 g/cm^3	Cadogan and Howick 2001
Odor	Slight odor	TURI 2006
Odor threshold:	No data	
Solubility:		
Water at 25 °C Water at 20 °C	41 µg/L[a] 1.9 µg/L[a]	Leyder and Boulanger 1983 Letinski et al. 2002
Organic solvents	Miscible in mineral oil; slightly soluble in carbon tetrachloride	Haynes 2014; Larranaga et al. 2016
Partition coefficients:		
Log K_{ow}	7.50	Staples et al. 1997
Log K_{oc}	4.9–6	Staples et al. 1997
Vapor pressure at 25 °C	1.0x10^{-7} mmHg	Staples et al. 1997
Henry's law constant at 25 °C	1.71x10^{-5} atm-m^3/mole	Staples et al. 1997
Autoignition temperature	735 °F (350 °C)	NIOSH 2001
Flashpoint	420 °F (216 °C) (open cup)	NIOSH 2016
Flammability limits	No data	
Conversion factors	1 ppm=15.94 mg/m^3	Clayton and Clayton 1981
Explosive limits	0.3% (lower limit) No data (upper limit)	NIOSH 2016

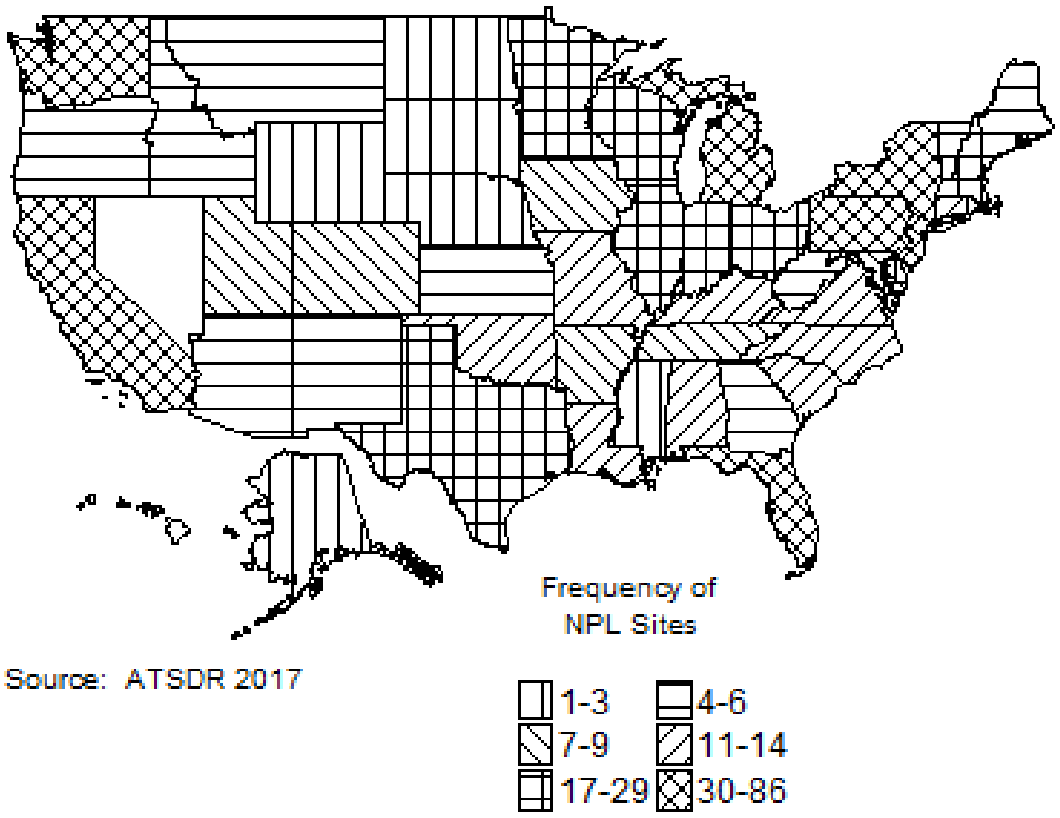
[a]The solubilities of DEHP in distilled water that have been determined both experimentally and theoretically vary between 1.1 and 1,200 µg/L (Staples et al. 1997). The highest values are likely to be overestimated as measurements that used the traditional shake flask method often led to these higher values. The value of 41 µg/L was the lowest experimentally derived value for the solubility of DEHP in distilled water. Yet, estimation models, SPARC and EPIWIN, provided solubility estimates of 2.6 and 1.1 µg/L, respectively (Staples et al. 1997), whereas Ellington (1999) found the chemical DEHP analog, dioctylphthalate, to have a solubility of 0.51 µg/L using the slow stir method. Letinski et al. (2002) determined DEHP solubility using the slow stir technique and reported a value of 1.9 µg/L in sterilized well water at 20 °C.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

DEHP has been identified in at least 755 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which DEHP has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 747 are located within the United States, 1 is located in the Virgin Islands, 1 is located in Guam, and 6 are located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with DEHP Contamination



Source: ATSDR 2017

- The most likely route of exposure for the general public to DEHP is through ingestion of food, inhalation or ingestion of house dust, and dermal contact with consumer products containing DEHP. Occupational exposures may be significant in some settings. However, the highest DEHP exposures result from medical procedures.

- DEHP is ubiquitous in the environment, although usually at low levels. The majority of DEHP in the environment sticks to soils and sediment.

- DEHP tends to sorb strongly to soils and sediments and to bioconcentrate in aquatic organisms. Biodegradation is expected to occur under aerobic conditions. The dominant fate pathway is determined by local environmental conditions.

DEHP is a widely used chemical that enters the environment both through disposal of industrial and municipal wastes in landfills and by leaching into consumer products stored in plastics. It tends to sorb strongly to soils and sediments and to bioconcentrate in aquatic organisms; however, biomagnification of DEHP in the food chain is not expected to occur due to metabolism. Biodegradation is expected to occur under aerobic conditions. Sorption, bioconcentration, and biodegradation are likely to be competing processes, with the dominant fate being determined by local environmental conditions, such as pH, soil texture, and oxygen levels.

The principal route of human exposure to DEHP is oral. Much of the monitoring database is old and might not represent current exposures, especially since the uses of DEHP in certain applications has been changing (CPSIA 2008; Wilkinson and Lamb 1999). The U.S. Department of Health and Human Services estimates that the average U.S. adult exposure to DEHP is on the order of 3–30 µg/kg/day (NTP 2006). Populations residing near hazardous waste disposal sites or municipal landfills might be subject to higher than average levels of DEHP in ambient air and drinking water. Even so, the concentrations of DEHP in these media will be greatly limited by the low volatility and low water solubility of DEHP. Occupational exposures might be significant, but the highest exposures to DEHP result from medical procedures such as blood transfusions (e.g., estimated upper bound limit of 8.5 mg/kg/day) or hemodialysis (e.g., estimated upper bound limit of 0.36 mg/kg/day), during which DEHP might leach from plastic equipment into biological fluids (FDA 2001). Exposures of neonates to DEHP can be especially high as a result of some medical procedures; TPN administration (e.g., estimated upper bound limit of 2.5 mg/kg/day), and extracorporeal membrane oxygenation (ECMO) (e.g., estimated upper bound limit of 14 mg/kg/day) (FDA 2001). A report published by the European Union Scientific Committee on Emerging and Newly-Identified Health Risks estimated that the highest acute/short-term exposures to DEHP were from the plastics (intravenous bags and lines) used during blood transfusions or ECMO (SCENIHR 2016). Maximum exposures to DEHP during these procedures were estimated at 8–10 mg/kg/day. The highest risk from chronic treatment comes from patients undergoing hemodialysis, with a maximum reported exposure of 2.2 mg/kg/day (SCENIHR 2016).

When DEHP is present in the environment, it is usually at very low levels. Since DEHP is a ubiquitous laboratory contaminant, it is very difficult to determine these low levels accurately due to the potential for false identification of elevated phthalate concentrations from sample contamination. Laboratory

contamination often undermines the credibility of the data and, therefore, reported concentrations of DEHP in environmental samples must be carefully reviewed.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

DEHP is a member of a group of compounds commonly referred to as the phthalate esters, which are predominantly used as plasticizers in flexible products made from PVC (CPSC 2010). DEHP is produced by the esterification of phthalic anhydride with 2-ethylhexyl alcohol in the presence of an acid catalyst (CPSC 2010). Phthalate plasticizers can be produced using this reaction in batch methods or in highly automated continuous operations (TURI 2006). DEHP can also be manufactured by the dimerization of butyraldehyde (Cadogan and Howick 2001). The production volume of DEHP in the United States was 120,000 metric tons (265 million pounds) in 2002 (TURI 2006). Production and/or use in the United States in 2006 was reported as 45,000–230,000 tons (90–460 million pounds) (Zolfaghari et al. 2014). Worldwide production was estimated to be 2 million metric tons (4.4 billion pounds) in 2004 (Erythropel 2014). Worldwide production of DEHP is decreasing, mainly related to the regulations being enforced against certain uses of DEHP (Zolfaghari et al. 2014).

There are 23 companies producing DEHP in the United States (IARC 2012); however, five companies appear to be the primary U.S. producers (CPSC 2010). Table 5-1 summarizes the number and location of U.S. facilities that reported the use and production of DEHP in 2015 (TRI15 2016). The Toxics Release Inventory (TRI) data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use DEHP

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	5	0	999,999	7, 11, 12
CA	9	100	999,999	2, 3, 6, 7, 11, 14
CO	1	100,000	999,999	7
CT	1	100	999	7
FL	1	100,000	999,999	7
GA	6	10,000	999,999	6, 7, 8
IA	2	100	99,999	7, 8, 9

Table 5-1. Facilities that Produce, Process, or Use DEHP

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
IL	6	0	99,999	7, 8, 10
IN	5	1,000	999,999	7, 8, 12
KS	2	1,000	9,999	7, 9, 12
LA	1	10,000	99,999	1, 5, 12
MA	5	10,000	99,999,999	2, 3, 7, 8, 10
MI	13	1,000	999,999	7, 9, 10
MN	1	Not reported	Not reported	Not reported
MO	6	1,000	999,999	7, 8, 12
MS	3	1,000	99,999	8
NC	10	0	999,999	1, 2, 3, 5, 7, 8, 13, 14
NE	1	10,000	99,999	7, 8
NJ	4	1,000	499,999,999	6, 7
NY	4	10,000	9,999,999	7, 8
OH	18	1,000	99,999	7, 8, 9, 12
OR	3	10,000	99,999	7, 8, 12
PA	4	10,000	999,999	7, 8
PR	3	1,000	999,999	8, 10
RI	1	100,000	999,999	7, 14
SC	3	1,000	999,999	7, 8, 14
TN	8	1,000	9,999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
TX	8	1,000	999,999	7, 8, 10, 12
VA	2	1,000,000	9,999,999	7
WA	3	1,000	9,999,999	7, 9
WI	5	0	99,999	7, 8, 12
WV	1	Not reported	Not reported	Not reported

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI15 2016 (Data are from 2015)

Decreasing demand for DEHP due to continued concern over health effects might further impact production volume (Zolfaghari et al. 2014).

5.2.2 Import/Export

Estimated annual imports and exports from the United States in 2006 were reported to be approximately 69 and 13 million pounds, respectively (CPSC 2010).

5.2.3 Use

DEHP is principally used as a plasticizer in the production of flexible PVC products, with about 97% of DEHP produced being used for this purpose (CPSC 2010). PVC is made flexible by addition of plasticizers and is used in many common items such as wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, toys, shoes, automobile upholstery and tops, packaging film and sheet, sheathing for wire and cable, medical tubing, and blood storage bags. PVC is also used to produce disposable medical examination and surgical gloves, flexible tubing used to administer parenteral solutions, tubing used in hemodialysis treatment, syringes, and blood, dialysis, and storage bags (CPSC 2010; NTP 1989). DEHP is also used as a plasticizer in products such as polyvinyl acetate, polyvinyl butyral, natural and synthetic rubber, chlorinated rubber, ethyl cellulose, nitrocellulose, and polyurethane resins (CPSC 2010). DEHP plasticizer use in medical devices and industrial/commercial products accounts for 25 and 45% of the overall consumption of DEHP, respectively (CPSC 2010). DEHP plasticizers have been replaced with citrate-based plasticizers, such as acetyl tri-*n*-butyl citrate (ATBC) and 1,2-cyclohexanedicarboxylic acid, diisononyl ester (DINCH), for some uses (EPA 2012; Messerlian et al. 2017; Tickner 2001).

Numerous nonplasticizer uses of DEHP have been reported and account for <3–5% of the national use of DEHP (CPSC 2010). These uses include as a solvent in erasable ink and ultrasound gel, as a carrier for pesticides, in ceramics, in cosmetics, in vacuum pump oil, as a component of dielectric fluids in electrical capacitors, to detect leaks in respirators, in paints, lacquers, and adhesives, and in testing the efficiency of air filtration systems (CPSC 2010; Mannsville Chemical Products Corporation 1990; Messerlian et al. 2017; NTP 1989).

Because of concerns regarding health effects from exposure to DEHP, many toy manufacturers have discontinued use of all phthalates in their products (Wilkinson and Lamb 1999). The use of DEHP in domestically produced teethers and rattles has also been discontinued (CPSC 1999). In 2008, Congress permanently banned DEHP in any amount >0.1% in children's toys and certain child care articles, such as those to help sleeping, feeding, sucking, or teething of children ≤3 years old (CPSIA 2008). Risk assessments have supported this permanent ban (CPSC 2014; Lioy et al. 2015). DEHP has been removed

from or replaced as a plasticizer in most food packaging products (CDC 2016); however, the FDA still approves its use as an indirect additive in food contact substances as a component of adhesives, coatings, paper and paperboard, acrylic polymers, cellophane, and metallic foil (FDA 1999a, 1999b, 1999c, 1999d, 1999e, 1999f, 1999g). Finally, in the future, polyolefin metallocene plastomers or elastomers might replace flexible applications for PVC and other plastics altogether because they provide flexibility without the need for plasticizers. DEHP has also been replaced with DINCH in some ultrasound gels (Messerlian et al. 2017).

5.2.4 Disposal

When DEHP (as a commercial chemical product or chemical intermediate) becomes a waste, its disposal is regulated by law, as shown in Chapter 7. DEHP disposal is regulated under the Resource Conservation and Recovery Act (RCRA). Regulations promulgated under this Act control the treatment, storage, and disposal of waste DEHP. Land disposal restrictions are the responsibility of the EPA Office of Solid Waste. In 2015, it was estimated that about 460 thousand pounds of waste DEHP were transported from production facilities or points of usage for disposal, including publicly owned treatment works (TRI15 2016). No data were located regarding the quantity of waste DEHP that was disposed of by any specific means. No data were located regarding trends in DEHP disposal.

Bioremediation of DEHP-contaminated soils has been studied through bench experiments. It has been reported that 89% removal of DEHP, with an initial concentration of 5.51 mg/g dry soil, was achieved in 76 days through the addition of nutrients and inoculum to the soil (Carrara et al. 2011). However, these bench studies cannot be inferred directly to field use, as parameters such as DEHP adsorption to organic matter in soil will vary; therefore, *in situ* and intrinsic bioremediation studies in various soil conditions are needed. Carrara et al. (2011) performed pilot *ex situ* bioremediation tests on tropical soils using a slurry-phase reactor and were able to achieve 99% removal of DEHP in 49 days.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or

oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Industrial manufacturers, processors, and users of DEHP are required to report the quantities of this substance released to environmental media annually (EPA 2005). The data compiled in the TRI (TRI15 2016) are for releases in 2015 to air, water, soil, and transfers for offsite disposal. These data are summarized in Table 5-2. Total releases of DEHP to the environment in 2015 were approximately 545,000 pounds (approximately 247 metric tons) (TRI15 2016).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use DEHP[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	5	1,670	5	0	1,354	No data	1,675	1,354	3,029
CA	9	1,737	1,677	0	4,422	250	3,414	4,672	8,086
CO	1	5	0	0	0	No data	5	No data	5
FL	1	0	0	0	0	No data	0	No data	0
GA	6	3,229	0	0	39,630	No data	3,229	39,630	42,859
IA	2	97	0	0	547	No data	97	547	644
IL	6	318	1	0	7,079	No data	318	7,079	7,397
IN	5	680	0	0	6,601	No data	685	6,596	7,281
KS	2	0	0	0	0	No data	0	No data	0
LA	1	0	0	0	0	No data	0	No data	0
MA	5	18,232	0	0	0	0	18,232	0	18,232
MI	13	242	0	0	2,290	No data	242	2,290	2,532
MN	1	No data	No data	No data	No data	No data	No data	No data	No data
MO	6	2,395	0	0	91,698	1,129	2,395	92,827	95,222
MS	3	45	0	0	944	No data	45	944	989
NC	10	2,269	0	0	58,922	No data	2,269	58,922	61,191
NE	1	6	0	0	3,005	No data	6	3,005	3,011
NJ	4	102	0	0	0	81	102	81	183

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use DEHP[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
NY	4	1,669	0	0	153,553	No data	1,669	153,553	155,222
OH	18	871	0	0	20,910	23,535	871	44,445	45,316
OR	3	49	0	0	35,608	No data	35,657	No data	35,657
PA	4	8	0	0	3,299	No data	8	3,299	3,307
PR	3	36	0	0	0	No data	36	No data	36
RI	1	381	0	0	250	No data	381	250	631
SC	3	403	0	0	5,039	No data	403	5,039	5,442
TN	8	10,011	211	0	25,590	201	10,456	25,557	36,013
TX	8	206	6	0	5,802	No data	212	5,802	6,014
VA	2	265	0	0	0	No data	265	No data	265
WA	3	1,848	0	0	0	No data	1,848	No data	1,848
WI	5	100	0	0	4,241	No data	100	4,241	4,341
WV	1	No data	No data	No data	No data	No data	No data	No data	No data
Total	144	46,873	1,901	0	470,783	25,196	84,620	460,132	544,752

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI15 2016 (Data are from 2015)

Industrial releases are only a fraction of the total environmental releases of DEHP. Release of DEHP into the environment is thought to originate from diffuse sources, mainly from end-uses of DEHP (e.g., as an additive to plastics) by leaching or evaporating (Clara et al. 2010). Disposal of plastic products containing DEHP (Section 5.2.4) is also a possible source of environmental release (Bauer and Herrmann

1997; EPA 1981). Quantitative information on releases of DEHP to specific environmental media is discussed below.

5.3.1 Air

Estimated releases of 46,873 pounds (~21 metric tons) of DEHP to the atmosphere from 144 domestic manufacturing and processing facilities in 2015, accounted for about 8% of the estimated total environmental releases from facilities required to report to the TRI (TRI15 2016). These releases are summarized in Table 5-2.

As presented in Chapter 4, DEHP 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 (Staples et al. 1997). Nonetheless, DEHP appears to be a common air contaminant that is present globally in low ng/m^3 concentrations (Section 5.5.1), although specific information that quantifies emissions of DEHP to air appears to be insufficient to account for this apparent widespread presence. For example, while monitoring data show that elevated fallout concentrations of DEHP are associated with industrial activity (Thurén and Larsson 1990), elevated fallout concentrations were only seen near a stack, and no elevated concentrations could be seen 2 km away from the stack. In addition, these authors could not correlate DEHP fallout rates with specific sources or transport routes on a nationwide basis in Sweden. They found no "distributional patterns or gradient," which possibly suggests that any local patterns were obscured by DEHP contribution from other sources or that emission sources of roughly equal magnitude are diffuse. By contrast, a pattern associating distance from sources and concentration was seen with DEHP by Ritsema et al. (1989) in Lake Yssel in the Netherlands, while for other lower-molecular-weight phthalate esters, no pattern was evident. The authors suggested that an upstream source was the dominant mechanism by which DEHP enters the lake, not atmospheric deposition.

The possibility of many diffuse sources of DEHP is potentially supported by some of the uses. For example, some of the products that use DEHP include thin sheets and coatings, such as floor tiles, shower curtains, tablecloths, and furniture upholstery. These products characteristically have large surface area-to-volume ratios, which might allow DEHP to volatilize more readily relative to other products with smaller surface area-to-volume ratios. Cadogan et al. (1994) and Cadogan and Howick (2001) reported that an indoor emission rate of 2.3×10^{-4} mg/second-m^2 at 25 °C has been calculated for all phthalate plasticizers in products such as wall coverings, flooring, upholstery, and wire insulation. These authors

used this emission estimate to calculate overall releases of phthalate esters to air. Cadogan and Howick (2001) also noted that approximately 47% of the phthalate ester used is DEHP. Applying this DEHP use percentage to their emission estimates, total end-use emissions of DEHP to the air from indoor household uses in Western Europe in 1990 is approximately 300 tons per year. Emissions from exterior end uses were estimated to be 5,600 tons per year for DEHP (the authors noted that this estimate was not well defined). These estimates support the conclusion that the major sources of DEHP are from end-uses and that these represent a geographically diffuse source. Finally, Jones et al. (1996) estimated that between 0.001 and 3.6 metric tons of DEHP are emitted per year (depending on assumptions about vapor equilibria and mass transfer used in model calculations) from sewer manholes in a large U.S. city having an average DEHP sewage concentration of 26 μg/L.

It has been estimated that <3% of the total U.S. domestic supply of DEHP is released to air (EPA 1981). Based on a reported U.S. production amount in 2002 of about 265 million pounds, discussed in Section 5.2.1, the estimated annual atmospheric emission of DEHP from all sources in the United States was about 8.0 million pounds in 2002.

DEHP may also be released into the air from burning domestic materials that still contain this compound from legacy use as a fire retardant, such as clothing and furnishing (Alexander and Baxter 2016; Lacey et al. 2014). DEHP detected on firefighter protective clothing has been attributed to release of semi-volatile toxic combustion products during structural fires (Alexander and Baxter 2016; Lacey et al. 2014).

5.3.2 Water

Estimated releases of 1,901 pounds (~0.86 metric tons) of DEHP to surface water from 144 domestic manufacturing and processing facilities in 2015, accounted for about 0.3% of the estimated total environmental releases from facilities required to report to the TRI (TRI15 2016). These releases are summarized in Table 5-2.

As a result of secondary treatment processes in publicly owned treatment works (POTWs), only a small percentage (<3%) of DEHP that enters POTWs is subsequently released to surface water (Yu and Chu 2009; Zolfaghari et al. 2014).

DEHP was detected in 13% of 86 samples of urban storm water runoff evaluated for the National Urban Runoff Program, at concentrations ranging from 7 to 39 ppb (Cole et al. 1984). In some locations, storm

and sanitary sewers are separated so that storm water runoff in these locations directly enters surface water. Even in locations with combined storm and sanitary sewers, DEHP is still expected to enter the environment, but probably to a lesser extent. For example, Stubin et al. (1996) reported that DEHP was present in 48% of the influent and 12% of the effluent samples taken from New York City sewage treatment plants during 1989–1993. Thus, storm water runoff, even when it goes through a sewage treatment plant, might enter the environment. In addition, DEHP also appears to be present in the treatment plant influent whether or not it receives storm water. It was reported that raw sewage samples had DEHP concentrations ranging from 3.4 to 34 µg/L and wastewater treatment plant effluent samples had concentrations of 0.083–6.6 µg/L (Clara et al. 2010). Influent at two wastewater treatment plants in eastern Tennessee contained total DEHP levels of 8,572 and 12,160 ng/L, while only one plant had detectable DEHP in its effluent discharge at 300 ng/L (Yu and Chu 2009). DEHP has also been reported in wastewater from a petrochemical plant (Castillo et al. 1998), leachate from industrial and municipal landfills (Brown and Donnelly 1988; Castillo et al. 1998; Ghassemi et al. 1984; Roy 1994), and sewage sludge (O'Connor 1996). It is anticipated that water from all of these sources enters the environment and might contain DEHP. Stubin et al. (1996) noted that DEHP was commonly present (48% of the samples) in municipal sewage treatment plant influent, suggesting that DEHP is present in domestic wastewater. DEHP in domestic wastewater can come from either the source tap water or from activities within the household such as washing floors that contain DEHP, showering using a shower curtain containing DEHP, or washing other DEHP-containing materials.

5.3.3 Soil

Estimated releases of 470,783 pounds (~214 metric tons) of DEHP to soils from 144 domestic manufacturing and processing facilities in 2015, accounted for about 86% of the estimated total environmental releases from facilities required to report to the TRI (TRI15 2016). There were no estimated releases of DEHP via underground injection (TRI15 2016). These releases are summarized in Table 5-2.

The principal source of DEHP release to land is likely the disposal of industrial and municipal waste to landfills (EPA 1981). Municipal wastes probably contain substantial quantities of DEHP-containing plastics, which might significantly increase the total quantity of DEHP released to land. Based on an estimate that 92% of U.S. domestic supplies of DEHP are released to landfills (EPA 1981) and a reported U.S. domestic production in 2002 of approximately 265 million pounds (Section 5.2.1), it was estimated that about 244 million pounds of DEHP are deposited in landfills annually. Bauer and Herrmann (1997)

reported the concentration of DEHP in 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. DEHP was found in all of the fractions. It is anticipated that household waste from continental Europe is similar to the United States, so that the same profile would be expected in both places. Further information on this study is presented in Section 5.5.4 and Table 5-7.

Land application of sewage sludge might also release DEHP to soil. The National Sewage Sludge Survey estimated that mean DEHP concentrations in sludge range from 55 to 300 ppm, with a national mean of 75 ppm (EPA 1990). It is also estimated that about 42% of sewage sludge generated in the United States annually, or 5.1 billion pounds, is applied to land. Another 20% (2.4 billion pounds) is deposited in landfills, and 14% (1.7 billion pounds) is incinerated (EPA 1990). Using the national mean concentration and a total of 7.5 billion pounds of sludge deposited in soils, sludge accounts for approximately 7,500 pounds of DEHP released to soils annually.

DEHP has also been reported in ocean sediments at levels up to 25 ppm at points of urban sewage outfall (Swartz et al. 1985), and in 100% of the sediments in rivers near combined sewer overflows in New Jersey (Ianuzzi et al. 1997). Concentrations of phthalates, including DEHP, are approximately 10 times higher in stream sediments that are influenced by urban activity than in areas under other land-use activities (Lopes and Furlong 2001).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. DEHP is ubiquitous in air at low concentrations (e.g., 0.06–5.0 ng/m^3) (Eisenreich et al. 1981; Ligocki et al. 1985a), 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 surfaces (Atlas and Giam 1981; Eisenreich et al. 1981; Ligocki et al. 1985a, 1985b). Eisenreich et al. (1981) calculated that wet and dry deposition of DEHP into the five Great Lakes amounted to approximately 47.7 metric tons per year, which corresponds to an average fallout rate of 16.2 μg/m^2 per month. A similar average fallout rate of 23.8 μg/m^2 per month (the range was 5.96–195.5 μg/m^2 per month) was reported by Thurén and Larsson (1990) for DEHP in Sweden. The authors noted that the deposition rate for DEHP decreased with increasing distance from a smokestack at a phthalate-consuming factory. DEHP has been found in

Antarctic surface and sub-surface snow (up to 3 m deep), and in pack ice (Desideri et al. 1994, 1998), as well as in the atmosphere over the Gulf of Mexico (Giam et al. 1980), suggesting that DEHP can be transported for long distances. Thus, the DEHP measured in one part of the world might have originated elsewhere. This transport is likely particle-sorbed DEHP (Atlas and Giam 1981) because vapor-phase DEHP reacts rapidly with hydroxyl radicals in the atmosphere (Section 5.4.2), while particle-sorbed DEHP does not react rapidly with hydroxyl radicals. Nearly half of the DEHP detected in the atmosphere over the Gulf of Mexico was in the particulate phase (Giam et al. 1980). Atmospheric fallout is negatively correlated with temperature; less DEHP 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 DEHP in the vapor state in the warm summer and less in the cold winter, and further indicates that the partitioning between particles and vapor is controlled by vapor pressure.

Water. In water, DEHP is predominantly sorbed to suspended particulates and sediments, but some remains dissolved in the aqueous phase. Volatilization is not a dominant transport process. Volatilization from water and soil is not expected to be important, based on the low Henry's law constant (estimated value 1.71×10^{-5} atm-m^3/mol; Staples et al. 1997). It has been estimated that the evaporative half-life of DEHP from water would be about 15 years (EPA 1979), and that only about 2% of DEHP loading of lakes and ponds would be volatilized (Wolfe et al. 1980a).

Sediment and Soil. Adsorption onto soils and sediments is a significant sink for DEHP. DEHP released to water adsorbs strongly to suspended particulates and sediments (Al-Omran and Preston 1987; Staples et al. 1997; Sullivan et al. 1982; Wolfe et al. 1980a). Distribution of DEHP between the water column and the sediments was modeled for several types of freshwater aquatic environments (Wolfe et al. 1980a). Between 69 and 99% of DEHP was estimated to partition to the sediments. Adsorption of DEHP to marine sediments might be greater than adsorption to freshwater sediments, due to reduced solubility of DEHP in saltwater and a salting-out effect (Al-Omran and Preston 1987; Sullivan et al. 1982; Yuwatini et al. 2013; Zhou and Liu 2000). Levels of DEHP in a marine environment ranged from 0.1 to 0.7 ppb in the water and from 280 to 640 ppb in the suspended particulates (Preston and Al-Omran 1989). DEHP shows greater adsorption to the smaller size particle fractions of suspended particulates or colloids (Al-Omran and Preston 1987; Zhou and Liu 2000). Complexation of DEHP with fulvic acid, a compound associated with humic substances in water and soil, might increase solubilization and thus increase the mobility of DEHP in aquatic systems (Johnson et al. 1977). Ritsema et al. (1989) noted that DEHP in the River Rhine was mainly associated with suspended particulates, but on some sampling days, dissolved DEHP was at a higher concentration than the sorbed material. By contrast, in Lake Yssel, DEHP

concentrations in the suspended material were approximately 100 times higher than the dissolved material. In addition, the authors reported that a distinct concentration gradient was noted across the lake, suggesting that DEHP entered the lake from the River Yssel rather than nonpoint sources as was the case with some other phthalates.

Other Media. Percolation of DEHP through the soil to groundwater might occur during times of rapid infiltration. DEHP concentrations were generally reduced by infiltration through a soil column, but all column effluents contained measurable levels (Hutchins et al. 1983). In hazardous waste sites, the presence of common organic solvents such as alcohols and ketones might increase the solubility of relatively insoluble compounds such as DEHP, thereby increasing the amounts that might leach from the waste site into subsoil and groundwater (Nyssen et al. 1987). This is consistent with the measurement of DEHP in leachate of some landfills at levels in excess of its usual water solubility (Section 5.3.2).

Bioconcentration of DEHP has been observed in invertebrates, fish, and terrestrial organisms. Mean bioconcentration factors (BCFs) have been reported for algae (3,173±3,149, two species), mollusks (1,469±949, five species), crustacea (1,164±1,182, four species), insects (1,058±772, three species), polychaetes (422, one species), fish (280±230, five species), and amphibians (605, one species) have been compiled by Staples et al. (1997). Residues of DEHP have been found in the organs of terrestrial animals such as rats, rabbits, dogs, cows, and humans (EPA 1979). However, accumulation of DEHP will be minimized by metabolism, and biomagnification of DEHP in the food chain is not expected to occur (EPA 1979; Johnson et al. 1977; Mackintosh et al. 2004; Staples et al. 1997; Wofford et al. 1981). Several metabolites of DEHP might be detected in animal tissues (Johnson et al. 1977). Uptake of DEHP from soil by plants has also been reported (EPA 1986; O'Connor 1996).

5.4.2 Transformation and Degradation

Air. Reaction of DEHP vapor with hydroxyl radicals in the atmosphere has been predicted, with an estimated half-life of about 6 hours using the Atmospheric Oxidation Program (Meylan and Howard 1993). The atmospheric half-life, however, is expected to be longer for DEHP adsorbed to atmospheric particulates. Based on the estimated half-life alone, extensive transport of DEHP would not be expected and concentrations in Antarctic snow would not be predicted. Nonetheless, DEHP appears to be present in urban and rural atmospheres (Section 5.5.1), and its transport might be mainly in the sorbed state. Data confirming this degradation pathway have not been located. Direct photolysis and photooxidation are not likely to be important (Wams 1987).

Water. Biodegradation might be an important fate process for DEHP in water under aerobic, but not anaerobic, conditions (O'Connor et al. 1989; O'Grady et al. 1985; Sugatt et al. 1984; Tabak et al. 1981; Thomas et al. 1986). DEHP was significantly biodegraded (>95%) after gradual acclimation of the microbial population over a period of about 3 weeks under conditions of the static-flask and shake-flask screening tests (Sugatt et al. 1984; Tabak et al. 1981). In the shake flask study using an acclimated inoculum, initial biodegradation was low on days 2 and 3, but increased 5–10-fold by days 6 and 7; degradation to carbon dioxide was 87% at 28 days (Sugatt et al. 1984). The reported half-life of DEHP due to microbial activity in river water is about 1 month (Wams 1987). In freshwater, degradation has been reported to range from 0 to >99%, and is dependent on many variables including temperature (Staples et al. 1997). Reported removal of DEHP from aqueous systems by activated sludge biodegradation under aerobic conditions ranged from 70 to >99%, and from 0 to 90% in wastewater depending on the microbial strains present and other variables (Kurane 1986; Nasu et al. 2001; O'Grady et al. 1985; Pradeep et al. 2015; Staples et al. 1997). In spite of the many reported rapid degradation rates, DEHP has been found in sewage sludge (O'Connor 1996) and in sewage treatment plant effluents (Stubin et al. 1996), indicating that under actual sewage treatment plant conditions (which are more rigorous than environmental waters), DEHP is not always completely degraded, but rather becomes sorbed to sludge solids. Nonetheless, DEHP does not appear to be accumulating in the environment so that biodegradation is removing the apparent constant influx of DEHP. Under anaerobic conditions, biodegradation of DEHP is slower (O'Connor et al. 1989; Staples et al. 1997; Wams 1987).

Chemical hydrolysis of DEHP occurs too slowly to be important (Howard 1989; Staples et al. 1997). The estimated half-life for DEHP hydrolysis in water is 100 years (Wams 1987).

Sediment and Soil. Biodegradation of DEHP also occurs in soil, but at a slower rate than in water, since adsorption onto the soil organic matter reduces the availability of DEHP for degradation (Carrara et al. 2011; Cartwright et al. 2000; Cheng et al. 2000; Wams 1987). According to Cartwright et al. (2000), DEHP is reported to be recalcitrant in soil and, as such, is predicted to account for the majority of phthalate contamination in the environment. Many other environmental factors, in addition to soil organic content, influence the rate of DEHP biodegradation (Cartwright et al. 2000; Gejlsbjerg et al. 2001). In sediments, optimum degradation of DEHP occurred at high concentrations, warm temperatures, and in a nutrient-rich system (Johnson et al. 1984). Biodegradation rates in sediments, like soil, can also decrease with increasing sorption, showing that DEHP has the inherent capacity to be quickly degraded by microbes; sorption will cause longer half-lives in natural sediments (Kickham et al. 2012). Anaerobic

biodegradation of DEHP in sediments was reported to occur, but more slowly than under aerobic conditions (Chang et al. 2005; Johnson et al. 1984).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to DEHP depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of DEHP in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on DEHP levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

One problem that is encountered when reviewing the concentrations of DEHP in environmental water samples is evaluating the accuracy of the reported values of DEHP dissolved in water. Many of the concentrations of DEHP that have been reported for environmental water samples often exceed the solubility of DEHP in distilled or deionized water (Staples et al. 1997). Evaluating the values is complicated by the fact that a true solubility of DEHP in water has been difficult to determine experimentally, with values ranging between 0.0006 and 0.40 mg/L depending on the method of analysis (Staples et al. 1997). In addition, the solubility of DEHP in aqueous environmental media can be greatly affected by the types and concentration of dissolved organics in the sampled water; for example, humic substrates in landfill leachates (Staples et al. 1997). Another complication to determining the concentration of DEHP in environmental water samples is the possible introduction of DEHP from other sources (Howard et al. 1985). For example, the measurement of DEHP in water can be confounded by a number of sampling problems. Samples can be contaminated by additional amounts of DEHP contained in sampling devices and laboratory containers. Since DEHP is a common laboratory contaminant, laboratory and field blanks often show concentrations similar to those in the media under study. Sampling of water through the air-water interface can be contaminated by DEHP that is contained in surface films, due to the limited solubility of DEHP in water and a density that is slightly lower than water. Consequently, the reliability of the values that have been reported to represent the concentration of DEHP dissolved in water will have to be judged upon the quality of the sampling and analytical techniques used to measure DEHP in aqueous environmental media.

Table 5-3 shows the lowest limits of detection that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	16 µg/m^3	OSHA 1994
Drinking water	0.46 µg/L	EPA 1995
Surface water and groundwater	0.27 µg/L	EPA 1996
Soil	27.9 µg/kg	USGS 2006
Sediment	27.9 µg/kg	USGS 2006
Whole blood	20 ng/mL	Kambia et al. 2001

[a]Detection list based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-4. Summary of Environmental Levels of DEHP

Media	Low	High	Mean
Outdoor air (ng/m^3)	<0.4	65	5.0
Indoor air (ng/m^3)	20	240	109
Dust (g/kg)	2.38	4.10	3.24
Surface water (µg/L)	<0.002	137	0.21
Groundwater (µg/L)	Not detected	470	15.7
Drinking water (µg/L)	0.16	170	0.55
Rainwater (µg/L)	0.004	0.68	0.17
Wastewater (µg/L)	0.01	4,400	27
Sediments (µg/kg)	0.00027	218	1.4
Soil (µg/kg)	0.03	1,280	0.03
Sludge (g/kg)	0.000420	58.3	0.301

Source: NTP 2006

Detections of DEHP in air, water, and soil at NPL sites are summarized in Table 5-5.

Table 5-5. DEHP Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	30.0	45.7	$1.25x10^4$	318	196
Soil (ppb)	$9.3x10^3$	$1.44x10^4$	$2.04x10^4$	304	189
Air (µg/m^3)	0.437	0.320	$2.87x10^3$	4	4

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

As presented in Chapter 4, DEHP 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, DEHP appears to be ubiquitous in air, with urban air having somewhat higher concentrations than air in rural or uninhabited areas. The monitoring studies reported appear to have taken reasonable efforts to eliminate contamination from their analyses. DEHP has been reported over the Pacific and Atlantic Oceans at mean levels of approximately $1.4x10^{-6}$ mg/m^3 ($3.2x10^{-7}$–$2.6x10^{-6}$ mg/m^3, 0.32–2.68 ng/m^3) (Atlas and Giam 1981; Giam et al. 1980), in outdoor air in Sweden at a median concentration of $2.0x10^{-6}$ mg/m^3 ($2.8x10^{-7}$–$77.0x10^{-6}$) mg/m^3, 0.28–77.0 ng/m^3) (Thurén and Larsson 1990), over Portland, Oregon at a mean level of $3.9x10^{-7}$ mg/m^3 ($6.0x10^{-8}$–$9.4x10^{-7}$ mg/m^3, 0.06–0.94 ng/m^3) (Ligocki et al. 1985a), and over the Great Lakes at a mean concentration of $2.0x10^{-6}$ mg/m^3 ($5.0x10^{-7}$–$5.0x10^{-6}$ mg/m^3, 0.50–5.0 ng/m^3) (Eisenreich et al. 1981). DEHP was not among the four phthalate esters detected in industrialized areas along the Niagara River (Hoff and Chan 1987). DEHP was detected but not quantified in a forest atmosphere in Germany (Helmig et al. 1990). Average atmospheric concentrations reported in the literature appear to be within a relatively narrow range regardless of whether monitored over oceans or in industrial areas.

DEHP levels in indoor air might be higher due to slow volatilization from plastic products (Bornehag et al. 2005; EPA 1981; Wams 1987). As noted in Section 5.3.1, Cadogan et al. (1994) reported that an indoor overall emission rate of $2.3x10^{-4}$ mg/second-m^2 at 25 °C has been calculated for all phthalate plasticizers in products such as wall coverings, flooring, upholstery, and wire insulation.

In an effort to quantify typical indoor chemical exposures, Rudel et al. (2001) measured DEHP (and other compounds) in air samples in various occupational and residential structures. A total of seven air samples were collected from a mobile trailer (two simultaneous samples), two office buildings (two samples), a residential home (one sample), a workplace where plastics were melted (one sample), and a personal air sample collected during an 11-hour period of shopping and errands (one sample). DEHP was detected in four out of seven air samples with the highest measured level (11.5 μg/m^3) observed in the workplace where plastics were melted. In another study, indoor measurements of DEHP taken in six homes in Tokyo, Japan in the spring of 2000 were 0.04–0.06 μg/m^3 at five of the homes and 0.23 μg/m^3 at the other (Otake et al. 2001). Indoor air collected from 32 homes in New York City over a period of 2 weeks had a mean DEHP concentration of 0.09 μg/m^3 (Adibi et al. 2008).

Emission of DEHP from PVC wall coverings (containing 30% phthalic esters) was measured in a test chamber at room temperature; a maximum concentration of 0.94 μg/m^3 was noted for DEHP in air over 14-day test period (Uhde et al. 2001). Increases in DEHP emissions with increasing ambient temperature are especially important within car interiors, where DEHP concentrations in air have been shown to range from 1 μg/m^3 at room temperature to 34 μg/m^3 at 65 °C (Uhde et al. 2001).

5.5.2 Water

DEHP has been detected infrequently (11%) in surface water, rainwater, and groundwater in the United States at concentrations generally in the low ppb (μg/L) range. DEHP was detected in drinking water concentrates from several U.S. cities (EPA 1984). Canter and Sabatini (1994) reported that the Biscayne aquifer in Florida had a maximum DEHP concentration of 8,600 μg/L, but no DEHP was detected in the municipal well fields that draw water from that aquifer. Eckel et al. (1993) also reported the presence of DEHP in the groundwater in Florida. DEHP was detected in samples from Long Island public water supply wells and groundwater collected between 1997 and 2011 at concentrations of 2.0–39 and 2.0–4.6 μg/L, respectively (NYDEC 2014). In water samples collected from private wells in close proximity to gas drilling in Pavillion, Wyoming, DEHP was detected in 15 of 41 wells at concentrations ranging from 0.15 to 9.80 μg/L (ATSDR 2010). In an analysis of occurrence data from public water systems from the Six-Year Review of National Primary Drinking Water Regulations conducted by the EPA (2009a), DEHP was detected in 3,098 of 27,667 systems (11%) in 42 states, which collectively serve more than 45 million people at concentrations ranging from 0.05 to 250 μg/L. DEHP was detected in 460 systems at concentrations above the maximum contaminant level (MCL) of 6 μg/L, which serve a population >11 million (EPA 2009a).

DEHP was detected in 24% of 901 surface water samples recorded in the STORET database at a median concentration of 10 ppb (µg/L) (Staples et al. 1985) and in water samples from four of the five Great Lakes (IJC 1983). DEHP was also found in water samples from several U.S. rivers (DeLeon et al. 1986; Hites 1973; Sheldon and Hites 1979). Reported concentrations ranged from 0.5 to 1 ppb (µg/L). DEHP was detected at concentrations of <2,000 ng/L in surface water collected from the Fremont Creek and Sulphur Creek in Capitol Reef National Park and the Grotto and North Creek in Zion National Park in 2015 (NPS 2016). Average concentrations of DEHP in seawater ranging from 0.005 to 0.7 ppb (µg/L) have also been reported (Giam et al. 1978; McFall et al. 1985b).

DEHP was detected in petrochemical plant wastewaters and industrial landfill leachate at <0.1–30 µg/L (Castillo et al. 1998) and in New York City municipal treatment plant effluents up to 50 µg/L (Stubin et al. 1996). Roy (1994) reported a range of 34–7,900 µg/L in U.S. landfill leachate.

Bauer and Herrmann (1997) reported that DEHP 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. Approximately 50 kg of these wastes were cut into 5–10 cm pieces, placed in laboratory fermenters, and then flooded with water. Stable methanogenic conditions were obtained in 3 months. Leachate from a mixture of all waste categories except food waste contained a maximum of 147 µg/L of DEHP, while leachate from a mixture of waste categories limited to plastic films, other plastics, textiles, 8–40 mm screened fraction, <8 mm screened fraction, compound materials contained a maximum of 56 µg/kg DEHP. The authors were careful to exclude inadvertent sources of phthalate esters. This report demonstrates that DEHP is present in European household waste and that it leaches from that waste to percolating water. DEHP was detected in untreated and treated wastewater and surface runoff from traffic roads in Europe (Clara et al. 2010).

5.5.3 Sediment and Soil

DEHP was detected in both marine and freshwater sediments at average levels ranging from 6.6 to 1,500 ppb. Maximum values were usually observed near industrial effluent discharge points (Fallon and Horvath 1985; Murray et al. 1981; Ray et al. 1983; Velinsky et al. 2011). One study, measuring historical contamination of sediment in the tidal Anacostia River in Washington, DC, found that DEHP

concentrations were the highest in the upper 200–300 cm with a subsurface maximum of up to 7,500 ng/g dry weight, showing only a slight decrease in concentration towards the sediment-water interface (Velinsky et al. 2011). In the New York Bight (a sector of the Middle Atlantic Ridge adjoining the New York and New Jersey shorelines), which is an area containing disposal sites for dredging mud, sewage sludge, and industrial acid waste, DEHP has been measured in sediments at concentrations ranging from 0.1 to 10.1 ppm (Friedman et al. 2000). Iannuzzi et al. (1997) reported that DEHP was present in every sediment sample taken adjacent to combined sewer overflows to the Passaic River in New Jersey at concentrations between 960 and 27,000 μg/kg (a total of 40 samples). Of the 431 stream bed sediments collected from throughout the United States, 39.2% showed DEHP concentrations, with a median concentration of 180 μg/kg (the high concentration was 17,000 μg/kg) (Lopes et al. 1997). DEHP was reported in 40% of 367 sediment samples recorded in the STORET database at a median concentration of 1,000 ppb (Staples et al. 1985) and in sediments near a hazardous waste site (Hauser and Bromberg 1982).

Current monitoring data for DEHP in soil were not located. One study measuring phthalate esters in five soils and leachate-sprayed soils from Pennsylvania and New York in the Susquehanna River basin in 1979 reported DEHP concentrations of 0.001–1.2 mg/kg (Russell and McDuffie 1983).

5.5.4 Other Media

DEHP has been found in several kinds of food. Fish and other seafood have been reported to be contaminated with concentrations ranging from 2 to 32,000 ppb (DeVault 1985; Giam and Wong 1987; Giam et al. 1975; McFall et al. 1985a; Ray et al. 1983; Stalling et al. 1973; Williams 1973). DEHP was detected in 33% of 139 biota samples (not necessarily edible) recorded in the STORET database at a median concentration of 3,000 ppb (Staples et al. 1985). DEHP has also been reported in processed canned and frozen fish in Canada at concentrations up to 160 ppb (Williams 1973).

DEHP can become an indirect additive in packaged foods due to its use in plastic wraps, heat seal coatings for metal foils, closure seals for containers, paper packaging with a plastic film, and printing inks for food wrappers and containers (Cao 2010; Gao et al. 2014). Table 5-6 summarizes the detections of DEHP in various foods and beverages. As discussed in Section 5.6, food is the primary source of DEHP exposure in the general population.

Table 5-6. Concentration of DEHP in Food

	Concentration of DEHP (µg/g)		
Food	Minimum	Maximum	Median
Beverages	0.006	1.7	0.043
Cereal	0.02	1.7	0.05
Dairy (excluding milk)	0.059	16.8	0.96
Eggs	<0.01	0.6	0.12
Fats and oils	0.7	11.9	2.4
Fish	0.00005	32.0[a]	0.001
Fruits	<0.02	0.11	0.02
Grains	<0.1	1.5	0.14
Meat, not processed	<0.01	0.8	0.05
Milk	<0.005	1.4	0.035
Nuts and beans	<0.08	0.8	0.045
Poultry	0.05	2.6	0.9
Processed meat	<0.1	4.32	0.45
Vegetables	0.0098	2.2	0.048
Infant formula, powdered	<0.012	0.98	0.12
Infant formula, liquid	<0.005	0.15	0.006
Baby food	0.01	0.6	0.12
Other food	<0.01	25	0.05

[a]From DeVault 1985.

DEHP = di(2-ethylhexyl)phthalate

Source: NTP 2006

Monitoring data indicate that DEHP residues are generally low in U.S. foods, but the available data are in excess of 10 years old and might not be representative of current conditions. In addition to fish (discussed above), DEHP has been detected in such foods as milk, cheese, meat, margarine, eggs, cereal products, baby food, and infant formula (Cerbulis and Byler 1986; EPA 1981; Petersen and Breindahl 2000). Most samples contained <1 ppm DEHP, but fatty foods had higher levels. Combined data from Europe, North America, and Asia show that the foods with the highest DEHP concentrations were animal fats, spices, and nut/nut spreads (Wormuth et al. 2006). Although one study found that levels of DEHP in fatty foods such as milk, cheese, and meat did not differ significantly from background levels (CMA 1986), high levels of DEHP in "blank" samples and other analytical problems indicate that laboratory contamination might have confounded the results. Chocolate bars contained DEHP at levels up to 2.4 ppm (Castle et al. 1989).

DEHP has also been detected in beverages. DEHP was detected in soft drinks at concentrations ranging from 0.03 to 3.50 ng/L and in different types of milk powder at levels up to 25.1 µg/kg (Khedr et al. 2013). DEHP has been detected in 61.7% of bottled water tested from 21 countries across the world. The mean concentration worldwide was 3.42±8.94 µg/L, with a maximum concentration of 94.1 µg/L (Luo et al. 2018). Military packaged water, filled in polyethylene terephthalate bottles in Afghanistan, contained a maximum DEHP concentration of 0.6 µg/L (Greifenstein et al. 2013). The maximum allowable limit for DEHP in bottled water in the United States is 6 µg/L (FDA 2016). Based on the survey by Luo et al. (2018), 14.2% of the 379 brands of bottled water tested worldwide contained DEHP at levels above the U.S. maximum allowable limit. Countries with the highest average levels were Thailand (61.1 µg/L), Croatia (8.8 µg/L), Czech Republic (6.3 µg/L), Saudi Arabia (6.2 µg/L), and China (6.1 µg/L).

DEHP has been detected in indoor dust samples. In an effort to quantify typical indoor chemical exposures, Rudel et al. (2001) measured DEHP (and other compounds) in dust air samples in various occupational and residential structures. A total of six dust samples were collected from an office building (one sample) and three residential homes (five samples). DEHP was detected in all dust samples, with concentrations ranging from 69.4 to 524 µg/g dust and a mean concentration of 315 µg/g dust. Øie et al. (1997) reported that sedimented dust samples from 38 dwellings in Oslo, Norway contained an average of 640 µg/mg sedimented dust (100–1,610 µg/g), while suspended particulate matter from six dwellings contained an average of 600 µg/g (240–940 µg/g). In a study of 390 homes in Sweden, DEHP was found in nearly all dust samples collected (99.1%) from 346 children's bedrooms at mean and median concentrations of 1.31 and 0.77 mg/g dust, respectively (Bornehag et al. 2005). DEHP was detected in 99% of house dust samples collected from 167 homes in California between 2010 and 2011 at a median concentration of 187 µg/g dust (Philippat et al. 2015).

Blood products available for transfusions might be contaminated with DEHP due to leaching from the plastic equipment used to collect and store the blood. The concentration of DEHP increases with storage time (Inoue et al. 2005). Reported concentrations of DEHP in blood products stored in PVC bags are: whole blood (2–620 ppm); platelet concentrates (23.4–267 ppm); red cell concentrates (4.3–152 ppm); and plasma (4.3–1,230 ppm) (Ching et al. 1981b; Cole et al. 1981; Contreras et al. 1991; Dine et al. 1991; FDA 2001; Inoue et al. 2005; Jaeger and Rubin 1972; Loff et al. 2000; NTP 2000; Rock et al. 1978; Shintani 2000; Sjöberg et al. 1985c; Vessman and Rietz 1974). DEHP was also detected in intravenous fluids, such as saline and glucose, used for parenteral therapy of hospitalized patients, at levels ranging from 9 to 13 ppb (Ching et al. 1981b). Karle et al. (1997) reported that DEHP concentrations at the end of the blood prime in ECMO circuits in an *in vitro* study had mean values of 18.3, 21.8, and 19.3 µg/mL

for different circuits and was dependent on the surface area of each circuit. After 3 days, DEHP concentrations in infants averaged 4.9±4.0 μg/mL. Shneider et al. (1991) reported that serum DEHP concentrations varied depending on the nature of the treatment. They reported serum DEHP concentrations ranges of 1.1–5.1 μg/mL for infant cardiopulmonary bypass, 0.4–4.2 μg/mL for pediatric hemodialysis, 5.4–21.5 μg/mL for exchange transfusion, and 18–98 μg/mL for ECMO.

DEHP was the most common plasticizer in soft PVC products intended for children until the early 1980s and these products may have contained low levels of DEHP. For example, DEHP was detected in four commercial pacifiers at concentrations of 31–42% by weight (Lay and Miller 1987). However, the use of DEHP in domestically produced pacifiers, teethers, and rattles has been discontinued (CPSC 1999). Yet, some PVC toys manufactured in a small number of foreign countries have been reported to contain up to 11–19% DEHP (Stringer et al. 2000).

As presented in Section 5.5.2 above, Bauer and Herrmann (1997) reported that mixed household waste contained DEHP. Table 5-7 summarizes the concentration of DEHP detected in various categories of waste. The authors also calculated that 177.5–1,469.5 mg/kg DEHP was present in the waste on a dry-weight basis and constituted the most commonly found phthalate ester, constituting 91.9–93.3% of the total phthalates found in the waste.

Table 5-7. Concentration DEHP in Categories of Household Waste

	Concentration of DEHP (mg/kg)[a]		
Waste fraction	Mean	Minimum	Maximum
Food waste	64.3	4.8	334.7
8–40 mm Fraction	1,259.1	584.9	2,253.5
<8 mm Fraction	95.5	76.1	132.5
Paper for recycling	29.7	10.0	60.3
Unusable paper	71.1	41.4	106.4
Cardboard	47.4	10.1	70.5
Plastic films	444.9	169.0	907.9
Other plastics	1,027.6	373.8	2,035.3
Textiles	205.7	14.9	686.1
Compound packing waste	151.9	57.7	393.7

Table 5-7. Concentration DEHP in Categories of Household Waste

	Concentration of DEHP (mg/kg)[a]		
Waste fraction	Mean	Minimum	Maximum
Compound materials	16,820.6	7,862.4	26,352.0
Disposable diapers[b]	74.1	14.2	322.2

[a]Results are from six extractions except “compound material” for which the results are for nine extractions.
[b]Described as “nappies” in the original paper.

Source: Bauer and Herrmann 1997

5.6 GENERAL POPULATION EXPOSURE

The general population is exposed to DEHP via oral, dermal, and inhalation routes of exposure. DEHP is present in environmental media and in numerous consumer articles that are used world-wide (Section 5.2.3). Biomonitoring data suggest that 95% of the U.S. population is exposed to DEHP based on detectible levels of DEHP metabolites in urine (Kato et al. 2004). Estimates of the average total daily individual ambient exposure to DEHP in the United States have ranged from 0.21 to 2.1 mg/day (Doull et al. 1999; Huber et al. 1996; Tickner et al. 2001; Zolfaghari et al. 2014). These estimates do not include workplace air exposures or exposures to DEHP offgassing from building materials. In the United States, estimated DEHP exposures for different age groups, reported in μg/kg body weight/day, were 5.0–7.3 (0–0.5 year), 25.8 (0.6–4 years), 18.9 (5–11 years), 10 (12–19 years), and 8.2 (20–70 years) (Clark et al. 2011). Some of the information presented might not represent current exposures, since there have been recent changes in the use patterns for DEHP; specific examples are discussed in Section 5.2.3.

The National Health and Nutrition Examination Survey (NHANES) periodically uses biomonitoring to provide estimates of exposure to the civilian U.S. population. Chemicals and their metabolites are measured in subsets of participants aged 6–59 years old, meant to be a representative sample of the population. Urine measurements are reported as both the concentration in urine and the concentration corrected for urine-creatinine level, which adjusts for urine dilution. Urinary levels of DEHP metabolites, including MEHP, MEHHP, MEOHP, and MECPP, were measured in several NHANES programs assessing exposure to subsets of the general population in the United States from 1999 to 2012 (CDC 2015). MEHP, the primary metabolite of DEHP, formed by hydrolysis, represents only approximately 6% of the total amount of DEHP metabolites excreted through urine. MEHHP, MEOHP, and MECPP, the secondary metabolites of DEHP formed from the metabolism of MEHP, represent approximately 70% of DEHP metabolites in urine, and can be present in amounts roughly 3–5 times higher than MEHP (CDC

2015; TURI 2006). The NHANES results for 1999–2014 are summarized in Tables 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, and 5-15 (CDC 2018). Urinary levels were generally higher in women than men and in children than adults. However, urinary levels for all metabolites have shown an overall decrease by approximately 2-fold or greater between 1999 and 2014 for age, gender, and ethnicity that represent a broad mix of the general public, indicating that regulations to reduce general population exposure to DEHP (CDC 2018; CPSIA 2008) may be effective. Still, these findings indicate widespread exposure among the general U.S. population; however, no correlation of these measurements with actual DEHP intake has yet been determined.

Hines et al. (2009b) explored the relationship of phthalate metabolites, including those of DEHP, in urine, serum, saliva, and breast milk and potential routes of exposure using samples collected from 33 lactating mothers in North Carolina; however, phthalates were detected in <50% of the samples collected across matrices, so a correlation could not be made. Only 2% of saliva samples contained detectable levels of DEHP metabolite MECPP (2.3 µg/L). Serum and urine samples contained detectable levels of DEHP metabolites (only MECPP for serum) at >50% of samples. Median concentrations for collective DEHP metabolites in urine samples ranged from 3.6 to 36.8 µg/g creatinine and mean concentrations of MECPP detected in plasma were 2.0–2.3 µg/L. Using an exposure questionnaire, the authors found an inverse correlation with the age of the primary car driven by participants and the urinary concentration of metabolites. This study is limited by the small sample size and low detection rate.

The predominant source of DEHP exposure to the general population by the oral route is through the diet (Doull et al. 1999; Gong et al. 2014; Huber et al. 1996; NTP 2000; Wormuth et al. 2006). Clark et al. (2011) reported that ingestion of food accounts for approximately 95% of total exposure for the toddler through adult age range. Similarly, up to 90% of the daily intake of DEHP in European children and adults is attributed to food consumption (Wormuth et al. 2006). Dietary contribution to the total daily DEHP intake is less in infants and toddlers, approximately 50%, due to differences in dietary patterns (Wormuth et al. 2006). A study in Germany (Koch et al. 2013) found that urinary DEHP metabolites in individuals fasting on bottled water only over a 48-hour period showed a rapid decline to levels 5–10 times lower than initial levels within 24 hours of the fast and remained low thereafter; levels rose again after food consumption, showing that food was a significant source of exposure. Some attempts have been made to estimate exposures of DEHP to the general population in the United States (3–30 µg/kg body weight/day) through ingestion that is based on current use patterns for DEHP (NTP 2000), but more information is still needed.

Table 5-8. Uncorrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	3.43 (3.19–3.69)	3.20 (3.00–3.60)	7.60 (6.80–8.40)	14.9 (13.5–17.4)	23.8 (19.2–28.6)	2,541
	2001–2002	4.27 (3.80–4.79)	4.20 (3.70–4.90)	9.80 (8.40–11.6)	23.0 (19.1–27.9)	39.2 (31.8–50.0)	2,782
	2003–2004	2.34 (2.10–2.62)	1.90 (1.70–2.40)	5.30 (4.50–6.60)	15.1 (11.4–20.6)	31.0 (21.4–42.0)	2,605
	2005–2006	3.04 (2.78–3.32)	2.50 (2.10–2.80)	6.30 (5.70–7.10)	17.7 (14.0–22.5)	39.7 (28.6–52.1)	2,548
	2007–2008	2.64 (2.29–3.05)	2.20 (1.80–2.50)	5.40 (4.30–6.90)	14.1 (11.2–20.2)	27.6 (19.8–39.8)	2,604
	2009–2010	1.59 (1.41–1.79)	1.51 (1.33–1.71)	3.52 (2.99–4.00)	7.54 (5.96–9.54)	14.1 (9.91–21.1)	2,749
	2011–2012	1.36 (1.25–1.49)	1.40 (1.20–1.50)	3.00 (2.70–3.30)	6.00 (5.30–6.40)	8.70 (7.60–9.70)	2,489
	2013–2014	Not calculated[b]	1.10 (0.900–1.20)	2.30 (2.10–2.60)	4.40 (4.00–5.00)	6.30 (5.60–7.10)	2,685
Age group							
6–11 years	1999–2000	5.12 (4.42–5.92)	4.90 (3.70–6.40)	11.1 (8.30–13.6)	19.0 (13.8–36.1)	35.3 (15.6–130)	328
	2001–2002	4.41 (3.90–5.00)	4.40 (4.10–5.30)	9.30 (7.90–11.7)	19.7 (14.6–25.9)	31.4 (21.8–47.9)	393
	2003–2004	2.84 (2.10–3.84)	2.70 (1.80–4.10)	6.40 (4.40–9.60)	13.9 (7.80–27.6)	27.6 (11.3–64.7)	342
	2005–2006	3.10 (2.78–3.47)	3.00 (2.60–3.30)	6.20 (5.10–7.10)	14.1 (9.40–19.3)	19.7 (14.7–36.6)	356
	2007–2008	2.39 (2.05–2.80)	2.20 (1.70–2.90)	4.50 (3.70–6.20)	8.70 (6.40–13.9)	15.1 (10.6–24.1)	389
	2009–2010	1.64 (1.45–1.85)	1.71 (1.26–2.02)	3.50 (3.09–3.94)	5.95 (4.56–7.56)	8.92 (6.94–12.9)	415
	2011–2012	1.41 (1.23–1.61)	1.50 (1.20–1.80)	2.90 (2.50–3.40)	5.30 (4.10–7.10)	7.60 (6.30–8.80)	396
	2013–2014	1.44 (1.24–1.66)	1.20 (1.00–1.50)	2.70 (2.20–3.20)	5.20 (3.70–8.50)	8.70 (5.20–11.8)	409
12–19 years	1999–2000	3.75 (3.24–4.35)	3.70 (2.90–4.60)	8.10 (6.40–9.40)	15.3 (11.4–20.5)	22.8 (19.1–29.2)	752
	2001–2002	4.57 (3.96–5.27)	4.50 (3.70–5.10)	11.0 (9.50–14.4)	23.0 (17.7–32.7)	42.5 (25.9–57.5)	742
	2003–2004	2.77 (2.25–3.41)	2.50 (2.00–3.00)	6.40 (4.50–8.60)	18.6 (10.2–35.6)	40.6 (20.7–58.4)	729
	2005–2006	3.72 (3.04–4.56)	3.20 (2.40–4.10)	8.80 (6.20–13.3)	22.6 (13.8–43.4)	48.7 (23.1–62.9)	702
	2007–2008	2.99 (2.39–3.75)	2.30 (1.80–2.70)	6.00 (4.40–9.90)	21.1 (11.8–32.8)	37.6 (24.8–74.1)	401
	2009–2010	1.82 (1.52–2.16)	1.66 (1.42–1.94)	3.98 (3.35–4.73)	9.53 (6.27–14.0)	17.6 (9.54–27.4)	420
	2011–2012	1.58 (1.33–1.87)	1.50 (1.00–2.30)	3.90 (3.10–4.40)	6.80 (5.20–10.3)	12.5 (8.90–14.3)	388
	2013–2014	1.43 (1.26–1.62)	1.20 (1.00–1.40)	2.60 (2.00–3.50)	4.90 (4.20–5.80)	8.30 (5.50–10.7)	462
≥20 years	1999–2000	3.21 (2.94–3.51)	3.00 (2.70–3.40)	7.30 (6.40–8.00)	14.5 (12.1–17.0)	22.7 (17.5–27.0)	1,461
	2001–2002	4.20 (3.63–4.86)	4.10 (3.50–5.00)	9.50 (8.10–11.9)	23.5 (18.0–29.8)	39.5 (30.3–57.1)	1,647
	2003–2004	2.23 (2.03–2.44)	1.70 (1.50–2.00)	5.10 (4.50–6.00)	15.1 (10.9–19.7)	29.5 (20.4–40.0)	1,534
	2005–2006	2.94 (2.68–3.21)	2.30 (1.90–2.70)	6.20 (5.60–6.70)	17.7 (13.6–24.5)	41.5 (28.6–54.1)	1,490
	2007–2008	2.62 (2.27–3.02)	2.10 (1.80–2.50)	5.40 (4.20–7.10)	14.4 (11.2–20.2)	27.3 (19.2–40.6)	1,814
	2009–2010	1.55 (1.36–1.78)	1.44 (1.25–1.68)	3.40 (2.88–4.03)	7.39 (5.94–9.58)	14.6 (9.91–21.1)	1,914
	2011–2012	1.33 (1.19–1.48)	1.30 (1.10–1.50)	2.90 (2.50–3.20)	5.90 (5.10–6.40)	8.30 (7.10–9.60)	1,705
	2013–2014	Not calculated[b]	1.00 (0.900–1.20)	2.30 (2.00–2.50)	4.30 (3.80–4.90)	6.10 (5.40–6.80)	1,814

Table 5-8. Uncorrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L) 50th	75th	90th	95th	Sample size
Gender							
Males	1999–2000	3.68 (3.31–4.10)	3.40 (2.90–3.90)	8.00 (7.40–8.80)	16.0 (14.0–19.0)	25.3 (19.5–36.7)	1,215
	2001–2002	4.31 (3.84–4.83)	4.30 (3.70–5.10)	9.70 (8.30–11.2)	23.0 (16.9–29.8)	37.9 (29.9–48.4)	1,371
	2003–2004	2.56 (2.26–2.90)	2.20 (1.70–2.60)	6.00 (4.60–7.70)	17.2 (11.3–26.3)	33.3 (24.9–55.5)	1,250
	2005–2006	3.40 (3.01–3.85)	2.80 (2.40–3.30)	7.00 (5.70–9.00)	22.6 (15.0–35.8)	49.8 (35.2–67.4)	1,270
	2007–2008	2.77 (2.35–3.27)	2.30 (1.90–2.80)	5.50 (4.20–7.60)	14.4 (11.2–20.5)	28.9 (19.2–40.0)	1,294
	2009–2010	1.83 (1.63–2.05)	1.77 (1.63–1.91)	3.97 (3.49–4.51)	8.63 (6.94–11.9)	18.0 (12.6–29.0)	1,399
	2011–2012	1.51 (1.33–1.70)	1.50 (1.20–1.80)	3.10 (2.60–3.90)	6.10 (5.50–7.00)	9.20 (7.70–11.3)	1,259
	2013–2014	1.29 (1.17–1.41)	1.10 (1.00–1.30)	2.30 (2.00–2.70)	4.20 (3.50–5.00)	5.70 (5.10–6.60)	1,285
Females	1999–2000	3.21 (2.91–3.54)	3.10 (2.80–3.50)	7.10 (5.90–8.50)	13.6 (12.1–17.2)	21.9 (15.6–28.5)	1,326
	2001–2002	4.23 (3.67–4.86)	4.10 (3.50–5.00)	9.80 (8.40–12.2)	23.0 (19.5–28.4)	43.5 (31.4–53.7)	1,411
	2003–2004	2.15 (1.92–2.42)	1.80 (1.50–2.10)	4.90 (4.10–5.70)	13.2 (10.0–18.1)	27.8 (17.5–40.7)	1,355
	2005–2006	2.72 (2.49–2.98)	2.10 (1.90–2.40)	6.00 (5.20–6.80)	13.9 (11.7–17.5)	30.8 (21.9–36.2)	1,278
	2007–2008	2.52 (2.18–2.92)	2.00 (1.70–2.40)	5.10 (4.20–6.30)	14.1 (9.50–21.4)	26.4 (19.2–42.1)	1,310
	2009–2010	1.39 (1.21–1.60)	1.30 (1.12–1.53)	3.00 (2.51–3.62)	6.48 (5.45–8.09)	10.3 (8.33–14.9)	1,350
	2011–2012	1.24 (1.14–1.34)	1.20 (1.00–1.40)	2.90 (2.50–3.10)	5.60 (4.90–6.30)	8.10 (6.80–9.20)	1,230
	2013–2014	Not calculated[b]	1.00 (0.900–1.10)	2.40 (2.10–2.60)	4.80 (4.20–5.30)	7.00 (5.70–8.70)	1,400
Race/ethnicity							
Mexican Americans	1999–2000	3.49 (3.16–3.85)	3.50 (3.10–3.90)	7.00 (5.70–8.60)	13.3 (10.7–18.7)	23.9 (17.4–27.3)	814
	2001–2002	4.32 (3.75–4.98)	4.70 (3.80–5.70)	10.1 (8.50–11.4)	19.6 (16.6–23.0)	28.5 (24.2–39.9)	677
	2003–2004	2.35 (1.87–2.96)	2.20 (1.50–3.00)	5.10 (4.30–6.60)	11.2 (7.50–16.5)	18.5 (11.6–38.2)	652
	2005–2006	2.99 (2.50–3.57)	2.30 (1.70–3.30)	5.70 (4.70–7.60)	18.4 (12.1–30.6)	36.4 (26.2–63.8)	637
	2007–2008	2.89 (2.38–3.50)	2.60 (2.00–3.10)	5.30 (4.40–8.20)	16.9 (10.3–27.3)	30.2 (22.9–34.3)	531
	2009–2010	2.08 (1.84–2.36)	2.10 (1.86–2.40)	4.44 (3.73–5.63)	9.67 (6.89–16.0)	17.9 (13.1–24.3)	566
	2011–2012	1.49 (1.16–1.91)	1.50 (1.00–1.90)	3.40 (2.50–4.30)	6.60 (5.10–8.90)	9.60 (6.60–12.9)	316
	2013–2014	1.55 (1.35–1.78)	1.50 (1.20–1.70)	2.90 (2.20–3.80)	5.60 (4.20–7.00)	7.40 (6.30–9.30)	438
Non-Hispanic blacks	1999–2000	4.82 (3.92–5.93)	5.20 (4.10–5.80)	9.50 (7.60–11.4)	19.5 (12.9–26.5)	29.5 (18.6–60.3)	603
	2001–2002	6.60 (5.57–7.82)	6.70 (5.40–8.10)	15.4 (13.0–18.7)	32.9 (26.5–41.4)	52.6 (41.0–84.0)	703
	2003–2004	3.61 (3.07–4.23)	3.50 (3.00–4.00)	8.50 (7.10–11.4)	22.9 (16.5–28.6)	35.2 (29.3–49.1)	699
	2005–2006	4.09 (3.51–4.75)	3.70 (3.10–4.10)	9.10 (6.90–11.9)	22.5 (17.4–40.7)	59.3 (34.5–86.7)	678
	2007–2008	3.30 (2.98–3.64)	3.20 (2.70–3.60)	7.20 (6.30–8.90)	15.3 (13.3–20.2)	25.5 (19.2–38.1)	597
	2009–2010	2.08 (1.79–2.41)	2.05 (1.70–2.42)	4.79 (3.80–5.95)	10.1 (7.50–14.4)	16.4 (9.60–38.4)	516
	2011–2012	1.89 (1.67–2.13)	2.00 (1.60–2.40)	4.00 (3.40–4.90)	8.00 (6.20–9.70)	11.3 (9.60–14.9)	665
	2013–2014	1.63 (1.39–1.92)	1.50 (1.10–2.00)	3.30 (2.50–4.00)	5.80 (5.10–6.70)	8.10 (6.50–10.5)	609

Table 5-8. Uncorrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L) 50th	75th	90th	95th	Sample size
Non-Hispanic whites	1999–2000	3.16 (2.89–3.46)	2.80 (2.50–3.10)	7.40 (6.30–8.40)	14.5 (12.2–17.4)	22.4 (16.9–28.5)	912
	2001–2002	3.85 (3.37–4.40)	3.70 (3.10–4.40)	8.70 (7.80–9.90)	20.9 (17.3–25.9)	37.9 (29.9–49.5)	1,216
	2003–2004	2.14 (1.92–2.39)	1.70 (1.40–1.90)	4.80 (4.00–5.80)	13.6 (9.50–20.0)	31.0 (18.1–48.9)	1,088
	2005–2006	2.83 (2.59–3.10)	2.20 (1.80–2.60)	5.90 (5.30–6.90)	17.0 (13.3–21.6)	36.3 (26.6–51.0)	1,038
	2007–2008	2.44 (2.07–2.88)	2.00 (1.70–2.30)	4.90 (3.70–6.20)	13.1 (8.70–20.1)	25.0 (15.8–42.1)	1,077
	2009–2010	1.41 (1.22–1.62)	1.30 (1.12–1.57)	3.04 (2.53–3.60)	6.12 (5.23–7.65)	11.8 (7.63–21.1)	1,206
	2011–2012	1.21 (1.07–1.37)	1.10 (.900–1.50)	2.70 (2.20–3.10)	4.90 (4.20–6.10)	6.70 (6.00–8.30)	813
	2013–2014	Not calculated[b]	0.900 (0.800–1.00)	2.00 (1.80–2.30)	3.90 (3.20–4.30)	5.50 (4.80–6.30)	987
All Hispanics	2011–2012	1.61 (1.40–1.83)	1.70 (1.30–2.00)	3.90 (3.10–4.70)	7.30 (6.30–8.70)	11.6 (9.20–12.9)	571
	2013–2014	1.55 (1.40–1.73)	1.50 (1.20–1.70)	2.90 (2.50–3.40)	5.20 (4.40–6.30)	7.20 (6.20–9.20)	690
Asians	2011–2012	1.69 (1.44–1.98)	1.70 (1.30–1.90)	3.60 (2.80–4.40)	7.80 (6.60–11.4)	13.8 (10.0–17.8)	352
	2013–2014	Not calculated[b]	1.00 (<LOD–1.20)	2.10 (1.80–2.80)	4.30 (3.50–6.10)	7.90 (4.90–10.5)	289

[a]The limit of detection for survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 1.2, 1.0, 0.9, 1.2, 1.1, 0.5, 0.5, and 0.8 μg/L, respectively.
[b]Not calculated: the proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval; MEHP = mono-(2-ethylhexyl)phthalate; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-9. Creatinine-Corrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2012

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	3.12 (2.95–3.31)	3.08 (2.82–3.27)	5.88 (5.38–6.25)	10.8 (9.62–12.5)	18.9 (15.0–21.8)	2,541
	2001–2002	4.00 (3.58–4.48)	3.90 (3.44–4.47)	7.94 (7.22–9.02)	18.0 (15.3–21.5)	32.8 (25.2–42.9)	2,782
	2003–2004	2.20 (2.01–2.41)	1.89 (1.68–2.19)	4.31 (3.84–4.74)	10.8 (8.72–13.8)	25.4 (16.7–34.7)	2,605
	2005–2006	2.96 (2.72–3.23)	2.61 (2.37–2.86)	5.69 (5.00–6.47)	13.7 (11.4–17.8)	30.1 (21.2–35.2)	2,548
	2007–2008	2.66 (2.37–2.99)	2.36 (2.11–2.67)	5.15 (4.35–6.00)	11.8 (8.89–15.6)	21.9 (14.6–33.4)	2,604
	2009–2010	1.66 (1.45–1.90)	1.52 (1.36–1.77)	3.09 (2.69–3.60)	6.28 (4.98–8.48)	11.2 (8.33–19.1)	2,749
	2011–2012	1.55 (1.43–1.68)	1.46 (1.33–1.67)	2.73 (2.50–2.92)	4.91 (4.55–5.52)	8.47 (6.72–9.86)	2,487
	2013–2014	Not calculated[b]	1.21 (1.11–1.33)	2.19 (2.05–2.38)	3.82 (3.46–4.15)	5.18 (4.66–5.74)	2,684
Age group							
6–11 years	1999–2000	5.19 (4.55–5.93)	5.37 (4.52–5.95)	9.11 (8.06–11.4)	21.6 (11.5–41.9)	41.9 (13.5–86.2)	328
	2001–2002	5.03 (4.47–5.65)	5.38 (4.51–6.21)	9.90 (7.87–11.5)	21.1 (13.8–28.8)	31.4 (24.3–40.7)	393
	2003–2004	3.00 (2.30–3.93)	2.80 (1.93–4.09)	5.86 (4.69–7.70)	14.3 (8.54–24.4)	28.7 (14.1–45.3)	342
	2005–2006	3.42 (3.08–3.79)	3.26 (2.63–3.92)	6.18 (5.40–6.85)	11.3 (8.96–17.4)	20.7 (11.3–31.8)	356
	2007–2008	2.95 (2.49–3.49)	2.80 (2.17–3.33)	5.42 (3.95–6.51)	10.6 (7.47–14.0)	15.6 (10.6–23.7)	389
	2009–2010	2.13 (1.90–2.40)	2.08 (1.88–2.33)	3.69 (3.13–4.20)	5.83 (4.80–7.95)	8.89 (5.88–20.1)	415
	2011–2012	2.02 (1.81–2.25)	2.07 (1.75–2.44)	3.45 (2.82–4.06)	5.26 (4.60–5.89)	7.15 (5.89–8.17)	395
	2013–2014	1.81 (1.57–2.09)	1.76 (1.53–2.01)	3.13 (2.59–3.86)	6.33 (4.02–8.32)	8.32 (5.53–14.1)	409
12–19 years	1999–2000	2.53 (2.14–2.99)	2.35 (2.05–2.76)	5.83 (4.38–6.29)	9.66 (7.41–11.5)	12.1 (10.5–17.3)	752
	2001–2002	3.53 (3.09–4.03)	3.67 (2.89–4.48)	7.47 (6.51–8.67)	15.2 (11.7–21.9)	25.2 (17.7–32.8)	742
	2003–2004	2.07 (1.74–2.48)	1.88 (1.60–2.23)	4.25 (3.19–5.62)	11.6 (6.83–23.2)	24.8 (11.6–37.9)	729
	2005–2006	2.77 (2.27–3.38)	2.43 (2.03–2.87)	5.24 (4.06–7.75)	15.2 (9.86–23.2)	27.1 (16.0–43.7)	702
	2007–2008	2.33 (1.90–2.86)	2.00 (1.67–2.57)	4.33 (3.55–6.23)	12.6 (8.31–16.3)	21.9 (12.0–45.7)	401
	2009–2010	1.46 (1.20–1.77)	1.33 (1.09–1.61)	2.85 (2.24–3.63)	7.47 (4.31–11.6)	13.2 (8.11–20.9)	420
	2011–2012	1.53 (1.33–1.78)	1.40 (1.12–1.88)	2.79 (2.20–3.88)	5.00 (4.11–6.94)	9.86 (5.00–11.1)	388
	2013–2014	1.16 (1.03–1.31)	1.15 (1.00–1.27)	1.88 (1.67–2.10)	3.35 (2.38–4.07)	4.79 (3.61–6.76)	462
≥20 years	1999–2000	3.03 (2.83–3.25)	2.98 (2.73–3.23)	5.55 (4.90–6.06)	10.0 (8.60–12.9)	17.5 (13.8–22.1)	1,461
	2001–2002	3.97 (3.49–4.52)	3.82 (3.26–4.38)	7.79 (7.00–9.00)	18.3 (15.3–21.8)	34.5 (23.1–47.9)	1,647
	2003–2004	2.14 (1.98–2.31)	1.84 (1.63–2.08)	4.14 (3.78–4.40)	10.5 (8.38–12.9)	25.6 (15.9–36.3)	1,534
	2005–2006	2.94 (2.69–3.23)	2.60 (2.36–2.83)	5.67 (4.77–6.52)	13.8 (11.3–18.1)	33.1 (21.9–47.4)	1,490
	2007–2008	2.69 (2.39–3.02)	2.36 (2.14–2.66)	5.20 (4.38–6.04)	11.8 (8.94–16.6)	22.1 (13.5–37.1)	1,814
	2009–2010	1.65 (1.43–1.90)	1.51 (1.34–1.75)	3.04 (2.63–3.60)	6.24 (4.98–8.61)	11.1 (8.03–19.4)	1,914
	2011–2012	1.51 (1.39–1.64)	1.46 (1.28–1.58)	2.59 (2.38–2.84)	4.81 (4.35–5.51)	8.49 (6.18–11.2)	1,704
	2013–2014	Not calculated[b]	1.19 (1.08–1.31)	2.19 (1.98–2.41)	3.70 (3.25–4.09)	5.00 (4.34–5.40)	1,813

Table 5-9. Creatinine-Corrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2012

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	2.89 (2.60–3.22)	2.76 (2.52–2.96)	5.58 (4.71–6.08)	10.3 (9.35–12.4)	21.6 (14.1–27.7)	1,215
	2001–2002	3.50 (3.08–3.99)	3.33 (2.83–3.90)	7.00 (6.49–7.77)	16.2 (12.8–20.9)	31.6 (20.5–49.4)	1,371
	2003–2004	2.01 (1.82–2.21)	1.71 (1.46–1.89)	4.14 (3.49–4.81)	10.4 (7.68–16.2)	23.3 (15.1–41.1)	1,250
	2005–2006	2.73 (2.43–3.07)	2.30 (2.12–2.61)	5.08 (4.29–6.14)	14.3 (11.2–20.5)	31.0 (21.5–50.9)	1,270
	2007–2008	2.33 (2.03–2.68)	2.00 (1.71–2.34)	4.36 (3.71–5.41)	11.6 (8.33–14.2)	20.2 (14.6–26.3)	1,294
	2009–2010	1.64 (1.45–1.85)	1.52 (1.39–1.74)	3.06 (2.70–3.60)	6.53 (5.18–9.49)	13.0 (8.65–22.2)	1,399
	2011–2012	1.41 (1.28–1.56)	1.36 (1.19–1.58)	2.52 (2.21–2.83)	4.58 (3.77–5.46)	7.19 (6.16–8.79)	1,258
	2013–2014	1.08 (0.984–1.19)	1.03 (0.950–1.12)	1.78 (1.58–2.00)	3.17 (2.73–3.60)	4.30 (3.94–5.06)	1,284
Females	1999–2000	3.36 (3.11–3.63)	3.33 (2.91–3.80)	6.15 (5.55–6.77)	11.1 (9.11–14.0)	17.3 (12.4–24.6)	1,326
	2001–2002	4.54 (4.02–5.13)	4.47 (3.85–5.14)	9.28 (7.94–10.3)	20.3 (16.6–24.4)	34.7 (27.1–42.0)	1,411
	2003–2004	2.40 (2.15–2.69)	2.16 (1.84–2.40)	4.40 (3.97–4.89)	10.9 (8.27–16.0)	27.0 (17.5–34.6)	1,355
	2005–2006	3.20 (2.89–3.55)	2.89 (2.58–3.17)	6.07 (5.00–7.00)	13.3 (10.4–16.3)	28.2 (18.2–37.4)	1,278
	2007–2008	3.02 (2.70–3.38)	2.76 (2.36–3.02)	5.57 (4.90–6.50)	12.1 (8.64–18.2)	24.7 (14.8–44.4)	1,310
	2009–2010	1.68 (1.44–1.96)	1.53 (1.35–1.89)	3.10 (2.68–3.69)	5.75 (4.58–8.03)	10.5 (7.36–17.5)	1,350
	2011–2012	1.70 (1.56–1.85)	1.58 (1.43–1.75)	2.86 (2.63–3.18)	5.36 (4.64–5.89)	8.89 (6.67–13.2)	1,229
	2013–2014	Not calculated[b]	1.48 (1.33–1.64)	2.59 (2.36–2.96)	4.29 (3.70–5.00)	5.74 (5.12–7.70)	1,400
Race/ethnicity							
Mexican Americans	1999–2000	3.16 (2.72–3.68)	3.15 (2.52–3.81)	5.88 (4.86–7.24)	11.6 (9.63–13.1)	15.7 (12.6–23.1)	814
	2001–2002	4.07 (3.60–4.61)	4.18 (3.82–4.90)	7.80 (6.64–9.49)	16.4 (13.6–18.9)	24.9 (19.8–28.7)	677
	2003–2004	2.12 (1.74–2.59)	1.94 (1.50–2.42)	4.06 (3.29–4.93)	9.38 (5.72–15.4)	16.8 (9.86–38.6)	652
	2005–2006	2.69 (2.36–3.07)	2.41 (2.04–2.73)	4.82 (4.09–6.05)	14.3 (10.0–16.9)	27.2 (16.3–40.1)	637
	2007–2008	2.82 (2.38–3.34)	2.45 (2.08–2.89)	5.00 (4.14–6.86)	12.3 (9.58–20.7)	29.0 (17.0–50.3)	531
	2009–2010	2.07 (1.83–2.34)	1.89 (1.69–2.31)	4.06 (3.50–4.98)	8.38 (6.08–11.3)	13.9 (9.70–20.0)	566
	2011–2012	1.68 (1.36–2.06)	1.67 (1.21–2.06)	2.91 (2.46–3.50)	6.23 (4.32–9.05)	11.3 (5.67–18.3)	316
	2013–2014	1.58 (1.35–1.85)	1.48 (1.24–1.83)	2.85 (2.46–3.39)	4.62 (4.07–5.56)	7.13 (5.53–8.04)	438
Non-Hispanic blacks	1999–2000	3.11 (2.59–3.73)	3.13 (2.50–3.61)	5.84 (4.43–7.32)	10.2 (8.05–15.6)	18.4 (11.6–35.2)	603
	2001–2002	4.63 (3.96–5.42)	4.59 (3.97–5.02)	9.93 (7.95–12.4)	21.2 (16.0–33.2)	39.9 (27.7–48.1)	703
	2003–2004	2.56 (2.24–2.92)	2.28 (2.02–2.78)	5.17 (4.48–6.83)	13.2 (10.5–16.2)	27.5 (18.4–36.0)	699
	2005–2006	2.87 (2.45–3.38)	2.41 (2.09–2.78)	5.72 (4.40–7.29)	15.0 (12.0–20.6)	54.4 (18.4–84.0)	678
	2007–2008	2.56 (2.26–2.90)	2.40 (2.17–2.73)	4.77 (4.07–5.76)	11.4 (8.75–15.4)	18.0 (16.1–26.3)	597
	2009–2010	1.51 (1.22–1.86)	1.48 (1.14–1.93)	2.87 (2.26–3.69)	5.73 (3.69–10.7)	10.7 (5.61–19.1)	516
	2011–2012	1.47 (1.29–1.67)	1.44 (1.26–1.75)	2.75 (2.37–3.14)	5.16 (4.17–7.05)	8.69 (6.07–12.1)	665
	2013–2014	1.20 (1.07–1.36)	1.13 (0.957–1.39)	2.11 (1.85–2.44)	3.46 (2.96–4.07)	5.05 (3.74–6.31)	609

Table 5-9. Creatinine-Corrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2012

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	1999–2000	3.09 (2.84–3.36)	3.08 (2.73–3.47)	5.87 (5.11–6.67)	10.6 (8.95–13.5)	20.0 (14.0–24.6)	912
	2001–2002	3.81 (3.34–4.35)	3.67 (3.11–4.33)	7.78 (6.74–9.35)	17.0 (14.1–21.8)	32.8 (21.5–46.9)	1,216
	2003–2004	2.12 (1.91–2.35)	1.82 (1.60–2.13)	4.11 (3.49–4.42)	10.7 (7.42–15.1)	27.0 (15.1–37.4)	1,088
	2005–2006	2.98 (2.77–3.21)	2.66 (2.43–2.93)	5.73 (5.00–6.47)	13.4 (11.3–17.8)	27.7 (19.5–37.4)	1,038
	2007–2008	2.55 (2.20–2.94)	2.26 (1.97–2.67)	4.90 (3.99–5.92)	11.0 (7.80–14.8)	20.5 (11.9–30.2)	1,077
	2009–2010	1.58 (1.36–1.84)	1.49 (1.27–1.76)	2.94 (2.50–3.49)	5.64 (4.53–7.96)	10.3 (6.85–18.3)	1,206
	2011–2012	1.47 (1.29–1.68)	1.45 (1.25–1.65)	2.51 (2.17–2.84)	4.43 (3.77–5.00)	6.77 (5.00–9.54)	811
	2013–2014	Not calculated[b]	1.16 (1.02–1.31)	2.11 (1.84–2.33)	3.56 (3.00–4.10)	4.68 (4.19–5.62)	987
All Hispanics	2011–2012	1.80 (1.63–1.98)	1.79 (1.59–2.00)	3.32 (2.86–3.76)	6.37 (5.67–8.07)	11.3 (7.79–14.4)	571
	2013–2014	1.54 (1.38–1.73)	1.43 (1.22–1.67)	2.80 (2.48–3.10)	4.39 (3.98–5.09)	6.61 (5.53–7.64)	690
Asians	2011–2012	2.26 (1.98–2.58)	1.98 (1.71–2.33)	4.18 (3.26–5.00)	8.89 (6.40–12.6)	14.0 (10.0–20.1)	352
	2013–2014	Not calculated[b]	1.43 (<LOD–1.70)	2.76 (2.31–3.13)	5.00 (3.96–5.87)	6.85 (5.17–9.73)	288

[a]The limit of detection (not corrected for creatinine) for survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 1.2, 1.0, 0.9, 1.2, 1.1, 0.5, 0.5, and 0.8 µg/L, respectively.
[b]Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval; MEHP = mono-(2-ethylhexyl)phthalate; LOD = limit of detection; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-10. Uncorrected Urinary MEHHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Total	2001–2002	20.0 (17.8–22.5)	20.1 (17.8–22.4)	43.6 (38.0–49.7)	92.3 (77.0–108)	192 (131–256)	2,782
	2003–2004	21.7 (19.3–24.4)	21.2 (18.7–24.1)	49.1 (40.5–56.9)	121 (91.3–164)	266 (165–383)	2,605
	2005–2006	25.5 (23.0–28.2)	23.8 (21.5–26.8)	55.1 (50.2–61.0)	153 (132–180)	306 (240–421)	2,548
	2007–2008	22.1 (18.7–26.0)	20.7 (17.6–23.7)	48.2 (39.8–61.8)	123 (83.7–181)	238 (171–336)	2,604
	2009–2010	12.9 (11.3–14.7)	12.9 (11.4–14.8)	25.8 (22.1–30.3)	53.2 (41.7–75.2)	103 (74.2–149)	2,749
	2011–2012	7.91 (7.47–8.36)	8.30 (7.50–9.00)	16.0 (14.4–17.4)	29.0 (25.8–32.5)	43.1 (40.6–47.2)	2,489
	2013–2014	6.47 (5.98–7.00)	6.90 (6.30–7.70)	13.2 (11.9–14.7)	23.7 (20.7–26.6)	33.7 (28.2–37.6)	2,685
Age group							
6–11 years	2001–2002	33.6 (29.7–37.9)	32.9 (26.9–39.1)	66.9 (49.7–74.0)	127 (103–148)	216 (137–280)	393
	2003–2004	36.9 (28.4–47.9)	36.5 (26.5–47.0)	77.4 (49.1–103)	164 (79.9–350)	318 (164–400)	342
	2005–2006	34.9 (30.8–39.6)	35.7 (31.3–40.7)	68.9 (56.5–76.0)	140 (101–169)	206 (133–401)	356
	2007–2008	28.6 (23.4–34.8)	27.0 (20.1–36.4)	56.1 (45.4–67.8)	113 (76.5–218)	242 (109–351)	389
	2009–2010	15.0 (13.2–17.1)	17.0 (14.1–19.8)	28.9 (24.4–37.4)	49.3 (41.2–70.2)	75.1 (55.2–117)	415
	2011–2012	10.5 (8.82–12.4)	11.8 (10.4–14.2)	23.3 (19.9–26.1)	39.5 (30.6–50.3)	55.4 (41.8–68.5)	396
	2013–2014	9.54 (7.94–11.5)	9.40 (7.50–12.8)	18.7 (16.2–23.0)	36.4 (26.5–44.8)	50.8 (37.3–76.5)	409
12–19 years	2001–2002	24.9 (21.3–29.1)	25.3 (22.9–31.3)	50.6 (40.7–64.5)	107 (78.5–148)	216 (117–330)	742
	2003–2004	28.3 (23.0–34.8)	29.8 (25.9–33.9)	56.9 (45.4–73.7)	157 (84.1–299)	317 (176–553)	729
	2005–2006	34.8 (28.0–43.3)	32.5 (27.1–42.2)	79.5 (66.9–103)	213 (131–384)	424 (232–836)	702
	2007–2008	29.8 (22.5–39.3)	26.6 (20.0–35.4)	66.7 (43.7–96.6)	224 (101–417)	417 (209–615)	401
	2009–2010	15.3 (12.4–18.8)	14.9 (12.0–18.0)	28.8 (22.7–41.0)	70.2 (41.0–110)	117 (61.0–215)	420
	2011–2012	8.55 (6.93–10.6)	8.80 (6.80–10.6)	18.3 (14.3–23.2)	36.0 (27.4–46.6)	56.7 (38.1–99.8)	388
	2013–2014	7.62 (6.43–9.04)	7.70 (6.20–10.3)	15.8 (12.3–19.3)	26.8 (21.9–32.5)	35.3 (27.6–59.5)	462
≥20 years	2001–2002	18.1 (15.7–20.9)	17.8 (14.7–20.7)	39.8 (32.7–48.0)	86.2 (65.7–107)	175 (110–279)	1,647
	2003–2004	19.5 (17.7–21.5)	18.4 (16.6–21.0)	41.9 (36.9–51.2)	107 (88.2–136)	225 (148–384)	1,534
	2005–2006	23.4 (21.1–25.9)	21.4 (19.5–23.7)	48.6 (43.7–55.1)	148 (121–172)	306 (238–421)	1,490
	2007–2008	20.5 (17.4–24.1)	19.6 (17.1–22.2)	46.3 (37.2–59.9)	110 (75.0–169)	214 (157–303)	1,814
	2009–2010	12.4 (10.7–14.3)	12.5 (10.8–14.3)	24.5 (21.1–29.3)	52.5 (40.1–72.6)	104 (72.6–151)	1,914
	2011–2012	7.58 (7.03–8.16)	8.00 (7.20–8.90)	15.0 (13.5–16.9)	26.7 (23.8–30.6)	41.5 (34.7–46.2)	1,705
	2013–2014	6.06 (5.63–6.51)	6.70 (5.70–7.30)	12.3 (11.3–13.4)	22.3 (19.6–24.0)	30.3 (26.5–35.9)	1,814

Table 5-10. Uncorrected Urinary MEHHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2001–2002	22.0 (19.5–24.7)	21.2 (19.4–24.2)	48.0 (41.4–54.4)	94.2 (80.8–110)	212 (130–256)	1,371
	2003–2004	24.1 (20.9–27.9)	22.9 (19.2–27.9)	51.0 (40.5–59.8)	133 (94.8–220)	317 (162–470)	1,250
	2005–2006	29.6 (26.0–33.8)	27.2 (22.9–31.0)	63.1 (54.3–71.9)	180 (143–263)	494 (285–626)	1,270
	2007–2008	23.2 (19.4–27.8)	20.8 (18.1–24.5)	46.0 (39.2–57.3)	132 (85.4–190)	277 (162–349)	1,294
	2009–2010	15.2 (13.1–17.6)	14.6 (12.9–16.4)	29.5 (24.6–36.2)	71.0 (50.3–93.5)	128 (90.6–181)	1,399
	2011–2012	8.71 (7.98–9.51)	9.40 (7.80–10.6)	16.4 (14.2–19.5)	31.1 (26.7–35.8)	46.2 (41.5–55.4)	1,259
	2013–2014	6.98 (6.32–7.71)	7.40 (6.70–8.40)	13.1 (11.7–14.8)	22.7 (20.1–24.9)	32.9 (27.3–36.0)	1,285
Females	2001–2002	18.3 (15.7–21.4)	18.2 (14.9–22.1)	39.8 (34.3–46.0)	86.0 (69.4–115)	170 (119–273)	1,411
	2003–2004	19.7 (17.4–22.2)	19.4 (16.7–22.8)	46.4 (37.5–54.4)	103 (84.1–148)	214 (140–318)	1,355
	2005–2006	22.0 (19.2–25.2)	21.4 (19.5–23.4)	47.1 (42.6–54.3)	135 (113–156)	232 (186–300)	1,278
	2007–2008	21.0 (17.8–24.8)	19.9 (16.8–23.3)	51.0 (39.9–64.6)	121 (76.9–183)	223 (171–336)	1,310
	2009–2010	11.0 (9.58–12.8)	11.6 (9.73–13.5)	22.5 (19.2–27.2)	42.8 (33.2–59.1)	82.2 (53.1–116)	1,350
	2011–2012	7.20 (6.77–7.66)	7.60 (6.90–8.20)	15.5 (14.4–17.1)	27.6 (25.0–30.5)	40.7 (35.1–46.4)	1,230
	2013–2014	6.02 (5.40–6.72)	6.30 (5.30–7.20)	13.4 (11.5–15.3)	24.8 (20.7–27.8)	35.3 (27.4–40.8)	1,400
Race/ethnicity							
Mexican Americans	2001–2002	18.5 (16.2–21.1)	19.1 (16.3–21.6)	36.3 (31.6–44.0)	79.9 (66.4–93.9)	123 (100–161)	677
	2003–2004	18.9 (15.4–23.4)	19.8 (17.6–22.3)	37.5 (30.0–45.6)	72.2 (52.4–115)	116 (71.6–327)	652
	2005–2006	23.0 (18.0–29.3)	19.9 (15.7–23.9)	47.8 (34.8–65.3)	136 (84.6–223)	244 (157–520)	637
	2007–2008	22.7 (18.5–27.7)	19.8 (17.5–23.8)	43.6 (33.5–66.6)	104 (82.8–157)	238 (158–282)	531
	2009–2010	15.3 (12.9–18.2)	15.8 (13.3–18.3)	31.5 (26.6–39.2)	64.5 (46.4–94.9)	108 (70.7–153)	566
	2011–2012	9.13 (7.22–11.5)	9.60 (7.30–11.7)	17.7 (12.7–24.7)	32.1 (24.8–37.7)	50.2 (36.4–56.3)	316
	2013–2014	7.71 (6.53–9.10)	8.00 (7.40–8.80)	14.4 (12.5–16.2)	28.1 (18.9–42.0)	43.7 (31.8–50.3)	438
Non-Hispanic blacks	2001–2002	29.8 (26.1–34.1)	30.9 (27.2–34.3)	61.9 (52.6–69.4)	126 (108–157)	276 (157–339)	703
	2003–2004	30.8 (26.8–35.5)	29.1 (25.3–32.3)	65.6 (53.7–76.3)	154 (113–178)	275 (174–401)	699
	2005–2006	34.8 (30.3–39.9)	30.2 (27.6–33.2)	73.8 (61.0–96.7)	206 (156–275)	395 (274–547)	678
	2007–2008	25.7 (23.1–28.6)	25.8 (22.4–28.9)	55.9 (47.1–64.7)	121 (99.1–150)	184 (137–255)	597
	2009–2010	15.5 (12.8–18.8)	15.7 (13.4–17.7)	30.4 (24.4–35.7)	54.5 (37.7–84.1)	94.6 (51.5–229)	516
	2011–2012	11.3 (10.1–12.7)	11.2 (10.2–12.7)	22.1 (17.4–26.8)	38.8 (34.9–47.9)	56.2 (46.8–65.1)	665
	2013–2014	8.06 (6.79–9.56)	8.80 (7.30–10.4)	16.5 (14.0–18.6)	27.4 (22.8–32.7)	38.7 (32.7–48.1)	609

Table 5-10. Uncorrected Urinary MEHHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2001–2002	19.1 (16.7–21.9)	19.2 (16.9–21.4)	41.7 (35.3–50.7)	91.1 (75.6–110)	212 (130–275)	1,216
	2003–2004	20.8 (18.6–23.3)	19.7 (17.2–22.5)	47.5 (39.4–56.1)	120 (91.3–165)	270 (155–403)	1,088
	2005–2006	24.3 (21.9–26.9)	23.0 (21.1–26.0)	54.6 (48.4–61.0)	148 (121–172)	302 (221–421)	1,038
	2007–2008	21.3 (17.6–25.8)	20.2 (16.5–24.1)	46.7 (36.1–65.2)	123 (75.1–203)	277 (161–373)	1,077
	2009–2010	12.2 (10.5–14.1)	12.3 (10.5–14.2)	24.4 (20.7–29.1)	51.7 (37.7–77.1)	104 (72.6–151)	1,206
	2011–2012	7.20 (6.73–7.70)	7.40 (6.80–8.30)	14.6 (12.9–17.2)	25.0 (23.4–27.9)	36.6 (30.6–42.9)	813
	2013–2014	6.05 (5.54–6.61)	6.70 (5.60–7.20)	12.6 (10.8–14.2)	22.4 (19.1–24.6)	30.1 (26.3–35.3)	987
All Hispanics	2011–2012	9.28 (8.07–10.7)	9.40 (7.70–10.8)	18.8 (15.3–22.9)	37.5 (32.1–43.9)	53.8 (46.3–70.6)	571
	2013–2014	7.56 (6.92–8.26)	8.00 (7.40–8.60)	14.4 (13.1–15.5)	27.2 (21.3–37.3)	39.3 (35.1–46.4)	690
Asians	2011–2012	6.85 (5.53–8.48)	6.70 (5.40–7.90)	15.1 (11.5–18.6)	31.8 (22.5–41.9)	64.2 (35.7–82.8)	352
	2013–2014	4.78 (4.07–5.61)	4.50 (3.70–5.60)	10.2 (8.30–12.4)	17.1 (14.6–21.8)	26.7 (17.9–47.0)	289

[a]The limit of detection for survey years 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 1.0, 0.3, 0.7, 0.7, 0.2, 0.2, and 0.4 μg/L, respectively.

CI = confidence interval; MEHHP = mono-2-ethyl-5-hydroxyhexyl phthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-11. Creatinine-Corrected Urinary MEHHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/g of creatinine)	Selected percentiles (95% CI) (μg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Total	2001–2002	18.8 (17.0–20.7)	16.6 (14.9–18.5)	32.2 (27.8–37.1)	71.1 (58.7–88.3)	143 (101–200)	2,782
	2003–2004	20.4 (18.7–22.3)	17.7 (16.3–19.6)	35.8 (30.5–43.3)	93.5 (74.0–128)	182 (134–262)	2,605
	2005–2006	24.8 (22.4–27.5)	21.4 (19.1–23.4)	46.1 (40.0–52.1)	117 (97.8–148)	235 (197–272)	2,548
	2007–2008	22.2 (19.4–25.5)	19.3 (17.4–22.1)	40.5 (34.1–50.3)	99.3 (69.7–134)	179 (135–252)	2,604
	2009–2010	13.5 (11.6–15.6)	11.9 (10.5–13.9)	22.3 (18.6–26.4)	44.0 (35.3–61.0)	86.3 (59.2–131)	2,749
	2011–2012	8.99 (8.55–9.46)	8.46 (7.90–9.27)	14.1 (13.5–14.9)	25.3 (23.1–27.8)	37.7 (32.9–45.3)	2,487
	2013–2014	6.49 (5.97–7.05)	6.15 (5.67–6.86)	10.5 (9.47–11.7)	18.1 (15.4–20.4)	25.8 (22.9–29.3)	2,684
Age group							
6–11 years	2001–2002	38.2 (34.3–42.6)	34.3 (29.9–38.9)	60.6 (51.9–76.4)	107 (96.3–147)	211 (122–313)	393
	2003–2004	39.0 (31.1–48.9)	36.6 (25.3–49.3)	65.6 (49.8–91.3)	129 (77.1–253)	211 (123–708)	342
	2005–2006	38.5 (34.2–43.3)	37.0 (32.9–40.3)	65.5 (55.4–71.9)	115 (85.1–165)	213 (119–333)	356
	2007–2008	35.2 (29.1–42.5)	31.4 (25.6–37.8)	53.5 (44.8–72.3)	139 (79.9–230)	258 (141–303)	389
	2009–2010	19.6 (17.3–22.2)	18.6 (16.5–21.5)	34.2 (27.3–40.4)	55.4 (44.0–64.8)	72.1 (56.3–140)	415
	2011–2012	14.9 (12.9–17.2)	14.8 (13.0–18.2)	26.5 (22.9–28.2)	42.6 (30.9–46.5)	58.1 (43.2–75.1)	395
	2013–2014	12.0 (10.4–14.0)	11.6 (9.32–14.4)	19.3 (17.2–24.2)	36.9 (24.6–61.7)	61.7 (34.3–130)	409
12–19 years	2001–2002	19.2 (17.0–21.8)	17.8 (15.6–20.0)	34.9 (29.2–42.7)	73.4 (58.4–80.7)	102 (86.6–160)	742
	2003–2004	21.2 (18.1–24.7)	18.6 (16.9–21.7)	38.7 (29.7–53.4)	103 (62.7–209)	212 (100–358)	729
	2005–2006	26.0 (21.2–31.7)	23.7 (18.8–28.4)	49.4 (37.4–74.0)	131 (79.0–228)	278 (132–375)	702
	2007–2008	23.2 (18.1–29.6)	20.0 (14.6–23.9)	46.1 (31.5–66.3)	148 (66.6–234)	234 (146–373)	401
	2009–2010	12.3 (9.73–15.5)	10.5 (8.95–13.3)	20.9 (14.2–31.0)	45.3 (28.9–91.9)	110 (44.6–200)	420
	2011–2012	8.33 (7.38–9.41)	7.60 (6.41–8.29)	12.6 (10.4–15.5)	28.7 (20.1–37.2)	53.9 (31.7–68.8)	388
	2013–2014	6.19 (5.36–7.14)	5.94 (5.00–7.14)	9.82 (8.59–11.5)	16.9 (13.0–21.1)	24.8 (19.9–31.1)	462
≥20 years	2001–2002	17.1 (15.2–19.3)	15.0 (13.3–16.7)	27.7 (23.2–34.0)	63.7 (48.3–86.9)	137 (84.4–203)	1,647
	2003–2004	18.8 (17.5–20.2)	16.3 (15.4–17.5)	31.6 (28.1–35.3)	83.8 (67.2–106)	171 (129–246)	1,534
	2005–2006	23.4 (21.1–26.0)	19.4 (17.6–21.8)	42.5 (37.6–49.2)	115 (93.1–153)	235 (184–298)	1,490
	2007–2008	21.0 (18.5–24.0)	18.5 (16.3–20.2)	38.1 (30.9–49.2)	94.3 (62.6–126)	164 (120–235)	1,814
	2009–2010	13.1 (11.3–15.2)	11.5 (10.1–13.4)	20.9 (17.7–25.1)	40.6 (32.4–64.9)	86.3 (59.2–131)	1,914
	2011–2012	8.61 (8.17–9.07)	8.20 (7.63–8.94)	13.5 (12.6–14.1)	22.5 (20.1–25.3)	32.0 (28.1–39.3)	1,704
	2013–2014	6.10 (5.62–6.63)	5.93 (5.40–6.41)	9.81 (8.89–10.8)	15.4 (14.1–18.3)	22.2 (19.2–26.0)	1,813

Table 5-11. Creatinine-Corrected Urinary MEHHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/g of creatinine)	Selected percentiles (95% CI) (μg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2001–2002	17.9 (16.2–19.7)	15.4 (13.8–17.9)	32.2 (27.8–36.8)	73.4 (55.3–91.8)	137 (97.7–224)	1,371
	2003–2004	18.9 (17.1–20.9)	17.1 (15.2–18.6)	32.7 (26.6–41.6)	93.4 (68.8–123)	193 (108–291)	1,250
	2005–2006	23.8 (21.0–26.9)	20.2 (17.5–23.3)	44.8 (38.5–54.1)	129 (92.5–166)	251 (202–352)	1,270
	2007–2008	19.6 (16.8–22.7)	16.8 (14.6–20.0)	34.8 (28.7–41.8)	90.3 (65.2–119)	164 (111–258)	1,294
	2009–2010	13.6 (11.7–15.9)	11.6 (10.5–13.1)	22.9 (17.8–27.4)	52.8 (39.1–74.3)	103 (73.3–173)	1,399
	2011–2012	8.15 (7.67–8.66)	7.80 (7.18–8.21)	12.2 (11.5–13.2)	24.2 (20.9–25.9)	37.2 (29.5–50.2)	1,258
	2013–2014	5.86 (5.38–6.39)	5.68 (5.26–6.12)	8.97 (8.48–9.79)	15.2 (13.9–16.7)	22.3 (19.8–26.3)	1,284
Females	2001–2002	19.7 (17.3–22.4)	17.6 (15.4–19.5)	32.1 (26.8–38.6)	70.5 (57.8–93.7)	156 (93.7–201)	1,411
	2003–2004	21.9 (19.7–24.5)	18.7 (16.8–20.9)	39.3 (33.8–46.9)	94.3 (72.8–136)	171 (146–261)	1,355
	2005–2006	25.9 (23.2–28.8)	22.5 (19.6–25.5)	47.3 (40.5–52.3)	108 (88.8–131)	202 (157–278)	1,278
	2007–2008	25.2 (22.1–28.6)	22.1 (19.6–24.4)	47.4 (38.5–56.1)	112 (84.6–150)	190 (162–268)	1,310
	2009–2010	13.3 (11.4–15.6)	12.4 (10.4–14.6)	21.9 (18.3–26.7)	38.8 (30.9–52.2)	74.0 (46.9–115)	1,350
	2011–2012	9.89 (9.16–10.7)	9.64 (8.33–11.1)	15.6 (14.7–17.3)	27.0 (23.9–28.8)	37.7 (33.2–44.4)	1,229
	2013–2014	7.15 (6.38–8.01)	6.94 (6.25–7.58)	12.0 (10.3–13.7)	20.4 (16.4–23.6)	28.3 (22.9–36.4)	1,400
Race/ethnicity							
Mexican Americans	2001–2002	17.4 (15.9–19.1)	15.7 (14.4–17.5)	30.6 (26.0–34.7)	65.9 (50.6–83.9)	103 (75.5–128)	677
	2003–2004	17.1 (14.3–20.4)	15.4 (13.2–17.7)	29.3 (23.8–36.8)	57.3 (45.7–97.6)	105 (70.1–195)	652
	2005–2006	20.7 (17.2–25.0)	17.5 (15.3–21.3)	37.3 (30.9–45.7)	99.9 (67.6–159)	181 (110–357)	637
	2007–2008	22.1 (17.7–27.7)	18.8 (15.2–23.4)	38.6 (28.3–54.9)	91.4 (61.0–170)	197 (141–282)	531
	2009–2010	15.2 (12.9–17.8)	14.6 (12.8–16.2)	27.0 (21.3–33.3)	60.0 (42.3–77.7)	94.8 (66.4–142)	566
	2011–2012	10.3 (8.35–12.7)	9.10 (7.02–12.5)	18.6 (14.4–21.1)	30.4 (25.1–36.0)	49.6 (30.4–114)	316
	2013–2014	7.86 (7.13–8.66)	7.54 (6.78–8.10)	12.6 (10.8–16.5)	23.5 (19.6–32.1)	37.2 (25.8–54.9)	438
Non-Hispanic blacks	2001–2002	20.9 (18.8–23.3)	19.7 (17.5–21.8)	38.3 (32.1–46.0)	93.5 (69.2–123)	164 (130–183)	703
	2003–2004	21.9 (20.1–23.8)	19.5 (17.3–22.6)	40.1 (35.8–45.3)	102 (75.5–122)	164 (133–269)	699
	2005–2006	24.5 (21.2–28.2)	18.9 (17.1–22.8)	46.1 (37.9–59.7)	128 (100–158)	308 (158–399)	678
	2007–2008	20.0 (18.1–22.0)	18.3 (16.5–19.2)	36.9 (27.9–46.7)	85.5 (65.8–103)	136 (107–227)	597
	2009–2010	11.2 (8.71–14.5)	10.5 (8.26–13.5)	18.9 (13.6–25.3)	32.9 (22.3–58.4)	47.2 (33.6–153)	516
	2011–2012	8.80 (7.84–9.87)	8.12 (7.37–8.96)	14.7 (12.4–17.8)	28.2 (20.7–37.4)	46.2 (29.7–57.5)	665
	2013–2014	5.94 (5.28–6.70)	5.68 (4.84–6.85)	9.94 (9.02–11.4)	17.1 (15.0–20.1)	23.9 (19.2–32.4)	609

Table 5-11. Creatinine-Corrected Urinary MEHHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2001–2002	18.9 (17.0–21.0)	16.3 (14.8–18.4)	32.1 (27.3–37.3)	70.8 (56.9–93.7)	177 (98.0–242)	1,216
	2003–2004	20.5 (18.5–22.8)	17.8 (16.2–19.7)	35.3 (29.7–44.9)	96.2 (75.8–136)	211 (136–283)	1,088
	2005–2006	25.6 (23.1–28.2)	22.4 (19.6–24.5)	47.6 (40.7–54.1)	119 (98.2–148)	231 (181–297)	1,038
	2007–2008	22.2 (18.7–26.3)	19.5 (16.7–23.0)	40.4 (32.1–54.8)	99.1 (68.1–145)	179 (129–258)	1,077
	2009–2010	13.7 (11.7–16.1)	11.9 (10.4–13.9)	22.4 (18.0–27.6)	43.0 (34.2–61.0)	84.1 (54.7–142)	1,206
	2011–2012	8.74 (8.02–9.53)	8.36 (7.62–9.58)	13.5 (12.5–14.5)	23.1 (19.7–25.9)	32.7 (27.8–42.9)	811
	2013–2014	6.37 (5.74–7.07)	6.06 (5.56–6.74)	10.0 (8.72–11.6)	16.2 (14.2–20.0)	23.1 (20.8–27.7)	987
All Hispanics	2011–2012	10.4 (9.42–11.5)	9.29 (8.14–10.5)	18.7 (16.7–21.1)	30.5 (27.1–35.6)	49.6 (33.4–67.9)	571
	2013–2014	7.50 (7.04–8.00)	7.19 (6.58–7.77)	12.3 (11.1–14.1)	22.3 (19.0–27.0)	34.9 (27.1–40.6)	690
Asians	2011–2012	9.18 (7.54–11.2)	8.45 (7.34–10.0)	16.2 (12.7–21.0)	33.0 (23.6–42.6)	57.4 (35.8–85.4)	352
	2013–2014	6.06 (5.35–6.86)	5.63 (4.83–6.50)	11.0 (9.79–13.2)	19.6 (16.0–24.5)	26.3 (19.6–41.9)	288

[a]The limit of detection (not corrected for creatinine) for survey years 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 1.0, 0.3, 0.7, 0.7, 0.2, 0.2, and 0.4 µg/L, respectively.

CI = confidence interval; MEHHP = mono-2-ethyl-5-hydroxyhexyl phthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-12. Uncorrected Urinary MEOHP Concentrations for the U.S. Population NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Total	2001–2002	13.5 (12.0–15.0)	14.0 (12.5–15.1)	29.6 (25.2–34.0)	59.9 (50.4–70.9)	120 (87.2–156)	2,782
	2003–2004	14.5 (13.0–16.1)	14.4 (12.4–16.7)	31.4 (27.4–36.6)	76.7 (59.4–102)	157 (106–232)	2,605
	2005–2006	16.2 (14.6–18.0)	15.1 (13.5–17.1)	35.5 (32.1–40.3)	94.8 (78.5–112)	183 (147–250)	2,548
	2007–2008	12.2 (10.3–14.3)	11.3 (10.0–13.3)	27.1 (21.8–33.8)	64.2 (47.3–93.6)	130 (93.6–177)	2,604
	2009–2010	8.02 (7.11–9.06)	8.02 (7.27–9.04)	16.1 (13.8–19.0)	32.5 (25.2–41.8)	55.7 (41.8–80.9)	2,749
	2011–2012	5.08 (4.78–5.41)	5.30 (4.90–5.80)	10.3 (9.40–11.5)	18.4 (17.0–19.5)	26.5 (23.7–30.2)	2,489
	2013–2014	4.24 (3.94–4.57)	4.70 (4.20–5.00)	8.50 (7.60–9.30)	15.2 (13.3–17.3)	20.2 (18.2–23.7)	2,685
Age group							
6–11 years	2001–2002	23.3 (20.9–26.1)	22.9 (18.5–28.1)	46.5 (38.1–52.0)	81.6 (64.7–109)	142 (93.9–178)	393
	2003–2004	25.1 (19.6–32.3)	25.8 (19.3–31.4)	51.1 (32.1–76.5)	97.9 (58.8–197)	197 (97.6–261)	342
	2005–2006	23.0 (20.3–26.1)	24.5 (19.9–27.6)	44.3 (38.1–52.3)	83.8 (63.6–115)	126 (77.3–253)	356
	2007–2008	16.9 (13.9–20.6)	16.6 (12.4–22.6)	34.5 (26.2–40.9)	64.4 (46.9–129)	137 (63.8–179)	389
	2009–2010	9.78 (8.72–11.0)	11.1 (8.87–12.7)	20.0 (17.1–21.6)	35.4 (24.8–41.4)	48.4 (36.0–74.0)	415
	2011–2012	6.96 (5.86–8.28)	8.10 (6.90–9.70)	14.6 (12.8–17.1)	26.1 (22.6–28.4)	34.7 (27.9–42.5)	396
	2013–2014	6.51 (5.49–7.72)	6.60 (5.10–8.30)	12.4 (10.2–16.4)	23.4 (17.1–30.0)	33.0 (24.2–50.7)	409
12–19 years	2001–2002	17.5 (15.1–20.3)	18.6 (16.2–20.7)	35.0 (27.7–42.1)	70.7 (52.2–104)	118 (74.0–174)	742
	2003–2004	19.5 (16.0–23.7)	20.3 (18.4–23.5)	37.8 (32.6–44.6)	110 (54.6–168)	212 (103–326)	729
	2005–2006	23.0 (18.7–28.4)	22.1 (18.0–26.2)	50.7 (42.7–62.2)	134 (82.3–240)	263 (134–511)	702
	2007–2008	16.9 (12.8–22.3)	15.9 (11.9–19.3)	38.2 (24.0–55.5)	121 (58.1–258)	258 (120–354)	401
	2009–2010	10.0 (8.32–12.1)	9.82 (7.96–12.3)	19.0 (15.9–23.5)	40.0 (26.7–61.5)	68.4 (32.6–154)	420
	2011–2012	5.70 (4.64–7.01)	5.70 (4.60–7.30)	12.2 (10.5–13.7)	22.2 (19.1–29.5)	35.1 (23.0–46.8)	388
	2013–2014	5.34 (4.57–6.24)	5.50 (4.40–7.00)	10.5 (8.10–13.3)	17.5 (14.9–29.5)	25.6 (17.6–33.7)	462
≥20 years	2001–2002	12.0 (10.5–13.9)	12.3 (10.4–14.1)	26.0 (21.6–32.1)	52.3 (41.8–68.3)	116 (74.9–160)	1,647
	2003–2004	12.9 (11.8–14.1)	12.4 (10.9–14.5)	27.0 (25.0–30.9)	68.9 (55.0–86.5)	139 (92.7–216)	1,534
	2005–2006	14.7 (13.2–16.4)	13.4 (12.2–15.1)	31.9 (28.2–36.2)	91.6 (74.6–104)	182 (138–247)	1,490
	2007–2008	11.1 (9.48–13.1)	10.7 (9.30–12.3)	25.5 (20.2–31.4)	59.8 (42.3–88.9)	108 (80.0–155)	1,814
	2009–2010	7.59 (6.64–8.68)	7.55 (6.69–8.58)	15.3 (12.6–18.6)	30.6 (24.1–41.5)	54.9 (41.8–81.0)	1,914
	2011–2012	4.83 (4.45–5.23)	5.10 (4.70–5.60)	9.60 (8.50–10.8)	16.7 (14.5–18.6)	23.0 (20.8–26.5)	1,705
	2013–2014	3.91 (3.65–4.19)	4.40 (3.90–4.80)	7.80 (7.10–8.70)	13.9 (12.1–15.7)	19.1 (17.1–20.8)	1,814

Table 5-12. Uncorrected Urinary MEOHP Concentrations for the U.S. Population NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2001–2002	14.5 (13.0–16.2)	14.6 (13.1–16.2)	31.6 (25.6–34.7)	60.4 (52.3–71.4)	129 (84.4–167)	1,371
	2003–2004	15.6 (13.6–17.9)	14.7 (12.7–18.1)	31.8 (27.2–39.5)	83.8 (59.4–134)	185 (96.2–277)	1,250
	2005–2006	18.3 (16.0–20.9)	16.3 (14.7–19.7)	39.3 (33.4–48.1)	104 (80.7–140)	258 (180–337)	1,270
	2007–2008	12.5 (10.5–15.0)	11.3 (9.80–13.4)	26.1 (21.8–32.2)	61.8 (46.8–98.1)	139 (83.7–189)	1,294
	2009–2010	9.14 (8.01–10.4)	8.76 (7.87–9.88)	18.2 (14.8–21.0)	39.3 (27.5–50.9)	69.6 (50.0–109)	1,399
	2011–2012	5.50 (5.07–5.95)	5.70 (5.10–6.30)	10.5 (8.90–12.2)	18.7 (16.9–21.2)	28.1 (23.4–34.3)	1,259
	2013–2014	4.45 (4.05–4.89)	4.90 (4.40–5.30)	8.10 (7.30–9.00)	13.7 (12.6–15.9)	19.8 (17.3–23.6)	1,285
Females	2001–2002	12.5 (10.8–14.6)	13.1 (11.2–15.0)	28.1 (23.7–33.5)	57.5 (45.8–72.7)	115 (81.8–147)	1,411
	2003–2004	13.4 (11.9–15.1)	13.7 (11.4–16.4)	29.5 (26.1–36.6)	68.6 (53.7–88.1)	143 (88.2–210)	1,355
	2005–2006	14.4 (12.6–16.5)	13.8 (12.5–15.7)	32.5 (29.3–36.4)	81.7 (68.6–104)	159 (114–182)	1,278
	2007–2008	11.8 (10.0–14.0)	11.7 (9.80–13.5)	27.9 (21.3–37.5)	64.2 (43.9–93.6)	122 (92.0–191)	1,310
	2009–2010	7.09 (6.17–8.14)	7.35 (6.13–8.67)	15.2 (12.1–17.5)	27.1 (21.6–36.9)	48.2 (31.3–67.1)	1,350
	2011–2012	4.71 (4.39–5.07)	5.00 (4.70–5.60)	10.2 (9.20–11.1)	18.1 (15.8–19.3)	25.4 (21.9–29.6)	1,230
	2013–2014	4.06 (3.65–4.50)	4.20 (3.60–4.80)	9.00 (7.70–9.90)	16.2 (13.9–18.2)	21.5 (17.6–25.5)	1,400
Race/ethnicity							
Mexican Americans	2001–2002	13.1 (11.6–14.9)	13.4 (11.6–15.0)	25.5 (21.6–30.8)	56.6 (40.6–70.3)	77.3 (70.5–101)	677
	2003–2004	12.8 (10.5–15.5)	13.6 (11.4–15.6)	25.3 (20.4–29.9)	46.6 (32.3–70.8)	76.0 (51.6–153)	652
	2005–2006	14.8 (11.7–18.8)	12.8 (10.5–16.1)	30.9 (22.6–42.9)	79.1 (51.7–131)	152 (92.9–276)	637
	2007–2008	12.6 (10.5–15.1)	11.4 (10.4–12.9)	25.1 (18.7–37.2)	53.4 (43.2–91.7)	118 (88.4–147)	531
	2009–2010	9.57 (8.10–11.3)	9.65 (8.17–11.3)	19.2 (16.3–23.3)	39.0 (30.9–54.7)	64.6 (43.0–95.3)	566
	2011–2012	5.86 (4.69–7.33)	5.90 (4.40–7.50)	11.6 (8.40–14.4)	20.5 (15.4–25.4)	31.5 (22.5–35.1)	316
	2013–2014	5.03 (4.21–6.01)	5.20 (4.60–5.80)	9.40 (7.70–11.5)	18.3 (12.3–24.2)	25.1 (19.5–34.3)	438
Non-Hispanic blacks	2001–2002	19.6 (17.1–22.5)	20.1 (17.9–22.4)	39.0 (34.8–44.2)	80.5 (71.4–97.4)	153 (102–228)	703
	2003–2004	20.2 (17.7–23.0)	20.1 (17.0–22.5)	40.0 (33.9–46.9)	92.6 (68.8–130)	173 (104–247)	699
	2005–2006	21.8 (18.9–25.2)	18.8 (16.8–21.0)	46.0 (38.0–59.1)	130 (104–168)	243 (159–304)	678
	2007–2008	14.2 (12.7–15.9)	14.0 (12.7–16.3)	30.5 (25.8–35.9)	64.2 (52.1–76.1)	110 (71.9–136)	597
	2009–2010	9.57 (8.17–11.2)	9.64 (8.15–11.1)	19.8 (16.5–22.1)	31.4 (25.5–44.0)	50.9 (31.4–129)	516
	2011–2012	7.30 (6.48–8.22)	7.40 (6.70–8.00)	14.0 (11.5–16.0)	26.0 (21.1–32.1)	36.9 (30.8–48.2)	665
	2013–2014	5.38 (4.58–6.31)	5.80 (5.00–7.00)	10.8 (9.10–12.0)	17.5 (15.2–21.8)	25.3 (21.7–29.7)	609

Table 5-12. Uncorrected Urinary MEOHP Concentrations for the U.S. Population NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (µg/L)	Selected percentiles (95% CI) (µg/L)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2001–2002	12.8 (11.2–14.6)	13.2 (11.6–14.6)	28.5 (23.6–34.0)	58.6 (48.8–70.9)	126 (83.7–172)	1,216
	2003–2004	13.8 (12.4–15.4)	13.4 (11.3–16.3)	31.0 (27.0–36.3)	77.6 (59.4–102)	161 (98.7–241)	1,088
	2005–2006	15.5 (13.9–17.3)	15.0 (13.3–16.5)	35.3 (30.1–40.8)	92.6 (74.6–111)	182 (134–247)	1,038
	2007–2008	11.7 (9.66–14.2)	11.0 (9.20–13.6)	26.9 (20.2–35.1)	64.2 (43.4–108)	137 (90.0–197)	1,077
	2009–2010	7.59 (6.60–8.73)	7.55 (6.81–8.63)	15.7 (12.9–18.6)	29.1 (22.9–46.5)	55.7 (41.5–83.5)	1,206
	2011–2012	4.62 (4.31–4.96)	4.90 (4.50–5.50)	9.50 (8.40–10.8)	16.1 (13.8–18.6)	21.2 (19.0–25.9)	813
	2013–2014	3.95 (3.63–4.30)	4.40 (3.90–4.80)	7.90 (7.00–9.10)	14.2 (12.0–16.5)	19.1 (16.5–23.4)	987
All Hispanics	2011–2012	5.94 (5.17–6.83)	6.00 (4.80–7.30)	11.8 (9.70–14.0)	22.5 (19.8–25.8)	34.3 (26.2–39.8)	571
	2013–2014	4.95 (4.46–5.49)	5.30 (4.80–5.70)	9.20 (8.30–10.4)	17.5 (12.9–20.2)	24.2 (19.7–28.5)	690
Asians	2011–2012	4.39 (3.63–5.31)	4.20 (3.30–5.20)	9.40 (7.20–11.3)	19.0 (15.0–27.8)	36.8 (25.4–52.4)	352
	2013–2014	3.25 (2.81–3.76)	3.20 (2.60–4.10)	6.20 (5.10–7.30)	11.0 (9.50–13.7)	16.1 (11.7–23.3)	289

[a]The limit of detection for survey years 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 1.1, 0.5, 0.7, 0.6, 0.2, 0.2, and 0.2 µg/L, respectively.

CI = confidence interval; MEOHP = mono-2-ethyl-5-oxyhexyl phthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-13. Creatinine-Corrected Urinary MEOHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/g of creatinine)	Selected percentiles (95% CI) (μg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Total	2001–2002	12.6 (11.5–13.9)	11.2 (10.2–12.3)	21.3 (18.3–23.8)	45.2 (37.1–58.1)	87.0 (68.0–124)	2,782
	2003–2004	13.6 (12.4–14.8)	12.1 (11.0–12.9)	24.3 (20.9–27.8)	63.0 (47.8–75.8)	118 (94.1–153)	2,605
	2005–2006	15.8 (14.2–17.5)	13.5 (12.4–14.7)	28.9 (26.0–33.8)	77.7 (62.4–91.1)	144 (118–172)	2,548
	2007–2008	12.3 (10.7–14.0)	11.0 (9.72–12.2)	22.3 (18.4–27.9)	52.9 (37.9–74.6)	107 (74.8–136)	2,604
	2009–2010	8.37 (7.31–9.59)	7.44 (6.71–8.42)	13.5 (11.5–15.7)	25.9 (21.4–34.6)	47.7 (34.6–67.8)	2,749
	2011–2012	5.78 (5.51–6.06)	5.51 (5.12–5.83)	8.99 (8.41–9.83)	15.6 (14.3–16.8)	23.4 (19.6–28.0)	2,487
	2013–2014	4.25 (3.92–4.61)	4.02 (3.74–4.43)	6.61 (5.93–7.26)	11.1 (9.73–12.7)	16.4 (13.9–18.1)	2,684
Age group							
6–11 years	2001–2002	26.6 (24.0–29.4)	22.8 (20.3–25.0)	43.3 (33.6–47.1)	74.7 (69.0–91.9)	131 (83.0–183)	393
	2003–2004	26.6 (21.4–33.0)	25.3 (17.8–32.4)	43.6 (34.2–63.2)	77.1 (63.0–118)	121 (76.3–435)	342
	2005–2006	25.4 (22.5–28.6)	24.4 (21.4–26.4)	42.7 (36.0–46.9)	70.4 (52.8–117)	136 (77.2–195)	356
	2007–2008	20.8 (17.1–25.4)	18.5 (15.6–21.5)	35.0 (26.4–46.0)	84.1 (47.2–137)	145 (84.8–187)	389
	2009–2010	12.7 (11.4–14.2)	12.6 (11.5–14.1)	20.8 (16.5–25.1)	33.3 (29.5–44.1)	45.5 (33.7–74.5)	415
	2011–2012	9.93 (8.63–11.4)	9.89 (8.25–11.4)	16.5 (14.3–18.9)	25.6 (22.9–30.2)	34.5 (27.9–41.9)	395
	2013–2014	8.23 (7.16–9.44)	7.77 (6.25–9.38)	12.8 (10.7–17.1)	24.7 (17.9–37.1)	37.4 (21.4–80.7)	409
12–19 years	2001–2002	13.5 (12.0–15.2)	12.0 (10.8–14.3)	23.4 (20.0–28.5)	48.4 (39.2–54.9)	70.5 (55.0–97.2)	742
	2003–2004	14.6 (12.6–16.9)	12.7 (11.6–14.4)	25.5 (20.7–33.8)	67.9 (42.3–143)	153 (61.8–209)	729
	2005–2006	17.2 (14.1–20.9)	15.3 (12.5–18.6)	32.5 (25.7–41.3)	84.2 (49.1–147)	163 (93.1–250)	702
	2007–2008	13.2 (10.3–16.7)	11.1 (9.08–13.5)	25.9 (18.9–35.6)	86.3 (39.4–128)	132 (84.3–203)	401
	2009–2010	8.06 (6.57–9.88)	7.05 (6.16–8.25)	13.3 (9.53–18.3)	24.8 (17.8–47.9)	55.2 (23.6–110)	420
	2011–2012	5.55 (4.95–6.23)	5.21 (4.81–5.61)	8.54 (7.09–11.1)	16.3 (12.9–21.3)	31.6 (16.8–35.3)	388
	2013–2014	4.33 (3.82–4.92)	4.07 (3.71–4.69)	6.55 (5.64–7.19)	10.7 (8.02–13.4)	15.3 (11.5–18.6)	462
≥20 years	2001–2002	11.4 (10.2–12.8)	10.1 (8.89–11.4)	17.5 (15.2–21.8)	38.4 (30.5–52.5)	84.3 (53.3–128)	1,647
	2003–2004	12.4 (11.5–13.3)	11.0 (10.0–12.0)	20.9 (18.6–22.8)	53.9 (40.7–70.2)	109 (88.6–130)	1,534
	2005–2006	14.8 (13.3–16.4)	12.4 (11.2–13.5)	26.7 (23.8–31.3)	76.3 (61.0–89.9)	144 (106–170)	1,490
	2007–2008	11.4 (10.0–13.0)	10.0 (9.15–11.2)	20.8 (16.7–25.6)	47.3 (33.2–65.3)	87.4 (62.7–136)	1,814
	2009–2010	8.04 (6.99–9.24)	7.19 (6.36–8.00)	12.7 (10.7–14.7)	24.3 (19.7–34.6)	47.4 (33.7–67.3)	1,914
	2011–2012	5.48 (5.23–5.74)	5.19 (4.89–5.56)	8.39 (7.95–8.98)	13.9 (12.8–15.3)	19.3 (16.6–25.4)	1,704
	2013–2014	3.95 (3.63–4.30)	3.85 (3.54–4.15)	6.15 (5.48–6.75)	9.83 (8.57–11.1)	13.6 (12.2–16.3)	1,813

Table 5-13. Creatinine-Corrected Urinary MEOHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (μg/g of creatinine)	Selected percentiles (95% CI) (μg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Gender							
Males	2001–2002	11.8 (10.7–13.0)	10.2 (8.93–11.7)	21.2 (18.5–23.3)	46.1 (35.3–58.7)	84.2 (69.6–104)	1,371
	2003–2004	12.3 (11.1–13.5)	11.1 (10.0–12.0)	21.6 (17.6–26.9)	59.1 (45.4–72.0)	120 (72.0–162)	1,250
	2005–2006	14.7 (12.9–16.7)	12.6 (10.9–14.3)	27.1 (23.3–35.6)	79.5 (59.6–96.9)	147 (120–190)	1,270
	2007–2008	10.5 (9.08–12.2)	9.25 (8.08–10.6)	18.9 (15.9–23.1)	46.7 (32.6–62.4)	86.4 (56.5–144)	1,294
	2009–2010	8.19 (7.15–9.38)	7.07 (6.59–7.55)	13.4 (10.8–15.8)	30.2 (21.7–41.2)	52.1 (41.2–82.3)	1,399
	2011–2012	5.14 (4.86–5.43)	4.86 (4.55–5.12)	7.83 (7.29–8.24)	14.7 (12.7–16.1)	22.6 (18.1–29.7)	1,258
	2013–2014	3.74 (3.45–4.06)	3.70 (3.46–3.91)	5.59 (5.13–3.67)	9.03 (8.37–9.74)	14.3 (11.6–16.8)	1,284
Females	2001–2002	13.5 (11.9–15.2)	12.0 (10.8–13.7)	21.5 (18.0–25.6)	44.8 (36.8–61.6)	92.3 (61.0–139)	1,411
	2003–2004	14.9 (13.4–16.7)	12.7 (11.4–14.2)	26.6 (21.8–30.6)	65.6 (48.0–90.1)	118 (97.0–157)	1,355
	2005–2006	16.9 (15.1–19.0)	14.7 (13.2–16.5)	30.3 (26.6–34.7)	76.4 (57.6–97.2)	137 (106–170)	1,278
	2007–2008	14.2 (12.5–16.0)	12.5 (11.5–13.8)	25.9 (21.2–31.0)	61.1 (40.9–84.1)	114 (84.3–142)	1,310
	2009–2010	8.55 (7.37–9.93)	8.06 (6.76–9.33)	13.6 (11.6–16.2)	24.1 (20.0–32.7)	43.2 (27.7–64.5)	1,350
	2011–2012	6.48 (6.07–6.91)	6.34 (5.71–6.91)	10.0 (9.34–11.0)	16.5 (14.7–18.6)	23.5 (19.5–27.9)	1,229
	2013–2014	4.81 (4.31–5.37)	4.58 (4.00–5.16)	7.42 (6.58–8.62)	12.6 (10.7–15.6)	17.2 (14.8–21.3)	1,400
Race/ethnicity							
Mexican Americans	2001–2002	12.4 (11.4–13.5)	11.0 (10.5–12.3)	20.9 (18.5–24.4)	44.6 (33.4–56.2)	65.9 (53.1–83.1)	677
	2003–2004	11.5 (9.81–13.6)	10.7 (9.04–12.3)	18.8 (15.6–24.6)	39.1 (31.8–53.9)	63.0 (47.2–121)	652
	2005–2006	13.3 (11.1–16.1)	11.4 (9.58–13.6)	24.0 (19.4–30.4)	61.2 (45.6–85.9)	102 (69.9–200)	637
	2007–2008	12.3 (10.0–15.0)	10.6 (8.57–14.1)	21.7 (16.1–28.7)	53.1 (32.7–85.2)	113 (79.7–149)	531
	2009–2010	9.50 (8.16–11.1)	8.72 (8.13–9.61)	16.6 (12.9–20.5)	35.4 (24.4–46.6)	56.7 (40.9–82.3)	566
	2011–2012	6.61 (5.43–8.05)	6.00 (4.83–7.45)	11.3 (8.87–13.9)	18.9 (15.8–22.8)	28.1 (18.2–60.8)	316
	2013–2014	5.13 (4.57–5.75)	4.90 (4.42–5.49)	8.51 (6.80–10.7)	14.3 (12.0–19.5)	20.7 (15.6–31.7)	438
Non-Hispanic blacks	2001–2002	13.8 (12.3–15.4)	13.1 (12.0–14.2)	23.9 (20.0–29.3)	58.3 (45.3–79.7)	101 (81.3–124)	703
	2003–2004	14.3 (13.1–15.6)	13.3 (11.3–15.5)	24.8 (21.7–27.7)	61.2 (46.8–76.6)	105 (79.7–152)	699
	2005–2006	15.3 (13.2–17.8)	11.6 (9.87–14.6)	29.1 (24.7–38.5)	77.1 (61.9–113)	172 (99.8–251)	678
	2007–2008	11.0 (9.94–12.2)	9.90 (9.16–11.1)	20.6 (16.6–23.5)	42.2 (33.8–58.6)	75.8 (57.2–124)	597
	2009–2010	6.92 (5.60–8.57)	6.49 (5.12–8.24)	11.4 (9.09–14.1)	19.2 (14.9–27.3)	28.1 (19.8–61.1)	516
	2011–2012	5.68 (5.11–6.32)	5.31 (4.71–5.70)	9.33 (7.79–10.8)	16.9 (13.6–23.4)	29.4 (18.8–39.2)	665
	2013–2014	3.97 (3.55–4.44)	3.79 (3.28–4.42)	6.43 (5.67–7.31)	10.6 (9.55–12.2)	14.1 (11.2–18.6)	609

Table 5-13. Creatinine-Corrected Urinary MEOHP Concentrations for the U.S. Population from NHANES 2001–2014

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	2001–2002	12.7 (11.4–14.0)	11.1 (9.90–12.3)	20.8 (18.0–23.9)	45.7 (35.9–64.9)	96.0 (68.5–161)	1,216
	2003–2004	13.7 (12.2–15.3)	12.0 (10.5–12.9)	24.9 (20.7–28.6)	69.5 (51.4–95.3)	124 (90.3–182)	1,088
	2005–2006	16.3 (14.8–18.0)	14.0 (12.9–15.7)	30.8 (27.3–34.8)	79.3 (66.0–93.8)	139 (117–163)	1,038
	2007–2008	12.2 (10.3–14.5)	11.0 (9.38–13.1)	22.3 (17.4–30.4)	51.4 (35.7–77.7)	107 (74.6–139)	1,077
	2009–2010	8.53 (7.35–9.90)	7.62 (6.76–8.54)	13.7 (11.2–16.2)	24.9 (20.3–35.7)	47.8 (32.8–76.4)	1,206
	2011–2012	5.61 (5.17–6.08)	5.41 (4.90–5.99)	8.42 (7.84–9.61)	14.3 (12.5–15.8)	20.5 (16.6–25.4)	811
	2013–2014	4.16 (3.75–4.62)	3.96 3.70–4.41)	6.37 (5.47–7.23)	10.3 (8.57–12.7)	15.6 (12.8–17.3)	987
All Hispanics	2011–2012	6.66 (6.05–7.33)	6.04 (5.49–6.74)	11.3 (10.0–13.5)	18.9 (16.9–21.0)	30.2 (20.8–41.9)	571
	2013–2014	4.91 (4.55–5.31)	4.60 (4.26–5.07)	7.76 (6.94–9.27)	13.6 (11.5–17.0)	20.2 (16.9–25.2)	690
Asians	2011–2012	5.88 (4.96–6.97)	5.30 (4.59–6.36)	10.0 (8.11–12.2)	20.2 (14.7–26.3)	39.3 (23.5–50.1)	352
	2013–2014	4.12 (3.68–4.62)	3.67 (3.20–4.49)	7.02 (5.79–8.62)	11.2 (10.0–13.9)	15.7 (12.1–24.4)	288

[a]The limit of detection (not corrected for creatinine) for survey years 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 1.1, 0.5, 0.7, 0.6, 0.2, 0.2, and 0.2 µg/L, respectively.

CI = confidence interval; MEOHP = mono-2-ethyl-5-oxyhexyl phthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-14. Uncorrected Urinary MECPP Concentrations for the U.S. Population from NHANES 2003–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	34.7 (31.0–38.9)	33.0 (29.1–37.4)	71.8 (61.7–84.8)	168 (133–240)	339 (235–506)	2,605
	2005–2006	38.6 (34.7–42.9)	35.6 (31.1–40.3)	79.7 (70.9–92.9)	211 (180–246)	386 (311–484)	2,548
	2007–2008	33.3 (28.7–38.6)	31.2 (27.1–36.0)	69.5 (55.8–86.3)	153 (120–216)	308 (220–397)	2,604
	2009–2010	20.7 (18.5–23.3)	20.4 (18.1–23.5)	39.9 (34.9–45.5)	78.4 (67.2–95.5)	127 (99.5–199)	2,749
	2011–2012	12.9 (12.0–13.9)	13.5 (12.4–14.8)	25.3 (23.6–26.7)	43.9 (40.0–51.1)	68.9 (60.4–75.2)	2,489
	2013–2014	10.5 (9.71–11.5)	11.1 (10.1–12.0)	20.0 (17.9–22.5)	36.4 (31.4–42.0)	50.7 (46.5–58.7)	2,685
Age group							
6–11 years	2003–2004	58.2 (44.7–75.6)	51.6 (39.2–67.6)	112 (71.4–182)	314 (124–524)	391 (238–781)	342
	2005–2006	57.4 (50.2–65.7)	53.5 (42.7–67.2)	94.7 (83.2–108)	200 (154–247)	297 (196–548)	356
	2007–2008	46.6 (39.2–55.3)	44.1 (34.9–54.7)	92.7 (64.7–112)	156 (117–278)	357 (176–441)	389
	2009–2010	27.7 (24.7–31.2)	29.4 (25.4–33.2)	48.5 (39.0–60.2)	87.1 (64.4–102)	118 (87.1–202)	415
	2011–2012	18.8 (16.1–21.9)	21.6 (17.3–24.1)	36.8 (31.5–41.4)	63.5 (51.5–71.5)	81.5 (68.1–95.1)	396
	2013–2014	18.2 (15.5–21.4)	18.1 (14.2–23.4)	33.9 (28.3–39.6)	54.3 (45.5–71.8)	81.1 (58.5–142)	409
12–19 years	2003–2004	44.6 (36.8–54.0)	42.7 (38.4–47.6)	86.5 (67.3–108)	220 (120–397)	448 (235–808)	729
	2005–2006	52.9 (43.0–65.2)	46.7 (39.4–61.6)	114 (85.6–173)	314 (195–515)	560 (324–1180)	702
	2007–2008	44.3 (35.2–55.9)	38.9 (28.9–49.3)	97.3 (64.3–127)	247 (140–456)	476 (231–977)	401
	2009–2010	26.2 (22.4–30.6)	25.7 (21.2–30.0)	50.1 (38.3–57.7)	90.3 (58.2–162)	147 (83.9–349)	420
	2011–2012	14.3 (11.3–18.0)	14.0 (11.6–17.5)	28.4 (23.5–36.8)	59.3 (47.1–70.2)	74.6 (59.3–135)	388
	2013–2014	13.6 (11.8–15.7)	13.8 (11.2–16.2)	25.7 (20.0–29.9)	44.4 (31.2–64.6)	64.9 (48.6–99.5)	462
≥20 years	2003–2004	31.3 (28.6–34.4)	29.2 (26.2–33.0)	63.5 (56.5–73.9)	157 (130–187)	312 (199–457)	1,534
	2005–2006	35.1 (31.5–39.0)	31.3 (28.1–35.7)	72.7 (65.4–82.4)	193 (163–237)	377 (285–460)	1,490
	2007–2008	30.7 (26.4–35.8)	29.2 (24.3–34.4)	63.2 (51.6–80.0)	145 (109–206)	286 (182–378)	1,814
	2009–2010	19.4 (17.0–22.0)	18.8 (15.7–22.3)	37.7 (32.8–44.0)	76.9 (63.1–92.8)	126 (96.1–197)	1,914
	2011–2012	12.2 (11.3–13.3)	13.0 (11.4–14.4)	23.8 (21.8–25.8)	40.2 (36.9–43.9)	61.8 (52.1–73.6)	1,705
	2013–2014	9.57 (8.84–10.4)	10.1 (9.10–11.3)	18.3 (16.6–19.8)	32.1 (27.5–37.8)	46.4 (39.5–51.8)	1,814
Gender							
Males	2003–2004	37.9 (33.1–43.5)	34.7 (30.0–39.5)	73.7 (60.8–91.9)	187 (133–300)	388 (222–660)	1,250
	2005–2006	43.6 (38.1–49.8)	39.7 (31.9–46.2)	87.0 (76.8–103)	260 (188–308)	460 (347–670)	1,270
	2007–2008	34.4 (29.3–40.5)	31.5 (27.3–35.7)	65.1 (52.1–87.4)	161 (120–217)	321 (213–422)	1,294
	2009–2010	23.4 (20.7–26.4)	23.0 (20.2–25.6)	44.9 (40.1–51.0)	87.1 (70.3–110)	162 (107–288)	1,399
	2011–2012	14.3 (13.0–15.6)	14.6 (12.7–16.4)	24.7 (23.1–27.6)	45.7 (40.2–54.9)	71.5 (59.8–88.4)	1,259
	2013–2014	11.1 (9.98–12.3)	11.6 (10.6–12.5)	19.3 (17.1–22.3)	35.1 (29.3–44.0)	50.7 (47.4–58.4)	1,285

Table 5-14. Uncorrected Urinary MECPP Concentrations for the U.S. Population from NHANES 2003–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Females	2003–2004	31.9 (28.1–36.2)	31.3 (27.5–35.8)	69.3 (58.9–81.9)	154 (128–199)	312 (182–441)	1,355
	2005–2006	34.3 (30.4–38.6)	31.7 (28.0–36.6)	71.0 (63.0–85.3)	192 (156–217)	309 (251–386)	1,278
	2007–2008	32.3 (27.8–37.5)	31.0 (26.4–38.3)	73.0 (56.9–90.2)	147 (112–220)	297 (185–420)	1,310
	2009–2010	18.5 (16.2–21.0)	18.8 (15.8–22.4)	34.7 (29.3–41.5)	72.9 (56.3–93.2)	111 (90.3–146)	1,350
	2011–2012	11.8 (10.8–12.9)	12.4 (11.2–13.7)	25.6 (23.4–26.6)	42.3 (37.4–49.5)	64.9 (54.4–76.8)	1,230
	2013–2014	10.1 (9.05–11.2)	10.2 (8.90–1.7)	20.6 (18.4–23.2)	36.9 (31.5–41.8)	51.7 (41.3–64.9)	1,400
Race/ethnicity							
Mexican Americans	2003–2004	31.9 (27.1–37.6)	31.5 (26.8–37.4)	57.4 (45.9–71.8)	116 (86.0–162)	175 (133–355)	652
	2005–2006	39.4 (30.3–51.2)	34.2 (24.1–47.1)	74.6 (54.0–111)	220 (124–338)	394 (222–673)	637
	2007–2008	36.7 (30.6–44.0)	31.3 (27.0–35.7)	71.9 (54.9–91.7)	162 (123–241)	321 (209–477)	531
	2009–2010	26.2 (22.5–30.4)	25.8 (22.3–29.8)	51.0 (41.3–57.4)	92.6 (74.5–122)	160 (113–245)	566
	2011–2012	15.8 (12.7–19.6)	14.9 (12.7–18.3)	28.1 (22.6–34.3)	51.3 (42.5–71.3)	72.6 (56.6–109)	316
	2013–2014	13.4 (11.0–16.2)	13.1 (12.1–14.2)	23.4 (18.0–30.2)	44.4 (31.8–67.9)	67.9 (42.0–95.0)	438
Non-Hispanic blacks	2003–2004	42.6 (37.0–49.2)	38.3 (33.8–46.9)	82.5 (68.7–103)	191 (146–246)	339 (244–468)	699
	2005–2006	46.6 (41.3–52.5)	40.3 (35.6–46.1)	96.3 (76.6–132)	256 (208–347)	455 (328–528)	678
	2007–2008	35.0 (31.1–39.4)	35.6 (30.7–38.8)	71.6 (59.1–84.5)	151 (113–192)	235 (184–338)	597
	2009–2010	21.9 (18.6–25.7)	22.3 (18.2–25.6)	40.5 (35.7–47.1)	77.0 (61.1–97.1)	127 (76.0–268)	516
	2011–2012	16.4 (14.5–18.5)	16.2 (14.4–18.8)	30.7 (26.0–36.6)	60.9 (47.5–69.9)	78.1 (68.2–96.7)	665
	2013–2014	11.5 (9.62–13.8)	12.7 (10.4–14.6)	21.5 (18.5–25.6)	36.4 (30.4–48.6)	58.5 (42.1–71.8)	609
Non-Hispanic whites	2003–2004	33.8 (30.1–37.9)	32.1 (27.6–37.5)	72.4 (62.0–87.7)	167 (133–240)	354 (220–560)	1,088
	2005–2006	37.0 (33.4–41.0)	35.4 (30.4–40.9)	79.7 (70.0–93.3)	203 (174–237)	380 (284–484)	1,038
	2007–2008	32.0 (26.7–38.3)	30.4 (24.5–38.0)	67.6 (52.5–90.9)	145 (105–244)	316 (197–476)	1,077
	2009–2010	19.6 (17.2–22.2)	19.3 (16.4–23.1)	39.3 (33.0–45.3)	75.0 (61.9–95.7)	120 (95.5–197)	1,206
	2011–2012	11.8 (10.9–12.9)	12.5 (11.0–14.6)	23.8 (21.8–25.7)	39.9 (34.8–44.2)	55.8 (47.1–76.8)	813
	2013–2014	9.81 (8.92–10.8)	10.3 (9.20–11.4)	19.3 (16.5–22.0)	34.1 (28.7–41.0)	49.1 (43.1–54.8)	987
All Hispanics	2011–2012	16.0 (14.0–18.2)	15.2 (12.9–18.2)	30.1 (24.5–37.8)	59.8 (50.0–68.9)	76.0 (70.2–104)	571
	2013–2014	13.1 (11.7–14.7)	13.4 (12.3–14.4)	23.1 (20.6–26.5)	41.6 (35.1–54.1)	63.5 (45.5–75.4)	690

Table 5-14. Uncorrected Urinary MECPP Concentrations for the U.S. Population from NHANES 2003–2014

	Survey years[a]	Geometric mean (95% CI) (μg/L)	Selected percentiles (95% CI) (μg/L)				Sample size
			50th	75th	90th	95th	
Asians	2011–2012	12.0 (10.2–14.2)	11.7 (10.2–13.7)	23.6 (19.5–27.7)	51.1 (36.5–70.0)	80.5 (58.7–138)	352
	2013–2014	9.01 (7.74–10.5)	9.20 (7.20–11.1)	16.5 (14.3–18.5)	27.3 (22.9–31.4)	39.4 (29.4–63.2)	289

[a]The limit of detection for survey years 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 0.3, 0.6, 0.5, 0.2, 0.2, and 0.4 μg/L, respectively.

CI = confidence interval; MECCP = mono-2-ethyl-5-carboxyhexyl phthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-15. Creatinine Corrected MECPP Concentrations for the U.S. Population from NHANES 2003–2014

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Total	2003–2004	32.6 (29.6–36.0)	27.0 (24.3–30.6)	54.6 (48.0–63.5)	139 (109–186)	251 (192–356)	2,605
	2005–2006	37.6 (33.7–42.0)	32.2 (29.5–37.0)	67.5 (58.2–80.8)	168 (139–209)	290 (261–328)	2,548
	2007–2008	33.6 (29.7–38.0)	29.1 (25.8–32.2)	58.7 (49.6–68.8)	138 (109–164)	233 (178–319)	2,604
	2009–2010	21.6 (19.0–24.7)	19.2 (16.8–22.1)	33.7 (30.0–40.0)	69.4 (54.0–84.3)	121 (85.1–184)	2,749
	2011–2012	14.7 (13.8–15.7)	14.1 (12.9–15.1)	22.7 (21.1–25.3)	38.9 (34.5–44.3)	59.8 (54.5–63.5)	2,487
	2013–2014	10.6 (9.68–11.6)	10.2 (9.32–11.0)	16.2(14.5–18.2)	28.5 (25.3–32.0)	40.3 (35.2–46.0)	2,684
Age group							
6–11 years	2003–2004	61.5 (49.0–77.2)	52.2 (41.6–73.8)	104 (74.2–140)	210 (111–500)	372 (192–988)	342
	2005–2006	63.2 (55.6–71.9)	54.2 (48.1–63.6)	92.8 (82.6–111)	160 (124–247)	312 (172–480)	356
	2007–2008	57.4 (49.2–66.9)	49.6 (42.7–61.5)	94.2 (79.5–122)	185 (138–294)	376 (188–404)	389
	2009–2010	36.1 (32.4–40.3)	33.6 (32.3–36.8)	55.4 (43.9–66.9)	88.7 (69.2–113)	121 (90.6–224)	415
	2011–2012	26.8 (23.6–30.3)	26.2 (22.6–29.4)	41.5 (36.5–47.2)	63.5 (57.5–70.7)	84.4 (71.3–107)	395
	2013–2014	23.0 (20.4–26.0)	21.1 (18.4–24.7)	33.8 (29.6–41.3)	64.7 (41.9–97.3)	97.3 (60.0–180)	409
12–19 years	2003–2004	33.4 (28.7–38.7)	27.1 (23.9–32.0)	55.0 (43.8–83.8)	168 (92.5–289)	294 (159–387)	729
	2005–2006	39.5 (32.5–47.8)	33.9 (27.9–41.0)	72.7 (56.9–96.7)	197 (106–327)	385 (216–531)	702
	2007–2008	34.5 (28.1–42.3)	28.0 (23.2–35.0)	65.9 (47.5–85.9)	159 (90.1–233)	246 (159–489)	401
	2009–2010	21.1 (17.4–25.5)	18.2 (15.6–20.7)	33.2 (25.5–43.3)	64.9 (42.7–158)	158 (58.4–246)	420
	2011–2012	13.9 (11.7–16.5)	12.5 (10.7–15.5)	22.2 (16.5–29.2)	41.4 (30.3–60.8)	70.9 (46.9–92.9)	388
	2013–2014	11.0 (9.68–12.6)	10.2 (8.77–12.2)	16.9 (14.4–20.5)	28.9 (23.2–35.5)	40.7 (33.8–48.8)	462
≥20 years	2003–2004	30.1 (27.7–32.7)	25.1 (22.9–27.6)	49.1 (44.1–55.2)	126 (101–154)	237 (191–315)	1,534
	2005–2006	35.2 (31.2–39.6)	29.8 (26.1–33.3)	60.8 (54.2–74.0)	167 (131–206)	279 (247–322)	1,490
	2007–2008	31.5 (27.8–35.8)	27.8 (24.1–30.8)	53.1 (45.0–65.4)	128 (101–155)	214 (162–319)	1,814
	2009–2010	20.5 (17.9–23.5)	18.2 (15.9–20.5)	31.7 (27.4–36.8)	65.0 (52.1–80.6)	118 (81.3–173)	1,914
	2011–2012	13.9 (13.0–14.8)	13.3 (12.4–14.4)	21.3 (19.5–22.8)	33.9 (30.6–39.0)	53.7 (42.9–63.2)	1,704
	2013–2014	9.65 (8.80–10.6)	9.62 (8.61–10.4)	14.5 (13.0–16.3)	24.4 (21.0–28.3)	34.2 (28.9–39.6)	1,813
Gender							
Males	2003–2004	29.8 (26.8–33.1)	23.5 (21.4–27.1)	50.7 (42.2–61.7)	132 (98.0–191)	248 (159–422)	1,250
	2005–2006	35.0 (30.7–39.9)	29.0 (25.7–32.1)	69.3 (54.2–82.9)	172 (141–210)	301 (249–376)	1,270
	2007–2008	29.0 (25.3–33.2)	25.1 (21.7–28.8)	47.6 (40.8–57.4)	120 (91.7–157)	210 (157–331)	1,294
	2009–2010	21.0 (18.4–23.9)	18.4 (16.1–20.4)	33.1 (29.2–38.5)	70.2 (53.4–94.6)	125 (92.8–210)	1,399
	2011–2012	13.3 (12.6–14.1)	12.5 (11.6–13.3)	20.1 (17.8–21.6)	35.0 (31.0–38.8)	56.4 (46.4–62.4)	1,258
	2013–2014	9.32 (8.50–10.2)	9.05 (8.18–9.88)	14.1 (12.6–15.5)	24.7 (21.0–29.0)	37.1 (33.8–41.9)	1,284

Table 5-15. Creatinine Corrected MECPP Concentrations for the U.S. Population from NHANES 2003–2014

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Females	2003–2004	35.5 (31.6–40.0)	30.6 (26.4–35.5)	58.3 (48.8–71.8)	144 (108–192)	251 (192–349)	1,355
	2005–2006	40.3 (36.2–44.9)	36.7 (31.6–40.0)	66.1 (58.2–83.7)	168 (127–206)	279 (240–341)	1,278
	2007–2008	38.7 (34.5–43.3)	32.8 (30.0–36.4)	67.8 (58.5–80.0)	147 (117–176)	266 (176–379)	1,310
	2009–2010	22.3 (19.3–25.7)	20.5 (17.2–23.9)	34.9 (30.0–41.7)	67.0 (53.5–80.8)	104 (80.8–170)	1,350
	2011–2012	16.2 (14.6–18.0)	15.8 (14.1–17.7)	25.8 (22.2–29.4)	44.1 (37.6–50.8)	63.2 (54.3–72.4)	1,229
	2013–2014	11.9 (10.6–13.4)	11.4 (10.1–12.8)	18.2 (15.9–21.6)	30.1 (27.2–35.2)	42.5 (35.2–57.4)	1,400
Race/ethnicity							
Mexican Americans	2003–2004	28.8 (25.4–32.6)	24.7 (22.4–26.3)	46.7 (39.0–56.3)	94.7 (73.2–137)	152 (118–238)	652
	2005–2006	35.5 (28.7–43.7)	29.8 (25.5–34.9)	61.5 (48.4–86.2)	165 (105–201)	278 (181–501)	637
	2007–2008	35.8 (29.1–44.0)	30.6 (23.2–38.6)	64.1 (47.2–84.8)	151 (92.3–240)	286 (198–402)	531
	2009–2010	26.0 (22.5–30.0)	23.8 (21.3–27.0)	40.1 (35.0–52.3)	88.8 (69.5–104)	148 (100–203)	566
	2011–2012	17.8 (14.6–21.6)	15.3 (12.7–19.8)	28.4 (21.9–39.0)	53.4 (44.7–62.9)	80.0 (52.4–115)	316
	2013–2014	13.6 (12.1–15.3)	12.1 (11.3–13.6)	22.0 (17.3–27.4)	39.5 (30.0–51.6)	55.9 (41.5–66.7)	438
Non-Hispanic blacks	2003–2004	30.3 (27.7–33.2)	27.0 (23.2–30.7)	51.1 (41.6–64.0)	135 (100–161)	212 (173–252)	699
	2005–2006	32.7 (28.9–37.1)	27.1 (22.4–31.5)	62.4 (53.1–76.0)	166 (119–260)	370 (231–429)	678
	2007–2008	27.2 (24.3–30.5)	23.5 (21.9–26.1)	49.1 (37.7–58.6)	103 (85.9–132)	178 (140–259)	597
	2009–2010	15.9 (12.6–19.9)	14.5 (11.5–18.8)	26.3 (19.5–32.9)	48.0 (32.6–66.4)	70.7 (46.1–209)	516
	2011–2012	12.8 (11.3–14.4)	11.8 (10.6–13.0)	20.8 (18.0–25.0)	40.4 (29.6–50.3)	59.4 (46.2–75.6)	665
	2013–2014	8.51 (7.48–9.68)	8.22 (7.07–9.65)	14.2 (12.1–16.4)	23.9 (20.9–27.1)	35.3 (27.3–41.6)	609
Non-Hispanic whites	2003–2004	33.4 (29.5–37.7)	27.0 (23.5–31.6)	56.8 (48.6–69.4)	145 (109–198)	294 (193–385)	1,088
	2005–2006	39.0 (34.9–43.4)	34.3 (30.3–39.1)	69.5 (59.5–83.7)	182 (143–214)	284 (237–324)	1,038
	2007–2008	33.4 (28.4–39.3)	29.2 (25.1–34.6)	57.7 (46.6–72.4)	138 (101–166)	233 (164–338)	1,077
	2009–2010	22.0 (19.1–25.3)	19.4 (16.8–22.9)	34.0 (29.3–42.5)	67.6 (52.5–84.3)	113 (81.3–188)	1,206
	2011–2012	14.3 (13.1–15.7)	13.9 (12.6–15.2)	21.8 (19.7–24.6)	34.3 (30.1–42.2)	54.9 (42.9–60.9)	811
	2013–2014	10.3 (9.23–11.6)	10.0 (9.02–11.1)	15.4 (13.0–18.6)	27.2 (21.6–32.0)	35.9 (30.0–48.2)	987
All Hispanics	2011–2012	17.9 (16.2–19.7)	15.7 (14.1–18.1)	30.0 (25.8–33.4)	53.4 (44.8–64.0)	80.0 (59.0–107)	571
	2013–2014	13.0 (12.0–14.1)	12.1 (11.3–12.9)	20.7 (17.7–23.8)	37.6 (30.9–42.5)	54.1 (42.5–64.4)	690

Table 5-15. Creatinine Corrected MECPP Concentrations for the U.S. Population from NHANES 2003–2014

	Survey years[a]	Geometric mean (95% CI) (µg/g of creatinine)	Selected percentiles (95% CI) (µg/g of creatinine)				Sample size
			50th	75th	90th	95th	
Asians	2011–2012	16.1 (13.7–18.9)	14.7 (12.3–17.2)	26.4 (21.7–33.0)	51.2 (41.5–76.9)	90.0 (51.0–142)	352
	2013–2014	11.5 (10.3–12.8)	10.8 (8.94–12.1)	18.2 (15.1–20.9)	30.7 (27.2–38.0)	40.8 (32.2–65.0)	288

[a]The limit of detection (not corrected for creatinine) for survey years 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were 0.3, 0.6, 0.5, 0.2, 0.2, and 0.4 µg/L, respectively.

CI = confidence interval; MECCP = mono-2-ethyl-5-carboxyhexyl phthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Much of the current literature on DEHP contamination of foodstuffs comes from outside the United States or does not reflect typical exposures of U.S. consumers; therefore, it is uncertain whether and for which products this information can be used in U.S.-centered exposure or risk calculations. Examples of available data include: migration of DEHP into bottled water, Saudi Arabia (Fayad et al. 1997); migration of DEHP from caps into foods, Italy (Gramiccioni et al. 1990); migration of DEHP from a plastic bag containing contaminated corn in a laboratory (the corn was not intended for consumer use), Canada/France (Cohen et al. 1991); migration of DEHP from PVC gloves to prepared food, Japan Tsumura et al. (2001); post-secretory migration of DEHP during milk processing and storage, Germany (Bluthgen 2000); and migration of DEHP into food simulants, Brazil (Morelli-Cardoso et al. 1999). Further, while the FDA allows the use of DEHP in food contact applications (e.g., can coatings [FDA 1999g]; adhesives [FDA 1999a]; defoaming agent in paper manufacture [FDA 1999e]; as a flow promoter at no more than 3% in acrylic and modified acrylic single and repeated use containers [FDA 1999c]; in cellophane used for food packaging at a concentration not to exceed 5% [FDA 1999b]; and as a surface lubricant in the processing of metal foil at a concentration not to exceed 0.015 mg/in^2 of metal surface [FDA 1999d]), it is not clear if industry currently uses DEHP in these applications. Thus, the uncertainty associated with current concentrations in food (as outlined above) makes quantifying intakes speculative. This might be especially true given the recent activity (as noted in Section 5.2.3) in eliminating phthalates from some consumer products.

While it is likely that food represents the major, chronic route of exposure to DEHP for the general population, the highest degree of acute exposure to individuals occurs in hospital patients through hospital equipment plastics, such as tubing and intravenous bags made using PVC. The amount of DEHP detected in liquids that have passed through hospital equipment are several orders of magnitude higher than the amounts detected in water and food samples (Inoue et al. 2005; Jaeger and Rubin 1972; Rock et al. 1978)—see Section 5.5.4 for further discussion. However, people who require only occasional medical care for conditions that do not require intravenous administration of fluids or medication, the use of medical devices, the use of invasive medical procedures, or instrumentation have a lower risk of exposure than people with chronic conditions who require regular treatment or the use of medical devices. Individuals with chronic conditions are discussed in Section 5.7 (Populations with Potentially High Exposures).

Oral exposure from drinking water is not expected to be a significant route of exposure (Doull et al. 1999; Huber et al. 1996; NTP 2000) based on a mean concentration of 0.55 µg/L for DEHP in drinking water (NTP 2006).

Dermal exposure to DEHP can occur when items containing DEHP as a plasticizer are handled. Schwope and Reid (1988) noted that DEHP migrated into dry materials in contact with PVC containing DEHP. However, the data available in this study did not indicate how much DEHP will be transferred. A study of the migration of DEHP from PVC film to rat skin found that the mean dermal uptake of DEHP was small, only 0.24 μg/cm^2-hour (Deisinger et al. 1998), a rate that is likely to be 2–4 times faster than is expected for human skin (Barber et al. 1992; Scott et al. 1987). In a study measuring the levels of phthalates in skin wipe samples from 20 Chinese adults not deliberately exposed to phthalates, mean DEHP concentrations collected from the skin were 678 μg/m^2 for the forehead, 867–884 μg/m^2 for the left and right forearm, 1,725–1,840 μg/m^2 for the left and right back-of-hand, and 4,104–4,155 μg/m^2 for the left and right palm (Gong et al. 2014). From this study, an estimated median total dermal adsorption from skin surface lipids of 0.66 μg/kg/day was determined for DEHP, accounting for roughly 10–20% of total daily uptake. Repeated sampling over a month for a subsample (six adults) showed that levels at measured body locations did not significantly change. Washing hands with soap and water reduced palm levels to about half.

Inhalation exposure can occur from breathing ambient air and indoor air, and is not considered to be a primary or significant route of exposure to DEHP. Huber et al. (1996) and Doull et al. (1999) have suggested, based on monitoring studies from the 1970s and 1980s, that inhalation exposures from breathing ambient air are low. During a study in which 96 women living in New York City wore personal ambient air samplers for 2 consecutive days, DEHP was detected in all air samples at a mean concentration of 0.18 μg/m^3 (Adibi et al. 2008). Ambient air studies found in the available literature reported concentrations that span a relatively narrow range, even in industrialized areas (Section 5.5.1); although industrial areas appeared to have higher concentrations in some cases. Thurén and Larsson (1990) reported that higher concentrations of DEHP were seen adjacent to a facility using DEHP, but these concentrations fell off rapidly. Thus, it is anticipated that people living near DEHP use and disposal areas might be exposed to elevated levels, but it is unclear how much higher these concentrations might be. It is further anticipated that use facilities where DEHP is actively used, such as DEHP production or PVC manufacturing facilities, will emit more DEHP into the ambient environment (e.g., through air-borne particulates or water) than storage or disposal facilities because of the tendency of DEHP to sorb to organic matter in the soil or sediment.

Occupational exposure to DEHP might be important during the manufacture and processing of this compound, mostly via inhalation, essentially in the form of an aerosol (IARC 2012). Workers might be

exposed to relatively high concentrations of DEHP during the compounding of this plasticizer with resins and the manufacture of PVC plastic products. The National Institute for Occupational Safety and Health (NIOSH) estimated that about 340,000 workers (of which approximately 106,900 were female) were potentially exposed to DEHP in the early 1980s (NOES 1990). Workplace air levels of DEHP ranging from 0.02 to 4.1 mg/m^3 were reported at facilities using or manufacturing the compound (Hill et al. 2001; IARC 1982; Liss et al. 1985). These levels are below the current OSHA Permissible Exposure Limit (PEL) for DEHP for an 8-hour work-day of 5 mg/m^3 (OSHA 2016a, 2016b, 2016c).

Exposures of phthalate and PVC production workers to DEHP are estimated to be typically less than 143 and 286 µg/kg body weight/workday, respectively (NTP 2000). Hines et al. (2009a, 2011) studied four DEHP urinary phthalate metabolite concentrations among 156 workers in 2003–2005 from eight industry sectors. Mean end-shift concentrations in plastic industries in µg/g creatinine were 3.75–25.4 (phthalate manufacturing), 16.7–158 (PVC film), 10.2–34.6 (vehicle filters), 12.1–124 (PVC compounding), 5.41–36.2 (rubber hoses), 5.37–69.3 (rubber boots), and 12.1–54.6 (rubber gaskets). In nail salons, mean end-shift concentrations were 17.9–34.4 µg/g creatinine. Mean end-shift concentrations of urinary DEHP metabolites in workers exceeded general population levels by 8-, 6-, and 3-fold in PVC film manufacturing, PVC compounding, and rubber boot manufacturing, respectively, where occupational exposure to DEHP was strongest (Hines et al. 2009a). Daily DEHP intake estimates were 0.6–850 µg/kg/day, where the highest mean intakes occurred in PVC film manufacturing (17 µg/kg/day) and PVC compounding (12 µg/kg/day) (Hines et al. 2011). The types of industries with reported TRI releases is described in Table 5-16.

Table 5-16. Types of Industries with Reported TRI Releases

NAICS Code	Description
313	Textiles
325	Chemicals
326	Plastic and rubbers
327	Non-metallic mineral products
331	Primary metals
332	Fabricated metals
334	Computers/electronic products
335	Electrical equipment
336	Transportation equipment
339	Miscellaneous manufacturing
4246	Chemical wholesalers

Table 5-16. Types of Industries with Reported TRI Releases

NAICS Code	Description
4247	Petroleum bulk terminals
526	Hazardous waste facilities

NAICS = North American Industry Classification System; TRI = Toxics Release Inventory

Source: TRI16 2018

Children are exposed to DEHP orally from mouthing toys and other soft PVC products and from ingestion of food, via inhalation from ambient and indoor air and from ingestion of house dust, and dermally from handling materials containing DEHP. In addition, children are potentially exposed from medical devices via the inhalation, dermal, oral, and intravenous routes. Exposures from medical devices will be treated separately in this section. It has been predicted that toddlers and infants are exposed to higher levels of DEHP than adults, with a major portion (as much as 35%) of this exposure resulting from the ingestion of contaminated dust (NTP 2006). It should be noted that assessing exposures to DEHP, and especially children's exposures, is difficult because the uses of DEHP, while constant for many years, have changed over the last 20 years (CPSC 1999; CPSIA 2008; Wilkinson and Lamb 1999). For example, manufacturers stopped using phthalates in teethers and rattles in early 1999 (CPSC 1999). Further, in 2008, Congress permanently banned DEHP in any amount >0.1% in children's toys and certain child care articles, such as those to help sleeping, feeding, sucking, or teething of children ≤3 years old (CPSIA 2008). This change, and others that might be made in the near future, makes an assessment of a child's exposure to DEHP more difficult than would otherwise be the case.

Just as is the case with the general population, food is likely the dominant source of oral exposure to DEHP for children. A Danish study published by Petersen and Breindahl (2000) estimated the dietary intake of DEHP in infants (based on measurements of DEHP in baby food and formula) to be between 0.005 and 0.010 mg/kg body weight. Drinking water is not anticipated to be a significant source of DEHP exposure. DEHP concentrations in human breast milk of 70–160 μg/kg milk (mean concentration of 93±37.5 μg/kg milk) and 0–110 μg/kg milk (mean concentration of 0.034±0.043 μg/kg milk) have been reported (FDA 2001). Calafat et al. (2004) reported a mean concentration of 7.8 ng/mL milk for MEHP, a DEHP metabolite, in three pooled breast milk samples. However, no information is available relating the concentration of DEHP in human breast milk obtained from women with high occupational exposures to DEHP or exposures that result from medical treatments (e.g., hemodialysis). One study explored the relationship of phthalate metabolites, including those of DEHP, in urine, serum, saliva, and breast milk

and potential routes of exposure using samples collected from 33 lactating mothers in North Carolina (Hines et al. 2009b); however, phthalates were detected in <50% of the samples collected across matrices, so a correlation could not be made. Of the total milk samples, only 8, 5, and 2% contained detectable levels of DEHP metabolites MECPP, MEHHP, and MEOHP, respectively, in low ppb concentrations (up to 0.4 µg/L). As previously noted, this study is limited by small sample size and low detection rate.

A source of DEHP exposure for young children by the oral route might be plastic toys. The exposure will be dependent on the time that a child spends mouthing a toy and the DEHP content of the toy. Information on children's mouthing behavior is available and indicates that the behavior is dependent on the age of the child and the items mouthed (CPSC 2001; Juberg et al. 2001). Juberg et al. (2001) found that children spend an average of 23 minutes/day (children between the ages of 0 and 18 months) and 5 minutes/day (children between the ages of 19 and 36 months) mouthing toys and teethers; these times are shorter than the estimated mouthing times (e.g., 1–3 hours) found elsewhere (Health Canada 1998). These average mouthing times provided by Juberg et al. (2001) included children who did not exhibit mouthing behavior. If the averages included only children exhibiting mouthing behavior, then the time spent by these children mouthing teethers and toys increases to 48 minutes/day (children between the ages of 0 and 18 months) and 41 minutes/day (children between the ages of 19 and 36 months). Juberg et al. (2001) also reported pacifier use to average 108±187 (mean±1 standard deviation [SD]) minutes/day for children ages 0–18 months and 126±246 minutes/day for children ages 19–36 months. However, manufacturers have discontinued the use of DEHP in pacifiers, teethers, rattles, and toys designed for very young children (CPSC 1999). Therefore, the mouthing of pacifiers, teethers, and toys is not expected to be a significant route of exposure of young children to DEHP. Yet, families might hand down toys containing DEHP from older children rather than buy new toys that contain no DEHP. At the present time, however, sufficient information is not available to quantify these exposures.

Some research has been conducted to examine the migration of DEHP and other plasticizers from PVC into saliva. Steiner et al. (1998) reported that migration of DEHP from PVC into a saliva simulant was dependent on the contact time and agitation of the test matrix. *In vivo* studies of the migration of DEHP into human saliva from four adult volunteers chewing PVC balls (185 mg DEHP/g) showed a migration rate of 44.4 µg/10 cm^2/hour (Niino et al. 2001). However, no other studies, especially in children, are available evaluating DEHP migration rates in toys.

Other potential sources of oral exposure for young children, as well as dermal exposure to all children, include general household items made from PVC including dolls, furniture upholstery, floor tiles, shower

curtains, and tablecloths (all of which are available for mouthing by children in addition to touching). In addition, young children might be exposed to DEHP when wearing such items as rainwear and shoes made from PVC. Dermal uptake of DEHP from PVC film to rat skin was found to be low, only 0.24 μg/cm^2-hour (Deisinger et al. 1998), but is expected to be 2–4 times lower for human skin (Barber et al. 1992; Scott et al. 1987). Gong et al. (2014) reported an estimated median total dermal adsorption from skin surface lipids of 0.66 μg/kg/day for DEHP for adults. Oral exposure also might occur when PVC items containing DEHP are handled by children, and then the children's hands are mouthed. However, no specific reference to DEHP transfer from items to skin was found in the available literature. Therefore, sufficient information is not available to assess this route of exposure to DEHP.

Children might have inhalation exposures from both vapor and particle bound DEHP as well as oral exposure to DEHP from inhalation of large particles containing DEHP followed by deposition in the upper airways and swallowing (Hill et al. 2001). Øie et al. (1997) reported that sedimented dust samples from 38 dwellings in Oslo, Norway (including samples taken from sheets in a child's bed and floor in a child's bedroom) contained an average of 640 μg/g sedimented dust (100–1,610 μg/g), while suspended particulate matter from six dwellings contained an average of 600 μg/g (24–94 μg/g). The authors noted that exposure to particle-bound DEHP is 0.4–1.2 μg/day for adults, but suggested that children, and especially small children, are "subject to the highest exposure risk" because they usually have small rooms that have higher surface to volume ratios and few doors or windows. In a study of 390 homes in Sweden, DEHP was found in nearly all dust samples collected (99.1%) from 346 children's bedrooms at mean and median concentrations of 1.31 and 0.77 mg/g dust, respectively (Bornehag et al. 2005). The authors found an association between DEHP concentrations in dust and the amount of PVC used as flooring and wall material, where bedrooms with PVC flooring (n=186) had a median DEHP concentration of 0.868 mg/g dust as opposed to a median concentration of 0.70 mg/g dust in bedrooms with no PVC flooring (n=157). Children's exposures to DEHP from inhalation of outdoor air is likely small because of the relatively low ambient concentrations (Doull et al. 1999; Huber et al. 1996). While the database of outdoor concentrations is dated (1970s through the 1980s), the concentrations appear to be very consistent both spatially and temporally.

A possible exception to the anticipated low exposure from inhalation to outdoor air might be in the vicinity of hazardous waste sites containing large concentrations of DEHP or use facilities. DEHP has a low volatility and is not expected to enter the air extensively; nonetheless, Thurén and Larsson (1990) noted higher concentrations of DEHP near a facility that used it, indicating that somewhat higher concentrations might be anticipated near use or storage facilities. Those industries that emitted

>10,000 pounds into the air in 2016 were chemical industries (TRI16 2018). Children living near the vicinity of one of these facilities might be exposed to somewhat elevated concentrations of DEHP, although exact concentrations are not known.

Children's exposures to DEHP during medical procedures have been reported (Hill et al. 2001; Karle et al. 1997; Latini and Avery 1999; NTP 2000; Plonait et al. 1993; Shneider et al. 1991). Shneider et al. (1991) reported that serum DEHP concentrations varied depending on the nature of the treatment. They reported that for an infant cardiopulmonary bypass, pediatric hemodialysis, exchange transfusion, and ECMO, serum DEHP concentrations ranges were 1.1–5.1, 0.4–4.2, 5.4–21.5, and 18–98 μg/mL, respectively. Karle et al. (1997) confirmed this study, but reported lower concentrations. The authors reported the results of blood DEHP concentrations using three different ECMO circuit designs (small surface area, larger surface area, and small surface area but with heparin-bonded tubing). The results indicated that DEHP leaches from ECMO circuits and that the exposure potential is correlated with the surface area of the tubing. There was almost no exposure for patients using the heparin-bonded circuit. After 3 days, DEHP concentrations in 18 infants averaged 4.9 μg/mL; the highest level seen was 8.3±5.7 μg/mL. Karle et al. (1997) calculated that DEHP exposures during ECMO therapy averaged 1.2 mg/kg (2.0 mg/kg maximum) for a 3-day exposure, based on an average patient weight of 3.3 kg and an average blood volume of 800 mL for the 18 infants studied. Patients treated for longer periods did not have higher DEHP concentrations during treatment. The study authors also reported that DEHP concentrations were below the detection limit in all patients before and after decannulation.

Latini and Avery (1999) reported that 60–120 mg of DEHP/g of tube was removed from endotracheal tubes during use (range of 44 samples). Plonait et al. (1993) studied 16 newborn infants receiving blood exchange transfusions. The authors calculated exposures of 1.2–22.6 mg/kg-body weight, based on the volume of blood transfused and the mean DEHP concentration in the plasma of the blood units. The study authors reported that for three infants, DEHP eliminated in the waste (exchanged) blood accounted for 12.5, 22.9, and 26.5% of the DEHP accumulated during transfusions, respectively (further details on this analysis were not available). The authors reported that no correlation was found between the volume of blood transfused and the serum DEHP concentration immediately after the transfusion. There was also no correlation between the concentration of DEHP in the plasma and the storage time of the red cell bag. The authors reported that serum DEHP concentrations decreased rapidly after the transfusion was complete. Plonait et al. (1993) also reported that ethylhexanoic acid concentrations in the urine of infants undergoing transfusion therapy was below the detection limit (45 ng/mL) before or during the transfusion, but ranged from 50 to 416 ng/mL (median 130 ng/mL) in six infants 6 hours after the transfusion. Peak

levels occurred within the first 18 hours, and then declined to close to the detection limit where they remained for 96 hours. Finally, these authors noted that for two infants, DEHP concentrations appeared to accumulate, resulting in higher concentrations in the post-exchange serum than the average DEHP concentration in the blood received by the patients.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Several population subgroups might have above-average exposure to DEHP. These include hemophiliacs and others who require frequent blood transfusions, dialysis patients who might be exposed to DEHP leached from the dialysis tubing (Section 5.5.4), and preterm infants (Doull et al. 1999; FDA 2001; Huber et al. 1996; Latini 2000; NTP 2000; Tickner et al. 2001). Estimates of exposure levels indicate that hemophiliacs might be exposed up to 1–2 mg/day and dialysis patients might receive average doses of 40 mg/day (Pollack et al. 1985a; Wams 1987). Faouzi et al. (1999) estimated that dialysis patients received an average of 75 mg of DEHP per treatment and an average of almost 12 g of DEHP over a 1-year period (assuming dialysis treatments 3 times a week). Adult exposures to DEHP from hemodialysis have been estimated at <5–155 mg/day or <0.1–3.1 mg/kg/day and can vary considerably between patients (Dine et al. 2000; FDA 2001; Huber et al. 1996; NTP 2000). Infants receiving exchange transfusions might be exposed to >4 mg/kg/day (FDA 2001; Sjöberg et al. 1985c), based on a worst-case scenario. Plonait et al. (1993) reported higher plasma concentrations than those in the Sjöberg et al. (1985c) study, but the blood units used had a lower initial DEHP concentration. Plonait et al. (1993) suggest that this can be explained by pauses during the exchange transfusion during the Sjöberg et al. (1985c) study, which resulted in a lowering of the DEHP concentration. Faouzi et al. (1994) reported that administration of teniposide is sometimes associated with a nonionic surfactant polyoxyethylated castor oil. The presence of this surfactant increases the concentration of DEHP that is leached from the PVC bags into the administered solution. The authors reported that 52 mg was extracted at 48-hour room temperature storage. Preterm infants can be exposed to DEHP at levels estimated to be as high as 10–20 mg/day during the course of their care (Loff et al. 2000). Measured concentrations of DEHP in TPN solutions (423±47 μg/mL), blood products (platelet-rich plasma, 13.9±2.5 μg/mL; fresh frozen plasma, 24.9±17 μg/mL), and selected drugs (propofol, 655±96 μg/mL) have been obtained in these solutions/products as a consequence of contact with PVC bags and tubing. Inoue et al. (2005) reported that the maximum exposure to DEHP released from blood bags would be 0.7 mg/kg body weight/day. Exposures to DEHP can be especially high for infants receiving TPN solutions (contains approximately 20% lipid emulsions), where a 24-hour infusion can deliver up to an estimated 10 mg of DEHP (Loff et al. 2000). It has been estimated that newborns and infants undergoing medical procedures, such as

transfusions, ECMO, and TPN might be exposed to DEHP levels ranging from 0.13 to 6.0 mg/kg/day (NTP 2006). The FDA's DEHP exposure estimates resulting from various medical treatments are presented in Table 5-17.

Table 5-17. FDA Estimates of DEHP Exposures Resulting from Medical Treatments

	Estimated DEHP dose (mg/kg body weight/day)	
Medical procedure	70 kg adult	4 kg neonate
Crystalloid IV solution infusion	0.005	0.03
Infusion of pharmaceuticals with solubilization vehicles		
Administered according to manufacturer instructions	0.04	0.03
Mixed and stored at room temperature for 24 hours	0.15	
TPN administration		
Without added lipid	0.03	0.03
With added lipid	0.13	2.5
Administered via ethyl vinyl acetate bag and PVC tubing	0.06	
Blood transfusion		
Trauma patient	8.5	
Transfusion/ECMO in adult patients	3.0	
Exchange transfusion in neonates		22.6
Replacement transfusions in neonates in NICU		0.3
Replacement transfusions to treat anemia in chemotherapy and sickle cell disease patients	0.09	
Replacement transfusions in patients undergoing coronary artery bypass grafting	0.28	
Treatment of cryodisorders with cryoprecipitate	0.03	
Cardiopulmonary bypass		
Coronary artery bypass grafting	1	
Orthotopic heart transplant	0.3	
Artificial heart transplant	2.4	
ECMO		14
Apheresis	0.03	
Hemodialysis	0.36	
Peritoneal dialysis	<0.01	
Enteral nutrition	0.14	0.14

Table 5-17. FDA Estimates of DEHP Exposures Resulting from Medical Treatments

	Estimated DEHP dose (mg/kg body weight/day)	
Medical procedure	70 kg adult	4 kg neonate
Aggregate exposures of NICU infants undergoing IV administration of sedatives, IV administration of TPN, and replacement transfusion		2.83

DEHP = di(2-ethylhexyl)phthalate; ECMO = extracorporeal membrane oxygenation; FDA = Food and Drug Administration; IV = intravenous; NICU = neonatal intensive care unit; PVC = polyvinyl chloride; TPN = total parenteral nutrition

Source: NTP 2006

Since the permanent ban of DEHP in children's toys or clothing articles, the main source of exposures are food, beverages, and drugs via direct ingestion (CPSC 2014; Lioy et al. 2015).

As discussed in Section 5.6, workers in industries manufacturing or using DEHP plasticizer might be frequently exposed to above-average levels of this compound. Firefighters and other emergency workers are also at a greater risk of DEHP exposure during structural fires due to potential release of DEHP from burning materials (Alexander and Baxter 2016; Lacey et al. 2014). Those living near industrial facilities or hazardous waste sites with higher than average levels of DEHP in water might also have potential above-average exposure (Section 5.5).

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

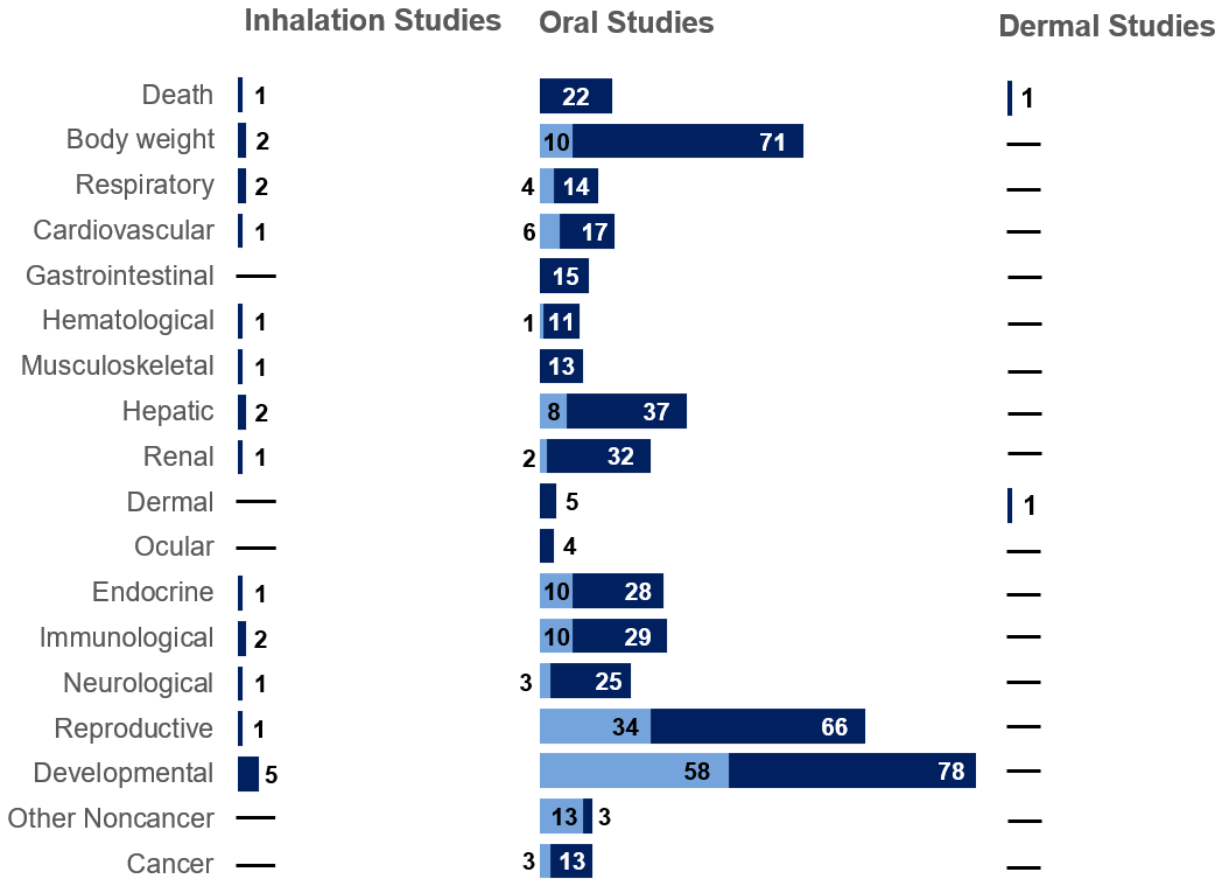
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to DEHP that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of DEHP. The number of human and animal 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



*Includes only studies discussed in Chapter 2; the number of studies include those finding no effect; most studies examined multiple endpoints.

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 a provisional MRL, a NOAEL value has not been established for the most sensitive effect (altered glucose homeostasis in offspring). Additionally, 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 provisional acute-duration oral MRL.

Intermediate-Duration MRLs. The available intermediate inhalation and oral databases were considered adequate for derivation of provisional 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 provisional 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 provisional MRLs.

Immunological. Low-exposure studies designed to identify a NOAEL for adjuvant effects of DEHP following oral exposure would decrease the uncertainties in the provisional MRLs. In particular, a study evaluating these endpoints following chronic oral exposure would fill a current data gap. 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 provisional 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 provisional 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. 2013); therefore, additional toxicokinetic data for these exposure routes would be useful.

Comparative Toxicokinetics. The development of a human model for DEHP and the optimization and validation of available PBPK models (Adachi et al. 2015; Keyes 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 2010; TRI15 2016). 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.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI) contains this information from 1988 to 2015.

While information on uses is available (CPSC 2010), 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 and soils and ingestion of 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. Detection of DEHP in blood, urine, and adipose tissue is an 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 child care 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			
Kelsey Lynne Clancy Dzwilewski	University of Illinois at Urbana-Champaign	Impact of prenatal exposure to endocrine disruptors on infant cognition	NIEHS
Russ B. Hauser	Harvard School of Public Health	Human exposure to bisphenol A, phthalates and fertility, pregnancy outcomes	NIEHS
Ran Jin	University of Southern California	Prenatal environmental exposures and markers of fatty liver disease in childhood	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
Katherine Whitney Reeves	University of Massachusetts Amherst	Phthalate metabolites and breast cancer risk in the Women's Health Initiative	NIEHS
Heather M. Stapleton	Duke University	Children's exposure to SVOC mixtures indoors and associations with obesity	NIEHS
Leonardo Trasande	New York University School of Medicine	Environmental oxidant stressors in pediatric chronic kidney disease	NIDDK
Leonardo Trasande	New York University School of Medicine	Phthalates, BPA, trajectories of in and ex utero growth and cardiometabolic risks	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	NYU pediatric obesity, metabolism, and kidney cohort center	Office of the Director, NIH
Derek Wildman	University of Illinois at Urbana-Champaign	Placental RNA expression as a function of gestational age and environmental exposures	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	Endocrine disrupting chemicals, diet and gonadal toxicity	NIEHS
Jodi A. Flaws	University of Illinois at Urbana-Champaign	Phthalates and ovarian toxicity	NIEHS
Nikki Gillum Potnack	Children's Research Institute	The effect of endocrine disrupting chemicals on cardiac physiology	NIEHS
Mehmet Uzumcu	Rutgers University	Detrimental effects on female reproduction of in utero and neonatal exposure to common phthalates DEHP and its replacement DINP	NIEHS

Table 6-1. Ongoing Studies on DEHP

Investigator	Affiliation	Research description	Sponsor
Mechanistic studies			
Dana Dolinoy	University of Michigan at Ann Arbor	Developmental exposures and diet: epigenetics of metabolic syndrome	NIEHS
Dana Dolinoy	University of Michigan	Perinatal exposures, tissue- and cell-specific epigenomics, and lifecourse outcomes	NIEHS
Rita K. Loch-Caruso	Northeastern University	Toxicant activation of pathways of preterm birth in gestational tissue	NIEHS
Motoko Mukai	Cornell University	Effect of endocrine disrupting compounds on gonadotropin-releasing hormone and its mechanisms	NIEHS
Romano A. Nowak	University of Illinois at Urbana-Champaign	The role of the peritoneum in the pathogenesis of endometriosis	NIEHS
Richard J. Pilsner	University of Massachusetts Amherst	Embryonic inheritance of sperm methylome after adult exposure to phthalates	NIEHS
Richard J. Pilsner	University of Massachusetts Amherst	Male preconception phthalates and offspring embryo and sperm allele-specific methylome programming	NIEHS
Richard J. Pilsner	University of Massachusetts Amherst	Paternal preconception phthalates and reproductive health – potential mediation through sperm DNA methylation	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
Susan E. Waltz	University of Cincinnati	Early exposure to phthalate and obesity: the role of PCNA tyrosine phosphorylation	NIEHS
Toxicokinetics/biomarkers			
Nathaniel W. Snyder	Drexel University	Prenatal biomarkers of exposure and individual susceptibility to endocrine disrupting chemicals	NIEHS

BPA = bisphenol A; DEHP = di(2-ethylhexyl)phthalate; DINP = diisononyl phthalate; DNA = deoxyribonucleic acid
NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NYU = New York University;
PCNA = proliferating cell nuclear antigen; RNA = ribonucleic acid; SVOC = semivolatile organic compound

Source: RePORTER 2018

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding DEHP in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for DEHP.

Table 7-1. Regulations and Guidelines Applicable to DEHP

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 1988
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018
	DWEL	0.7 mg/L	
	10^{-4} cancer risk	0.3 mg/L	
	National primary drinking water regulations		EPA 2009b
	Maximum contaminant level	0.006 mg/L	
	Public health goal	0	
	RfD	$2x10^{-2}$ mg/kg/day[a]	IRIS 1988
WHO	Drinking water quality guidelines		WHO 2017
	Guideline value	0.008 mg/L (8 µg/L)	
	Tolerable daily intake	25 µg/kg body weight	
FDA	EAFUS	No data[b]	FDA 2013
	Cancer		
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016b
EPA	Carcinogenicity classification	Group B2[c]	IRIS 1988
IARC	Carcinogenicity classification	Group 2B[d]	IARC 2013, 2017
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	5 mg/m^3	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	5 mg/m^3	NIOSH 2016
	STEL	10 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to DEHP

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
DOE	PACs-air		DOE 2016a
	DEHP		
	PAC-1[e]	10 mg/m^3	
	PAC-2[e]	1,000 mg/m^3	
	PAC-3[e]	6,100 mg/m^3	

[a]The RfD is based on a LOAEL of 19 mg/kg/day for increased relative liver weight in guinea pigs following subchronic oral exposure
[b]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[c]Group B2: probable human carcinogen.
[d]Group 2B: possibly carcinogenic to humans.
[e]Definitions of PAC terminology are available from DOE (2016b).

AEGL = acute exposure guideline levels; DEHP = di(2-ethylhexyl)phthalate; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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 route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. 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 NOAEL/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) 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 substance-induced endpoint 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 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide 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 MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: December 2019
Profile Status: Final, Draft for Public Comment
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL. The intermediate-duration MRL should be protective of acute inhalation exposures.

Rationale for Not Deriving an MRL: Only two acute inhalation studies were identified. Larsen et al. (2007) reported decreased tidal volume and increased respiratory rate in mice exposed to 19 ppm for 60 minutes; respiratory function was the only endpoint examined. The other available study was a developmental study by Merkle et al. (1988) that reported an increase in the percent of litters with visceral retardations following maternal exposure to 21 ppm on GDs 6–15; observed retardations were characterized as delays in development (not variations or anomalies). Incidence data were not provided for any specific lesions described as visceral retardations; however, the study authors indicated that effects were "mostly" renal pelvis dilation. These data are considered inadequate for MRL derivation due to limited reporting of lesion incidence, lack of fetus data for each litter (benchmark dose [BMD] modeling not advisable), and the fact that reported retardations may be developmental effects from multiple body systems (e.g., renal, reproductive, cardiovascular, etc.). In addition, no acute studies evaluated the most sensitive effects observed in intermediate-duration inhalation studies (immune effects, reproductive toxicity). These key data gaps preclude derivation of an acute-duration inhalation MRL; however, the provisional intermediate-duration inhalation MRL should be protective of acute exposures.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	DEHP
CAS Numbers:	117-81-7
Date:	December 2019
Profile Status:	Final, Draft for Public Comment
Route:	Inhalation
Duration:	Intermediate
MRL:	0.0002 ppm (provisional)
Critical Effect:	Altered reproductive system in developing males and females
Reference:	Kurahashi et al. 2005; Ma et al. 2006
Point of Departure:	$LOAEL_{HEC}$ of 0.05 ppm
Uncertainty Factor:	300
LSE Graph Key:	4, 5, 6, 7
Species:	Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of 0.0002 ppm was derived for DEHP based on evidence of reproductive effects in developing male and female rats exposed to 0.3 ppm for 3–9 weeks (6 hours/day, 5 days/week) after weaning. Observed effects included increased plasma testosterone in young males prior to sexual development, increased plasma testosterone and seminal vesicle weight in sexually mature males, and accelerated vaginal opening and first estrous in females (Kurahashi et al. 2005; Ma et al. 2006). The provisional MRL is based on the $LOAEL_{HEC}$ (adjusted for continuous exposure) of 0.05 ppm and a total uncertainty factor of 300 (3 for extrapolation from animals to humans after dosimetric adjustment, 10 for human variability, and 10 for use of a LOAEL).

Selection of the Critical Effect and Principal Study: Available data indicate that the immunological and developing reproductive systems are the most sensitive following intermediate-duration inhalation exposure to DEHP (Table A-1). While inhalation data are limited, these endpoints have been identified as sensitive targets of oral DEHP exposure (see oral MRL worksheets). BMD modeling was attempted for developmental endpoints reported by Ma et al. (2006) and Kurahashi et al. (2005); however, data were not amenable to modeling (no adequate models identified). Data from Larsen et al. (2007) were not modeled because exact animal numbers/group were not reported. After review of the available data, the developmental effects on the male and female reproductive system were selected as the critical effect because: (1) the study design for the immunological study is a poor model of intermediate-duration exposure since animals were only exposed once per week after the initial 2 weeks (and only 20 minutes/day, 5 days/week for the first 2 weeks, and (2) it is unclear whether an MRL based on the NOAEL of 0.11 ppm for immune effects in sensitized animals would be protective of developmental effects since a developmental NOAEL was not identified (i.e., developmental effects could potentially occur at 0.11 ppm). The developmental studies by Kurahashi et al. (2005) and Ma et al. (2006) were selected as co-principal studies.

Table A-1. Summary of Candidate POD Values for Intermediate Inhalation MRL for DEHP

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Immune effects					
BALB/c mouse	14 weeks (20 minutes/day, 5 days/week for 2 weeks plus 1 day/week for 12 weeks)	0.11	0.81	Enhanced immune response to OVA challenge in sensitized animals	Larsen et al. 2007
Developmental effects					
Wistar rat	PNWs 3–6 or 3–12 (6 hours/day, 5 days/week)	ND	0.3[a]	Accelerated vaginal opening and first estrous	Ma et al. 2006
Wistar rat	PNWs 4–8 or 4–12 (6 hours/day, 5 days/week)	ND	0.3[a]	Increased plasma testosterone (both time points); increased seminal vesicle weight (PNW 12 only)	Kurahashi et al. 2005

[a]Selected POD.

DEHP = di(2-ethylhexyl)phthalate; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; ND = not determined; OVA = ovalbumin; PNW = postnatal week; POD = point of departure

Summary of the Principal Studies:

Kurahashi N, Kondo T, Omura M, et al. 2005. The effects of subacute inhalation of di(2-ethylhexyl)phthalate (DEHP) on the testes of prepubertal Wistar rats. J Occup Health 47(5):437-444.

Ma M, Kondo T, Ban S, et al. 2006. Exposure of prepubertal female rats to inhaled di(2-ethylhexyl)phthalate affects the onset of puberty and postpubertal reproductive functions. Toxicol Sci 93(1):164-171.

Kurahashi et al. (2005) exposed groups of PND 28 prepubertal male rats to DEHP vapor for 4 or 8 weeks (6 hours/day, 5 days/week) at concentrations of 0, 5, or 25 mg/m^3. At sacrifice on PND 56 (around the time of sexual maturation) or PND 84 (sexually mature), body weight was recorded and blood was collected for determination of plasma testosterone, LH, and FSH. Testes, epididymides, seminal vesicles, and ventral prostate were removed and weighed. One testis was examined for histopathologic changes, and the other testis was evaluated for mRNA expression of androgen biosynthesis enzyme, cytochrome P450scc, 3βHSD, CYP17, and CYP19.

No statistically significant, exposure-related changes in body weight were observed. The only statistically significant reproductive organ weight change was a 30–31% increase in relative seminal vesicle weights in exposed groups at 8 weeks. Plasma testosterone was increased by approximately 2–4-fold in the low- and high-exposure groups at both timepoints, compared with respective controls. The increase was significant at both exposure levels after 8 weeks, but only at the low exposure level after 4 weeks. No exposure-related changes were observed in plasma LH or FSH or mRNA expression levels

at 4 or 8 weeks. No exposure-related histopathological changes in the testes were observed at either time point.

Ma et al. (2006) exposed groups of PND 21 prepubertal female rats to DEHP vapor for 3 or 9 weeks (6 hours/day, 5 days/week) at concentrations of 0, 5, or 25 mg/m^3. Food and water intake were measured. Body weight and vaginal opening were monitored daily. Beginning on the day of vaginal opening, vaginal smears were examined until the first estrous cycle was completed; the age at first estrus was recorded. For the group exposed for 3 weeks, vaginal smears were collected again just prior to necropsy on PND 42. For the group exposed for 9 weeks, estrous cyclicity was evaluated from PND 49 to 84, and animals were sacrificed on PNDs 84–85. Blood was collected at necropsy for determination of FSH, LH, estradiol, testosterone, and cholesterol levels. Lungs, liver, kidneys, ovaries, and uterus were removed and weighed. The vagina, right ovary, and uterus were prepared for histology. Left ovaries were removed and RNA was extracted for reverse transcription polymerase chain reaction (RT-PCR) analysis of the genes encoding enzymes responsible for estradiol biosynthesis.

No clinical signs of toxicity were observed. Body weights were significantly decreased by ~10–15% by the end of the 9-week exposure period in the high-exposure group; however, body weights at vaginal opening and first estrus were comparable to controls in all exposed groups. Mean age at vaginal opening and first estrus were significantly earlier in both exposed groups by 2.3–2.8 days in the 3-week experiment and 1.7–2.9 days in the 9-week experiment, compared with respective controls. In the 9-week experiment, the number of irregular estrous cycles was significantly elevated in the high-exposure group (25/61) compared with the control group (12/72). Serum LH and estradiol were significantly elevated by ~1.5–3-fold at the high exposure level following 3-week exposure, compared with controls; however, no exposure-related changes were observed in serum hormone levels following exposure for 9 weeks. Serum cholesterol was significantly elevated by 18–25% in both exposure groups at both time points, compared with controls. No exposure-related changes in organ weights were observed; histology data were not reported. The only exposure-related change in estradiol biosynthesis genes was a 145% increase in the mRNA level of CYP19 in the high-exposure group after 9 weeks, compared with controls.

Selection of the Point of Departure: The LOAEL of 5 mg/m^3 (0.3 ppm) for male and female developmental reproductive effects was selected as the POD for the provisional intermediate-duration inhalation MRL.

Calculations: Exposure levels of 0, 5, and 25 mg/m^3 were converted to concentrations of 0, 0.3, and 1.6 ppm using a molecular weight of 390.57 g/mol, assuming 25 °C and 1 atmosphere (1 ppm=15.94 mg/m^3).

Adjustment for Intermittent Exposure: The POD of 0.3 ppm was adjusted for time-weighted, continuous exposure as follows: 0.3 ppm × 6 hours/24 hours × 5 days/7 days = 0.05 ppm.

Human Equivalent Concentration: The adjusted LOAEL of 0.05 ppm was converted into a human equivalent concentration (HEC) for extrarespiratory effects using EPA reference concentration (RfC) methodology (EPA 1994), treating DEHP as a category 3 gas and using the default animal:human blood gas partition coefficient of 1 (DEHP value unknown):

HEC_{EXRESP} = $LOAEL_{adj}$ × ratio of animal:human blood gas partition coefficients
HEC_{EXRESP} = 0.05 ppm × 1 [default value]
HEC_{EXRESP} = 0.05 ppm

Uncertainty Factor: The $LOAEL_{HEC}$ is divided by a total uncertainty factor of 300:

- 10 for use of a LOAEL
- 10 for human variability
- 3 for extrapolation from animals to humans after dosimetric adjustment

Provisional MRL = $LOAEL_{HEC}$ ÷ UFs
0.05 ppm ÷ (3 × 10 × 10) = 0.0002 ppm (0.003 mg/m^3)

Other Additional Studies or Pertinent Information: No other inhalation studies evaluated these developmental reproductive endpoints following exposure to DEHP; however, Klimisch et al. (1991, 1992) did not observe impaired male fertility or testicular lesions in Wistar rats following exposure to concentrations up to 63 ppm for 4 weeks during adulthood. Evidence from oral studies indicates that both the developing and adult reproductive systems are a sensitive target of DEHP toxicity in rodents. In sexually immature males, the lowest identified LOAELs include potentially transient changes in reproductive organ weight and sperm parameters in mouse offspring at maternal doses of 0.05 mg/kg/day (Pocar et al. 2012), with evidence for severe and permanent reproductive tract malformations and lesions in rat offspring at maternal doses of 3–10 mg/kg/day (Arcadi et al. 1998; Christiansen et al. 2010; Klinefelter et al. 2012; Lin et al. 2008, 2009; Vo et al. 2009b). In sexually mature male rodents, the lowest identified LOAELs include various effects on the male reproductive system at oral doses of 10 mg/kg/day, including altered serum hormones, decreased Leydig cell hormone production, and Leydig cell proliferation (Akingbemi et al. 2004; Guo et al. 2013; Li et al. 2012a). In females, the lowest identified LOAELs include delayed meiotic progression of germ cells and accelerated folliculogenesis in mouse offspring at maternal doses of 0.04 mg/kg/day (Zhang et al. 2015) and evidence for decreased fertility in adult female mice at 130 mg/kg/day (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984).

Epidemiological studies show potential associations between altered male reproductive development (cryptorchidism, hypospadias, hydrocele, and/or AGD) and maternal DEHP exposure (Barrett et al. 2016; Sathyanarayana et al. 2106a; Suzuki et al. 2012; Swan 2008; Wenzel et al. 2018). Epidemiological studies also suggest that DEHP exposure may be associated with alterations in adult male reproductive endpoints, including decreased serum testosterone (Chang et al. 2015; Joensen et al. 2012; Jurewicz et al. 2013; Meeker et al. 2009a; Pan et al. 2006; Wang et al. 2016) and reduced sperm motility and/or concentration (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Huang et al. 2014b; Jurewicz et al. 2013).

In a systematic review, NAS (2017) concluded that DEHP is presumed to be a reproductive hazard to humans based on evidence integration of the animal and the human evidence on DEHP and effects on AGD and fetal testosterone. DEHP is also suspected to be a reproductive hazard to humans based on evidence integration of the animal evidence and the human evidence on DEHP and fetal hypospadias (NAS 2017).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: December 2019
Profile Status: Final, Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration studies examining noncarcinogenic effects following inhalation exposure were identified.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: December 2019
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Acute
MRL: 0.003 mg/kg/day (provisional)
Critical Effect: Altered glucose homeostasis in adult offspring following fetal exposure
Reference: Rajesh and Balasubramanian 2014a
Point of Departure: LOAEL of 1 mg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 37
Species: Rat

MRL Summary: A provisional acute-duration oral MRL of 0.003 mg/kg/day was derived for DEHP based on evidence of altered glucose homeostasis in adult rat offspring following maternal exposure to DEHP via gavage on GDs 9–21, including elevated serum glucose, decreased serum insulin, altered glucose and insulin tolerance, reduced insulin receptors, and reduced glucose uptake and oxidation in skeletal muscle (Rajesh and Balasubramanian 2014a). These effects were observed at all tested doses (≥1 mg/kg/day). The provisional MRL is based on the LOAEL of 1 mg/kg/day for altered glucose homeostasis following developmental exposure and a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for human variability, and 10 for extrapolation from animals to humans).

Selection of the Critical Effect: Numerous studies have evaluated the toxicity of DEHP following acute oral exposure. The most sensitive effects identified in acute oral studies included altered glucose homeostasis in offspring following developmental exposure and male reproductive toxicity following both developmental and adult exposure (Table A-2). In order to identify the most sensitive effect, BMD modeling was attempted for critical endpoints in Table A-2 when data were amenable to modeling, including measures of glucose homeostasis in offspring (Rajesh and Balasubramanian 2014a), Leydig cell clustering in fetal testes (Klinefelter et al. 2012), and testosterone production in Leydig cells from sexually immature testes (Akingbemi et al. 2001). Leydig cell proliferation data by Li et al. (2012a) and Guo et al. (2013) and sperm effects data by Vo et al. (2009a) were inadequate for modeling. The data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.6.0) using a BMR of 1 SD. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Adequate fit was achieved based on goodness-of-fit statistics for some of the available data sets from the Rajesh and Balasubramanian (2014a) and Akingbemi et al. (2001) studies; however, upon visual inspection, the models were highly influenced by the last dose, forcing model fit when there normally would be none (graphs available upon request). Dropping the highest dose from the female glucose oxidation data (the most sensitive endpoint) (Rajesh and Balasubramanina 2014a) resulted in questionable or unusable models. Because modeling was not suitable, ATSDR reverted to using the LOAEL calculation method to identify the candidate PODs for the Rajesh and Balasubramanian (2014a) and Akingbemi et al. (2001) studies.

Table A-2. Summary of Candidate POD Values for Acute Oral MRL for DEHP

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Developmental effects					
Long-Evans rat	PNDs 35–48 (GO)	1	10	Reduced testosterone production in Leydig cells	Akingbemi et al. 2001
Wistar rat	GDs 9–21 (GO)	ND	1[a]	Altered glucose homeostasis in adult offspring	Rajesh and Balasubramanian 2014a
Sprague-Dawley rat	GDs 13–19 (GO)	ND	10	Leydig cell clustering in fetal testes	Klinefelter et al. 2012
Sprague-Dawley rat	GDs 11–21 (GO)	ND	10	Sperm effects at PND 63	Vo et al. 2009a
Reproductive effects					
Long-Evans rat	14 days (GO)	ND	10	Increased Leydig cell number and proliferation	Li et al. 2012a
Long-Evans rat	7–11 days (GO)	ND	10	Increased Leydig cell proliferation	Guo et al. 2013

[a]Selected POD.

DEHP = di(2-ethylhexyl)phthalate; GD = gestation day; (GO) = gavage in oil vehicle; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; NA = not applicable (data unsuitable for modeling); ND = not determined; PND = postnatal day; POD = point of departure

Selection of the Principal Study: The acute oral study with the lowest identified POD (Rajesh and Balasubramanian 2014a) was selected as the principal study for the provisional acute oral MRL.

Summary of the Principal Study:

Rajesh P, Balasubramanian K. 2014a. Phthalate exposure in utero causes epigenetic changes and impairs insulin signalling. J Endocrinol 223(1):47-66.

Groups of pregnant Wistar rats (6/group) were administered DEHP at doses of 0, 1, 10, or 100 mg/kg/day via gavage in olive oil from GD 9 to 21 or until parturition. Litters were culled to 4/sex (day of culling not reported). Oral glucose tolerance and insulin tolerance tests were conducted in adult PND 60 offspring. Offspring were sacrificed around PND 60 (females were in diestrus phase). Body and visceral adipose weights were recorded. Blood was collected for analysis of serum glucose and insulin. Skeletal muscle was collected for analysis of genes and proteins involved in insulin signaling (RT-PCR, Western blot), DNA methylation, and evaluation of insulin receptors and glucose uptake and oxidation.

F1 male body weight was significantly reduced on PND 60 by 4, 12, and 19% at 1, 10, and 100 mg/kg/day, respectively, compared with control. F1 female body weight was similarly reduced by 8, 17, and 21%, respectively. In contrast, fat weight was significantly elevated in all dose groups, compared with control, by 2–7%. Fasting blood glucose was significantly elevated in both F1 males and females in

all dose groups by 16–49%, compared with control. Both insulin and insulin binding protein levels were significantly decreased in all dose groups by 21–70 and 13–36%, respectively. Elevated serum glucose levels were observed in both the glucose and insulin challenges. Additional significant findings observed in all dose groups included decreased glycogen content and decreased insulin binding, glucose uptake, and glucose oxidation in skeletal muscle. Several genes/proteins involved in insulin signaling were dysregulated. Key findings included decreased glucose transporter 4 (GLU4) gene expression, increased GLU4 phosphorylation (posttranslational modification that decreases activity), and epigenetic silencing of GLU4.

Selection of the Point of Departure: The LOAEL of 1 mg/kg/day for altered glucose homeostasis in adult rat offspring was selected as the basis of the provisional MRL.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The LOAEL is divided by a total uncertainty factor of 300:

- 10 for use of a LOAEL
- 3 for human variability; a full-factor of 10 was not warranted because the study population (F1 offspring exposed *in utero*) is considered a susceptible subpopulation since offspring are not fully developed until after puberty (or later)
- 10 for extrapolation from animals to humans

Provisional MRL = LOAEL ÷ UFs
1 mg/kg/day ÷ (10 x 3 x 10) = 0.003 mg/kg/day

Other Additional Studies or Pertinent Information: Altered glucose homeostasis was also observed at doses ≥1 mg/kg/day in rats following gestational plus lactational exposure or early postnatal exposure (Lin et al. 2011; Mangala Priya et al. 2014). In the gestational/lactational study, no changes in maternal serum insulin or blood glucose levels were observed at doses up to 6.25 mg/kg/day, indicating that developing offspring may be more susceptible to pancreatic toxicity (Lin et al. 2011). In adult rats, altered glucose homeostasis was also observed ≥10 mg/kg/day (lowest dose tested) for 30 days (Rajesh et al. 2013).

Available epidemiological studies suggest a potential association between impaired glucose homeostasis and DEHP exposure, with reported associations between increased fasting serum glucose or insulin resistance and higher levels of DEHP metabolites in urine in some studies (James-Todd et al. 2016a; Kim and Hong 2014; Kim et al. 2013; Sun et al. 2014a), but not others (Watkins et al. 2016).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	DEHP
CAS Numbers:	117-81-7
Date:	December 2019
Profile Status:	Final, Draft for Public Comment
Route:	Oral
Duration:	Intermediate
MRL:	0.0001 mg/kg/day (provisional)
Critical Effect:	Delayed meiotic progression of germ cells in GD 17.5 F1 fetuses; accelerated folliculogenesis in F1 and F2 PND 21 offspring
Reference:	Zhang et al. 2015
Point of Departure:	LOAEL of 0.04 mg/kg/day
Uncertainty Factor:	300
LSE Graph Key:	133
Species:	Mouse

MRL Summary: A provisional intermediate-duration oral MRL of 0.0001 mg/kg/day was derived for DEHP based on evidence of altered female reproductive development in F1 and F2 mouse offspring following F0 maternal exposure to 0.04 mg/kg/day from GD 0.5 to 18.5, compared with controls. The provisional MRL is based on the LOAEL of 0.04 mg/kg/day and a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for human variability, and 10 for extrapolation from animals to humans).

Selection of the Critical Effect: Numerous studies have evaluated the toxicity of DEHP following intermediate-duration oral exposure. The most sensitive effects identified in intermediate oral studies included immune adjuvant effects and developmental effects (ovarian developmental deficiency, decreased offspring body weight, impaired renal function and altered glucose homeostasis in offspring, and mild external dysgenesis of reproductive organs in male offspring); see Table A-3.

BMD modeling was attempted for immunological endpoints reported by Guo et al. (2012) and Han et al. (2014) and developmental renal endpoints in female offspring reported by Wei et al. (2012). Modeling was not attempted for additional datasets due to inadequate data reporting (Christiansen et al. 2010; Mangala Priya et al. 2014), identification of serious LOAELs (Lin et al. 2011; Pocar et al. 2012; Schmidt et al. 2012), or evaluation of high doses only (Yang et al. 2008). The only dataset providing an adequate statistical fit to the data using typical EPA methodology was OVA-specific serum IgG1 levels reported by Han et al. (2014); however, visual inspection indicated that models with all doses were highly influenced by the last dose, forcing model fit when there normally would be none (graph available upon request). Dropping the highest dose from the Han et al. (2014) dataset resulted in questionable or unusable models. Because modeling was not suitable, ATSDR reverted to using the LOAEL calculation method for the Han et al. (2014) study (0.03 mg/kg/day). When observable health effect endpoints are within 0.01 mg/kg/day, ATSDR may select studies that do not use a sensitized population realizing that BMD modeling and uncertainty factors influence the final calculated provisional MRL. Therefore, ATSDR considered the next lowest LOAEL of 0.04 mg/kg/day (Zhang et al. 2015) for calculating the provisional MRL.

Table A-3. Summary of Candidate POD Values for Intermediate Oral MRL for DEHP

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Immunological effects					
BALB/c mouse	28 days (GO)	ND	0.03	Enhanced immune response to OVA challenge in sensitized animals	Han et al. 2014
BALB/c mouse	52 days (GS)	ND	0.03	Enhanced immune response to OVA challenge in sensitized animals	Guo et al. 2012
Wistar rat	30 days (G)	ND	0.7	Enhanced immune response to OVA challenge in sensitized animals	Yang et al. 2008
Developmental					
CD-1 mouse	GD 0.5–18.5 (NS)	ND	0.04[a]	Delayed meiotic progression of germ cells in ovaries of GD 17.5 F1 fetuses; accelerated folliculogenesis in F1 and F2 PND 21 offspring	Zhang et al. 2015
CD-1 mouse	GD 0–PND 21 (F)	ND	0.05 (serious LOAEL)	>20% decrease in offspring body weight at PND 21 and 42; decrease in sperm count and viability, decrease in offspring seminal vesicle weight	Pocar et al. 2012
C3H/N mouse	1 week premating–PND 21 (F)	ND	0.05 (serious LOAEL)	>20% increase in offspring body weight at PND 21, increased visceral adipose tissue	Schmidt et al. 2012
Wistar rat	GD 0–PND 21 (GO)	ND	0.25	Impaired renal function in PNW 21 offspring, reduced pup weight at weaning	Wei et al. 2012
Wistar rat	PNDs 1–21 (GO)	ND	1	Altered glucose homeostasis in offspring	Mangala Priya et al. 2014
ICR mouse	GDs 8–17 (dams) and PNDs 3–7 (pups) (GO)	ND	1 (serious LOAEL)	>10% decrease in pup weight at PNW 2; increased relative brain weight at PNWs 2 and 4; decreased number and activity of dopaminergic neurons	Tanida et al. 2009

Table A-3. Summary of Candidate POD Values for Intermediate Oral MRL for DEHP

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Wistar rat	GD 0–PND 21 (GO)	ND	1.25 (serious LOAEL)	≥10% decrease in offspring weight; additional effects included decreased adipose tissue in offspring and pancreatic damage with impaired glucose homeostasis in adult offspring	Lin et al. 2011
Long-Evans rat	GD 1–PND 21 (W)	ND	3 (serious LOAEL)	Permanent testes damage and reversible liver and kidney damage	Arcadi et al. 1998
Wistar rat	GD 7–PND 16 (GO)	ND	3	Mild external dysgenesis of male offspring reproductive organs	Christiansen et al. 2010

[a]Selected POD.

DEHP = di(2-ethylhexyl)phthalate; (F) = feed; (G) = gavage (Tween-80 and sterile water vehicle); GD = gestation day; (GO) = gavage (oil vehicle); (GS) = gavage (TWEEN 80 plus saline vehicle); LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified (reported as "oral administration"; OVA = ovalbumin; PND = postnatal day; PNW = postnatal week; POD = point-of-departure; (W) = water

Selection of the Principal Study: The intermediate-duration oral study with the lowest identified developmental LOAEL (Zhang et al. 2015) was selected as the principal study for the provisional intermediate oral MRL (Table A-1).

Summary of the Principal Study:

Zhang XF, Zhang T, Han Z, et al. 2015. Transgenerational inheritance of ovarian development deficiency induced by maternal diethylhexyl phthalate exposure. Reprod Fertil Dev 27(8):1213-1221. http://doi.org/10.1071/rd14113.

Groups of plug positive female CD-1 mice (5/group) were administered DEHP at 0 or 0.04 mg/kg/day from GD 0.5 to 18.5 in saline containing 0.1% dimethylsulfoxide (DMSO); exact method of oral administration was not reported. Serum estradiol levels in F0 dams were measured on GD 12.5. F0 dams were allowed to deliver naturally and rear their young. Select female F1 offspring were mated with unexposed males. Folliculogenesis was assessed in F1 and F2 female offspring at PND 21. In a second set of experiments following the same exposure protocol, pregnant F0 and F1 mice were sacrificed on GD 13.5 for sodium bisulfite sequencing of female germ cells or GD 17.5 for analysis of oocyte meiosis in female fetuses. Total mRNA was extracted from female fetal genital ridges, ovary, and oocytes for RT-PCR.

Estradiol levels in exposed F0 mice were significantly decreased by 25%, compared with controls. Fetal meiotic progression of female germs cells in the fetal mouse ovary was significantly delayed, with increased percentage of immature leptotene and zygotene and decreased percentage of more mature

pachytene and diplotene oocytes in exposed fetuses, compared with controls. At GD 13.5, the meiosis-specific gene, *Stra8*, and its protein product were significantly reduced in exposed mice, and the gene was significantly more methylated. In PND 21 F1 offspring, altered folliculogenesis was observed, with rare follicles and large regions of germ-cell cysts; ovaries in control mice showed primarily primordial follicles. Further analysis showed accelerated folliculogenesis and premature ovary failure. The number of primordial follicles was significantly decreased, and the number of secondary follicles was significantly increased, in exposed PND 21 F1 and F2 females, compared with controls. Decreased expression of folliculogenesis-related genes (*Cx43*, *Egr3*, *Tff1*, and *Ptgs2*) was observed.

The only dose, 0.04 mg/kg/day, was identified as a developmental LOAEL for altered reproductive system development in F1 and F2 female mouse offspring. The decreased estradiol levels in F0 dams was not identified as a reproductive LOAEL because the biological significance is unknown in the absence of additional reproductive endpoint evaluation in F0 animals.

Selection of the Point of Departure: The LOAEL of 0.04 mg/kg/day for altered reproductive system development in F1 and F2 female mouse offspring was selected as the basis of the provisional MRL.

Adjustment for Intermittent Exposure: Not applicable.

Uncertainty Factor: The LOAEL is divided by a total uncertainty factor of 300:

- 10 for use of a LOAEL
- 3 for human variability; a full-factor of 10 was not warranted because the study population (offspring) is considered a susceptible subpopulation since offspring are not fully developed until after puberty (or later)
- 10 for extrapolation from animals to humans

Provisional MRL = LOAEL÷ UFs
0.04 mg/kg/day ÷ (10 x 3 x 10) = 0.0001 mg/kg/day

Other Additional Studies or Pertinent Information: As shown in Table A-3, several studies reported developmental effects at oral doses ranging from 0.04 to 3 mg/kg/day in intermediate-duration gestational and/or early postnatal studies; no NOAEL has been determined for developmental effects following intermediate-duration oral exposure. Additional higher-dose developmental studies also reported altered female reproductive system development following early-life exposure, including delayed puberty (vaginal opening) and increased number of tertiary atretic ovarian follicles at doses ≥135 mg/kg/day (Blystone et al. 2010; Grande et al. 2006, 2007; NTP 2005; Schilling et al. 1999, 2001). In males, evidence for severe and permanent reproductive tract malformations and lesions in rat offspring have been observed at maternal oral doses of 3–10 mg/kg/day (Arcadi et al. 1998; Christiansen et al. 2010; Klinefelter et al. 2012; Lin et al. 2008, 2009; Vo et al. 2009b). The sexually mature male and female reproductive systems are also targets of DEHP toxicity following intermediate exposure, with LOAELs of 12.3 and 95 mg/kg/day, respectively (Kitaoka et al. 2013; Price et al. 1988b).

Epidemiological data on the potential association between early-life exposure and female reproductive system development are limited, and results are mixed. Early onset of puberty was associated with increased maternal urinary MEHP levels in one study (Watkins et al. 2014); however, *delayed* pubertal onset was associated with increased childhood urinary metabolite levels in another study (Wolff et al. 2014). Some human epidemiological studies suggest potential associations between maternal DEHP exposure and increased risk of male genital anomalies (Sathyanarayana et al. 2016b; Swan 2008), reduced AGD (Barrett et al. 2016; Suzuki et al. 2012; Swan 2008; Wenzel et al. 2018), and delayed puberty (Ferguson et al. 2014b) in male offspring; however, results were mixed.

In a systematic review, NAS (2017) concluded that DEHP is presumed to be a reproductive hazard to humans based on evidence integration of the animal and the human evidence on DEHP and effects on AGD and fetal testosterone. Based on evidence integration for hypospadias, NAS (2017) concluded that DEHP is suspected to be a reproductive hazard to humans based on moderate level of evidence in rats and inadequate evidence in humans for hypospadias following prenatal exposure to DEHP.

The provisional MRL value is further supported by evidence of immune effects in OVA-sensitized rats at oral doses ≥0.03 mg/kg/day (Guo et al. 2012; Han et al. 2014). A provisional MRL based on these studies would be identical to the provisional MRL derived using developmental data: the LOAEL of 0.03 mg/kg/day divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for human variability [OVA-sensitized mice are susceptible population because they are considered a murine model of hypersensitivity diseases in humans], and 10 for extrapolation from animals to humans) yields a provisional MRL of 0.0001 mg/kg/day.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: December 2019
Profile Status: Final, Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: Several chronic-duration studies were identified, but the lowest identified candidate POD values were 2 orders of magnitude greater than the POD used to derive the provisional intermediate-duration MRL (Table A-4). Therefore, any provisional MRL derived based on available chronic data would be higher than the derived provisional intermediate MRL and may not be protective of developmental effects.

Table A-4. Summary of Candidate POD Values for Chronic Oral MRL for DEHP

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD (mg/kg/day)	BMDL (mg/kg/day)	Effect	Reference
Renal effects							
SV/129 mouse	22 months (F)	ND	9.5	NA	NA	Mild glomerulo-nephritis, cell proliferation, proteinuria	Kamijo et al. 2007
Reproductive effects							
F344 rat	104 weeks (F)	5.8	29	NA	NA	Testicular toxicity (aspermato-genesis)	David et al. 2000a

BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; DEHP = di(2-ethylhexyl)phthalate; (F) = feed; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; NA = not applicable (did not model or no suitable model); ND = not determined; POD = point of departure

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR DEHP

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to DEHP.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for DEHP. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as IARC documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of DEHP have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of DEHP are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for DEHP (ATSDR 2002). Standard protocol for an update literature search includes restricting the search to 2 years prior to the publication of the existing toxicological profile. However, to avoid interagency redundancy, EPA made available to ATSDR the screened results of their non-date restricted 2012 DEHP literature search and their November 2014 update DEHP literature search; thus, the literature search was restricted to studies published between August 2014 and September 2016. The following main databases were searched in September 2016:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Heading (MeSH) headings, and keywords for DEHP. The query strings used for the literature search are presented in Table B-2.

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
PubMed	
9/2016	("Diethylhexyl Phthalate"[mh] AND 2014/08/01:3000[mhda]) OR ((("1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester"[tw] OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester"[tw] OR "2-Ethylhexyl phthalate"[tw] OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate"[tw] OR "Bis(2-ethylhexyl) o-phthalate"[tw] OR "Bis(2-ethylhexyl) phthalate"[tw] OR "Bis(2-ethylhexyl)phthalate"[tw] OR "DEHP"[tw] OR "Di(2-ethylhexyl) orthophthalate"[tw] OR "Di(2-ethylhexyl) phthalate"[tw] OR "Di-(2-ethylhexyl) phthalate"[tw] OR "Di(2-ethylhexyl)orthophthalate"[tw] OR "Di(2-ethylhexyl)phthalate"[tw] OR "Di(isooctyl) phthalate"[tw] OR "Di-2-ethylhexyl phthalate"[tw] OR "Di-2-ethylhexylphthalate"[tw] OR "Diethylhexyl phthalate"[tw] OR "Dioctyl phthalate"[tw] OR "Di-sec-octyl phthalate"[tw] OR "Ethyl hexyl phthalate"[tw] OR "Ethylhexyl phthalate"[tw] OR "Octyl phthalate"[tw] OR "Phthalic acid di(2-ethylhexyl) ester"[tw] OR "Phthalic acid dioctyl ester"[tw] OR "Phthalic acid, bis(2-ethylhexyl) ester"[tw]) OR ("DOF plasticizer"[tw] OR "Bisoflex DOP"[tw] OR "Celluflex DOP"[tw] OR "Diacizer DOP"[tw] OR "Diplast O"[tw] OR "Ergoplast FDO"[tw] OR "Ergoplast FDO-S"[tw] OR "Fleximel"[tw] OR "Flexol DOD"[tw] OR "Flexol DOP"[tw] OR "Flexol Plasticizer DOP"[tw] OR "Hatco DOP"[tw] OR "Hatcol DOP"[tw] OR "Jayflex DOP"[tw] OR "Kodaflex DEHP"[tw] OR "Kodaflex DOP"[tw] OR "Mollan O"[tw] OR "Monocizer DOP"[tw] OR "Nuoplaz DOP"[tw] OR "Octoil"[tw] OR "Palatinol AH"[tw] OR "Palatinol AH-L"[tw] OR "Palatinol DOP"[tw] OR "Plasthall DOP"[tw] OR "Platinol AH"[tw] OR "Platinol DOP"[tw] OR "RC Plasticizer DOP"[tw] OR "Reomol DOP"[tw] OR "Sansocizer DOP"[tw] OR "Sconamoll DOP"[tw] OR "Staflex DOP"[tw] OR "Truflex DOP"[tw] OR "Vestinol AH"[tw] OR "ZS plasticizer"[tw] OR "PX-138"[tw] OR "Garbeflex DOP-D 40"[tw] OR "Reomol D 79P"[tw] OR "Eviplast 80"[tw] OR "Vinicizer 80"[tw] OR "Vinycizer 80"[tw] OR "Vinycizer 80K"[tw] OR "Bisoflex 81"[tw] OR "Eviplast 81"[tw] OR "ESBO-D 82"[tw] OR "Codan Set L 86P"[tw] OR "Pittsburgh PX 138"[tw] OR "Sicol 150"[tw] OR "Hercoflex 260"[tw] OR "Good-rite GP 264"[tw] OR "Witcizer 312"[tw] OR "Corflex 400"[tw] OR "Compound 889"[tw] OR "Scandinol SC 1000"[tw] OR "3315AF2"[tw] OR "Sansocizer R 8000"[tw]) AND (2014/08/01:3000[crdat] OR 2014/08/01:3000[edat])) NOT medline[sb])
Toxline	
9/2016	(117-81-7 [rn] OR "2-ethylhexyl phthalate" OR "3315af2" OR "bis (2-ethylhexyl) 1 2-benzenedicarboxylate" OR "bis (2-ethylhexyl) o-phthalate" OR "bis (2-ethylhexyl) phthalate" OR "bis (2-ethylhexyl) phthalate" OR "bisoflex 81" OR "bisoflex dop" OR "celluflex dop" OR "codan set l 86p" OR "compound 889" OR "corflex 400" OR "dehp" OR "di (2-ethylhexyl) orthophthalate" OR "di (2-ethylhexyl) phthalate" OR "di (2-ethylhexyl) orthophthalate" OR "di (2-ethylhexyl) phthalate" OR "di (isooctyl) phthalate" OR "di- (2-ethylhexyl) phthalate" OR "di-2-ethylhexyl phthalate" OR "di-2-ethylhexylphthalate" OR "di-sec-octyl phthalate" OR "diacizer dop" OR "diethylhexyl phthalate" OR "dioctyl phthalate" OR "diplast o" OR "esbo-d 82" OR "ergoplast fdo" OR "ergoplast fdo-s" OR "ethyl hexyl phthalate" OR "ethylhexyl phthalate" OR "eviplast 80" OR "eviplast 81" OR "fleximel" OR "flexol dod" OR "flexol dop" OR "flexol plasticizer dop" OR "garbeflex dop-d 40" OR "good-rite gp 264" OR "hatco dop" OR "hatcol dop" OR "hercoflex 260" OR "jayflex dop" OR "kodaflex dop" OR "mollan o" OR "monocizer dop" OR "nuoplaz dop" OR "octoil" OR "octyl phthalate" OR "px-138" OR "palatinol ah" OR "palatinol ah-l" OR "palatinol dop" OR "phthalic acid di (2-ethylhexyl) ester" OR "phthalic acid dioctyl ester" OR "pittsburgh

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	px 138" OR "plasthall dop" OR "platinol ah" OR "platinol dop" OR "rc plasticizer dop" OR "reomol d 79p" OR "reomol dop" OR "sansocizer dop" OR "sansocizer r 8000" OR "scandinol sc 1000" OR "sconamoll dop" OR "sicol 150" OR "staflex dop" OR "truflex dop" OR "vestinol ah" OR "vinicizer 80" OR "vinycizer 80" OR "vinycizer 80k" OR "witcizer 312" OR "zs plasticizer" OR "dof plasticizer") AND 2014:2016 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
9/2016	FILE 'TOXCENTER' ENTERED AT 12:14:23 ON 26 SEP 2016 CHARGED TO COST=EH011.11.LB.01.01 L1 12228 SEA 117-81-7 L2 11971 SEA L1 NOT TSCATS/FS L3 10697 SEA L2 NOT PATENT/DT L4 1507 SEA L3 AND ED>=20140101 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?)

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 1092 SEA L4 AND L30
	L39 976 SEA L38 AND PY>=2014
	L40 218 SEA L38 AND MEDLINE/FS
	L41 277 SEA L38 AND BIOSIS/FS
	L42 597 SEA L38 AND CAPLUS/FS
	L43 0 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L44 803 DUP REM L40 L41 L43 L42 (289 DUPLICATES REMOVED)
	L*** DEL 218 S L38 AND MEDLINE/FS
	L*** DEL 218 S L38 AND MEDLINE/FS
	L45 218 SEA L44
	L*** DEL 277 S L38 AND BIOSIS/FS
	L*** DEL 277 S L38 AND BIOSIS/FS
	L46 181 SEA L44
	L*** DEL 597 S L38 AND CAPLUS/FS
	L*** DEL 597 S L38 AND CAPLUS/FS
	L47 404 SEA L44
	L48 585 SEA (L45 OR L46 OR L47) NOT MEDLINE/FS

Table B-2. Database Query Strings Pre-Public Comment Searches

Database search date	Query string
	SAVE TEMP L48 DEHP/A D SCAN L48

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to DEHP were identified by searching international and U.S. agency websites and documents.

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
9/2016	Compounds searched: 117-81-7
NTP	
9/2016	"117-81-7" OR "2-ethylhexyl phthalate" OR "bis(2-ethylhexyl)1,2-benzenedicarboxylate" OR "bis(2-ethylhexyl)o-phthalate" OR "bis(2-ethylhexyl)phthalate" OR "bis(2-ethylhexyl)phthalate" OR "dehp" OR "di(2-ethylhexyl)orthophthalate" OR "di(2-ethylhexyl) phthalate" OR "di(2-ethylhexyl)orthophthalate" OR "di(2-ethylhexyl) phthalate" OR "di(isooctyl)phthalate" OR "di-(2-ethylhexyl)phthalate" OR "di-2-ethylhexyl phthalate" OR "di-2-ethylhexylphthalate" OR "di-sec-octyl phthalate" OR "diethylhexyl phthalate" OR "dioctyl phthalate" OR "ethyl hexyl phthalate" OR "ethylhexyl phthalate" OR "octyl phthalate" OR "phthalic acid di(2-ethylhexyl) ester" OR "phthalic acid dioctyl ester" (limited to 2010-2016 and NOT dated)
NIH RePORTER	
2/2017	"1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester" OR "1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester" OR "2-Ethylhexyl phthalate" OR "Bis(2-ethylhexyl) 1,2-benzenedicarboxylate" OR "Bis(2-ethylhexyl) o-phthalate" OR "Bis(2-ethylhexyl) phthalate" OR "Bis(2-ethylhexyl)phthalate" OR "DEHP" OR "Di(2-ethylhexyl) orthophthalate" OR "Di(2-ethylhexyl) phthalate" OR "Di-(2-ethylhexyl) phthalate" OR "Di(2-ethylhexyl)orthophthalate" OR "Di(2-ethylhexyl)phthalate" OR "Di(isooctyl) phthalate" OR "Di-2-ethylhexyl phthalate" OR "Di-2-ethylhexylphthalate" OR "Diethylhexyl phthalate" OR "Dioctyl phthalate" OR "Di-sec-octyl phthalate" OR "Ethyl hexyl phthalate" OR "Ethylhexyl phthalate" OR "Octyl phthalate" OR "Phthalic acid di(2-ethylhexyl) ester" OR "Phthalic acid dioctyl ester" OR "Phthalic acid, bis(2-ethylhexyl) ester") OR ("DOF plasticizer" OR "Bisoflex DOP" OR "Celluflex DOP" OR "Diacizer DOP" OR "Diplast O" OR "Ergoplast FDO" OR "Ergoplast FDO-S" OR "Fleximel" OR "Flexol DOD" OR "Flexol DOP" OR "Flexol Plasticizer DOP" OR "Hatco DOP" OR "Hatcol DOP" OR "Jayflex DOP" OR "Kodaflex DEHP" OR "Kodaflex DOP" OR "Mollan O" OR "Monocizer DOP" OR "Nuoplaz DOP" OR "Octoil" OR "Palatinol AH" OR "Palatinol AH-L" OR "Palatinol DOP" OR "Plasthall DOP" OR "Platinol AH" OR "Platinol DOP" OR "RC Plasticizer DOP" OR "Reomol DOP" OR "Sansocizer DOP" OR "Sconamoll DOP" OR "Staflex DOP" OR "Truflex DOP" OR "Vestinol AH" OR "ZS plasticizer" OR "PX-138" OR "Garbeflex DOP-D 40" OR "Reomol D 79P" OR "Eviplast 80" OR "Vinicizer 80" OR "Vinycizer 80" OR "Vinycizer 80K" OR "Bisoflex 81" OR "Eviplast 81" OR "ESBO-D 82" OR "Codan Set L 86P" OR "Pittsburgh PX 138" OR "Sicol 150" OR "Hercoflex 260" OR "Good-rite GP 264" OR "Witcizer 312" OR "Corflex 400" OR "Compound 889" OR "Scandinol SC 1000" OR "3315AF2" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Sansocizer R 8000" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects, 2017, 2016, 2015, 2014, 2013, 2012
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature from searches described in Table B-3, including unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, theses, and dissertations. Relevant unpublished studies were submitted to three peer reviewers for evaluation of animal care, dose adequacy, number of animals in dose groups, study design and reporting, and whether the reviewer agreed with the author's conclusive statements. Unpublished studies of a questionable nature were not included in the toxicological profile.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 686
- Number of records identified from other strategies: 317
- Total number of records to undergo literature screening: 1,003

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on DEHP:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile (Figure B-1).

- Number of titles and abstracts screened: 1,003
- Studies identified via EPA's 2014 literature search: 3,376
- Number of studies considered relevant and moved to the next step: 1,104

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile (Figure B-1).

- Number of studies undergoing full text review: 1,104
- Number of studies cited in the pre-public draft of the toxicological profile: 294
- Total number of studies cited in the profile: 827

Prioritization of Human Data. The epidemiological database for DEHP is extensive, but is largely focused on a small number of endpoints: body weight (BMI and waist circumference), cardiovascular (blood pressure), hepatic (serum lipids), endocrine (diabetes), immunological (allergy and asthma), and reproductive and developmental endpoints. For endpoints with few epidemiological studies (e.g., respiratory, hepatic effects other than serum lipids, hematological, neurological, and cancer), all relevant human data were considered. For the data-rich endpoints, a series of inclusion criteria were defined to facilitate the selection of human studies of greater utility in assessing the hazards of DEHP, and only studies meeting the criteria were included in the Toxicological Profile. The criteria are shown below, and Table B-4 summarizes how the criteria were applied to the available epidemiological data by health outcome.

- Exposure was assessed by analysis of a biomarker, and the levels of exposure were reported in the study; studies using indirect exposure assessment such as job-exposure matrix or proximity to sources of phthalate exposure such as flooring were not included, nor were those in which exposure levels were not reported.
- The biomarker used to assess exposure was the concentration(s) of one, or all, of the following metabolites in urine: MEHP, MEHHP, MEOHP, MECPP[1] (the metabolites included in the CDC's National Biomonitoring Program [see Section 3.1.3] and those most commonly reported in the available studies), or the summed concentrations of these metabolites. Studies using concentrations of DEHP or its metabolites in blood/serum, amniotic fluid, cord blood, breast milk, semen, or other biological fluids were not included. As discussed in detail in Section 3.3.1 (Biomarkers of Exposure), urinary metabolite levels are considered the optimal biomarkers of exposure to DEHP, for several important reasons (Calafat et al. 2015; Johns et al. 2016):
    - urine samples are the least invasive samples to obtain, improving participation in efforts to assess exposure;
    - urine samples are typically of larger volume than those of other biological fluids, facilitating detection of metabolites;
    - the concentration of DEHP metabolites in urine is higher than that of DEHP or its metabolites in other biological fluids, leading to fewer samples below the limit of detection;
    - enzymes present in blood, milk, amniotic fluid, etc., but not in urine, are known to hydrolyze DEHP to its monoester during sample storage, leading to underestimates of DEHP levels; and,
    - the potential for sample contamination by the parent diester and subsequent formation of metabolites is reduced in urine due to lack of metabolic enzymes.
- In addition, studies that analyzed exposure as the sum of high molecular weight phthalates that included DEHP as well as others such as butyl benzyl phthalate were not considered, as the effects attributable to DEHP itself could not be determined from such analyses.
- The statistical analysis of the association was multivariate, with consideration of at least one potential covariate. Studies limited to bivariate analyses (i.e., Pearson or Spearman correlation coefficients) were not included, nor were studies in which the analysis was limited to a comparison between urinary metabolite concentrations in cases and controls.
- The health outcomes evaluated in the study were not mechanistic in nature (e.g., oxidative stress) or nonspecific (e.g., nonspecific markers of inflammation).

[1] Two recent studies (Bloom et al. 2015a, 2015b and Valvi et al. 2015) included another metabolite of DEHP (MCMHP), but there were too few studies of this metabolite to warrant its inclusion.

Table B-4. Application of Selection Criteria to Epidemiological Data by Health Outcome

Outcome	Selection process
Death	All studies included
Body weight	Systematic review used for studies up through 2012; criteria applied to studies published from 2012 to 2016.
Respiratory	All studies included
Cardiovascular	Blood pressure: criteria applied Endpoints other than blood pressure: all studies included
Gastrointestinal	All studies included
Hematological	All studies included
Musculoskeletal	No studies identified
Hepatic	Serum triglycerides and cholesterol: criteria applied Other endpoints: all studies included
Renal	All studies included
Dermal	All studies included
Ocular	No studies identified
Endocrine	Criteria applied (diabetes was the only endpoint evaluated)
Immunological	Allergy and asthma endpoints: criteria applied Nonspecific inflammatory markers: not included
Neurological	All studies included
Reproductive	Criteria applied
Developmental	Criteria applied
Cancer	All studies included

In addition, for health outcomes with robust databases that included cohort as well as case-control or cross-sectional studies, only those studies in which exposure was measured prior to outcome determination (cohort studies) were included. For endpoints with fewer studies, all study designs were considered.

Prioritization of Animal Data. All inhalation studies were retained (small database); however, the full text review process returned a large database of oral animal studies. Therefore, the oral animal data were prioritized for efficient review. Studies were excluded from Chapter 2 if the design and/or reporting were inadequate to inform hazard identification, dose-response assessment, or derivation of MRLs. Studies were excluded from Chapter 2 based on the following criteria:

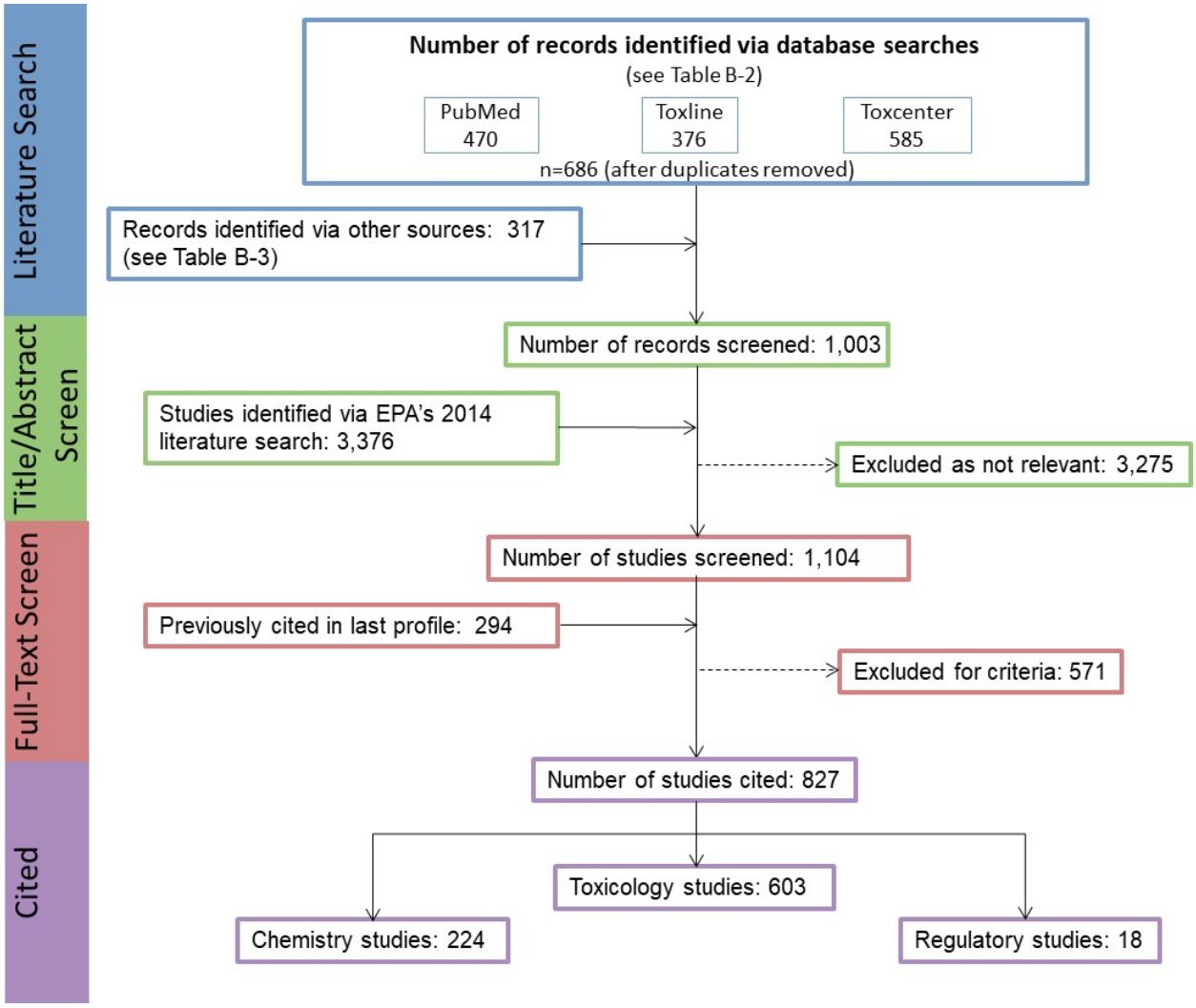
- Acute- and intermediate-duration single-dose studies were excluded when there was adequate information from multi-dose studies for the examined endpoints. All chronic studies, primate studies, and studies that filled data gaps were retained regardless of number of dose groups. Lethality data were retained from all studies.
- Only studies that evaluated at least one dose <100 mg/kg/day were included for acute- and intermediate-duration reproductive/developmental studies (reproductive/developmental effects have been consistently observed in numerous studies at doses <100 mg/kg/day). All chronic studies, primate studies, and studies that filled data gaps in developmental health effect categories

(e.g., developmental cardiovascular effects) were retained regardless of dose. Lethality data were retained from all studies.

- Only acute- and intermediate-duration studies evaluating at least one dose <1,000 mg/kg/day were included for endpoints other than reproductive/developmental effects. All chronic studies, studies in primates, and studies that provide information for data poor health effect categories (e.g., lethality, cardiovascular, neurological) were retained regardless of dose. Lethality data were retained from all studies.
- Any oral studies with major design and/or reporting deficiencies were excluded.

Summary of Literature Search and Screening. A summary of the results of the literature search and screening for the DEHP profile is presented in Figure B-1.

Figure B-1. September 2016 Literature Search Results and Screen for DEHP



*Some cited studies fall into multiple categories (e.g., chemistry and toxicology).

APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives 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.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 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 levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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 and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(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. Typically, when sufficient data exist, 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 figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are 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) Figure key. 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 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, 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.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. 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. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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 chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints 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) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

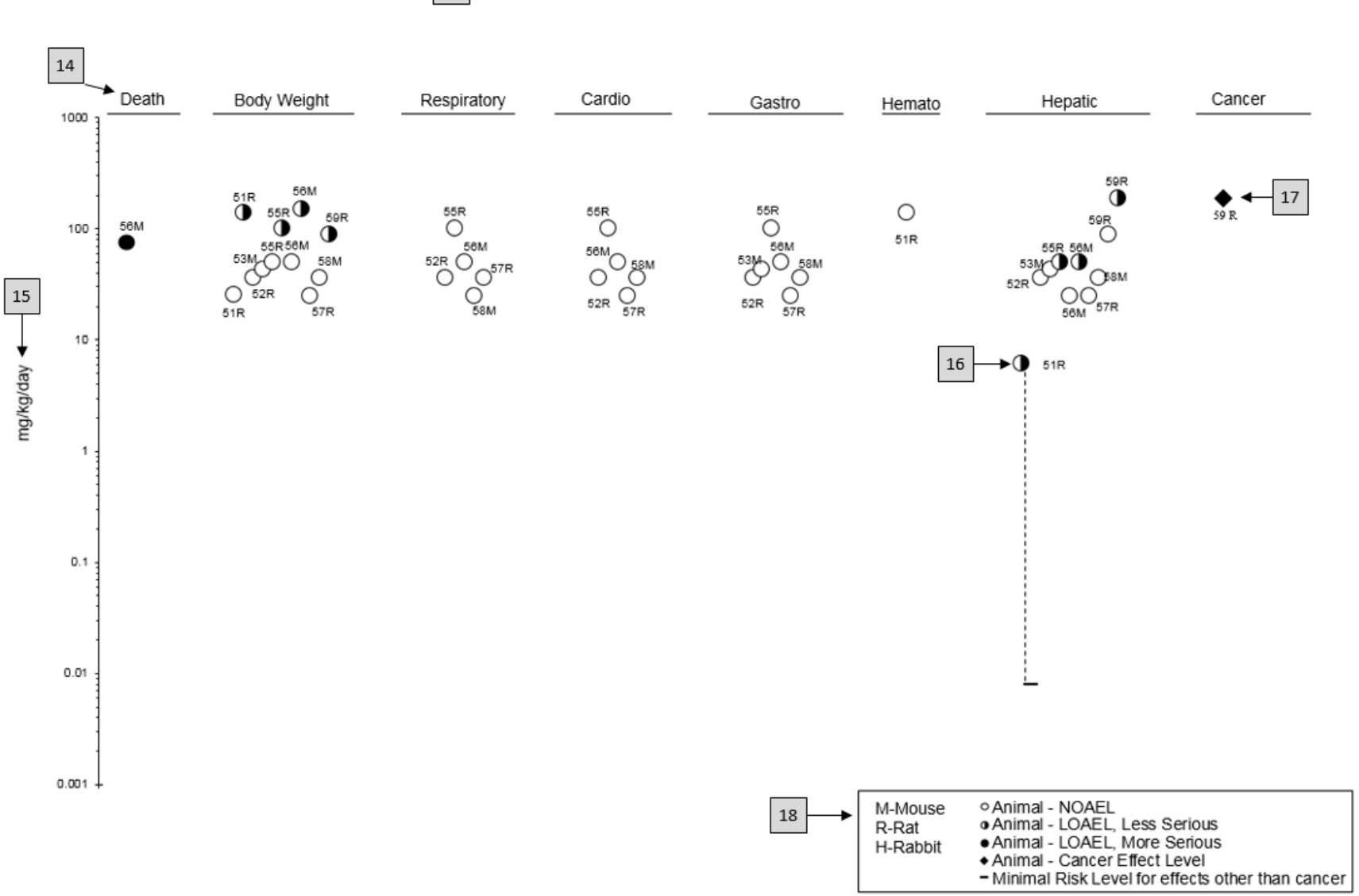
(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. 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 may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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 (see https://www.atsdr.cdc.gov/MHMI/index.asp). 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 (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/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 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to 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, 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 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) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a 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 that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

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

Ceiling Value—A concentration that must not be exceeded.

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

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

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, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

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

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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 response or amount of the response.

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 effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—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.

Excretion—The process by which metabolic waste products are removed from the body.

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.

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

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases 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.

***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 that 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 that 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.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

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

Mortality—Death; the 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, which are changes 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 hazardous substance.

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. Although effects may be produced at this dose, 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) that 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 that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict 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, whereas 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 that quantitatively describes the relationship between target tissue dose and toxic endpoints. 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—A type of physiologically based dose-response model that is 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, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air 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 a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration 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 RfC is 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 oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound 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 hazardous substance. 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 hazardous substance.

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

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

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

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

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DEHP	di(ethylhexyl)phthalate
DEHP-D_4	deuterium-labeled DEHP; all 4 hydrogens on the benzene ring replaced with deuterium
DINCH	diisononyl ester
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation

FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MECPP	mono-2-ethyl-5-carboxypentylphthalate
MEHP	monoethylhexylphthalate
MEHHP	mono-2-ethyl-5-hydroxyhexylphthalate
MEOHP	mono-2-ethyl-5-oxyhexylphthalate
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton

NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory

TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	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