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

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

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.

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 due to associated acute, intermediate, and chronic exposures;

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

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

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

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

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*Legislative Background

The toxicological profiles are developed 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.

VERSION HISTORY

Date	Description
January 2022	Final toxicological profile released
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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ATSDR, Office of Community Health and Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice; EPA, Center for Public Health and Environmental Assessment.

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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. DEHP was widely used as a plasticizer to help make polyvinyl chloride (PVC) products soft and flexible (CPSC 2010a). Because some DEHP is retained 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 had 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 children's items that contain DEHP at levels >0.1% by weight (CPSIA 2008).

DEHP also has non-PVC uses, and has been reported in several other consumer products, such as cosmetics, lubrication oil, and paint (CPSC 2010a; Mannsville Chemical Products Corporation 1990; NTP 1989); however, 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 childcare articles, such as those to help sleeping, feeding, sucking, or teething of children ≤3 years old (CPSIA 2008). Due to current restrictions on the use of DEHP, medical device manufacturers have begun producing PVC equipment with plasticizers other than DEHP or developing non-PVC devices (Van Vliet et al. 2011). In 2017, the European Union passed the new Medical Device Regulation, which restricted the use of DEHP and other substances of very high concern by 2020 and encourages the use of alternatives (Hansen 2019).

DEHP enters the environment predominantly through disposal of wastes into 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. 1980); 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.

1. RELEVANCE TO PUBLIC HEALTH

DEHP possesses low volatility, so it is typically found at low levels (<5 ng/m^3) in ambient air (Eisenreich et al. 1981; Ligocki et al. 1985a; Lunderberg et al. 2019) but can be detected in higher concentrations near highly populated urban areas (Quintana-Belmares et al. 2018). In the past, it was difficult to determine low levels accurately since DEHP was ubiquitously present in laboratory equipment, potentially leading to false identification of elevated phthalate concentrations due to sample contamination (Howard et al. 1985). In recent years, like DEHP-free medical devices, there exists DEHP-free laboratory equipment, which reduces the possibility for contaminating a sample. Indoor air and dust may contain low levels of DEHP due to emissions from building materials, such as vinyl floorings and wallpaper (Shinohara et al. 2019). Gradual emission of phthalates like DEHP from source materials occurs over time since they are not chemically bound to the polymer matrix and due to their low volatility, the emitted phthalates tend to sorb strongly to interior surfaces and indoor particles (Liang et al. 2019).

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; Wormuth et al. 2006). Occupational exposures may be significant in some settings, although engineering controls and good workplace practices are implemented to limit exposure.

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). Manufacturers have begun using plasticizers other than DEHP in PVC-containing materials, including medical devices, which should decrease this exposure route in the future (Hansen 2019).

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 (ATSDR 2017; 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 1–30 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 and dermal studies in laboratory animals. Although many epidemiology studies have examined potential associations between DEHP exposure and various adverse health effects, DEHP breaks down quickly in the body. Therefore, available studies rely on breakdown products of DEHP, or metabolites, as biomarkers to assess exposure.

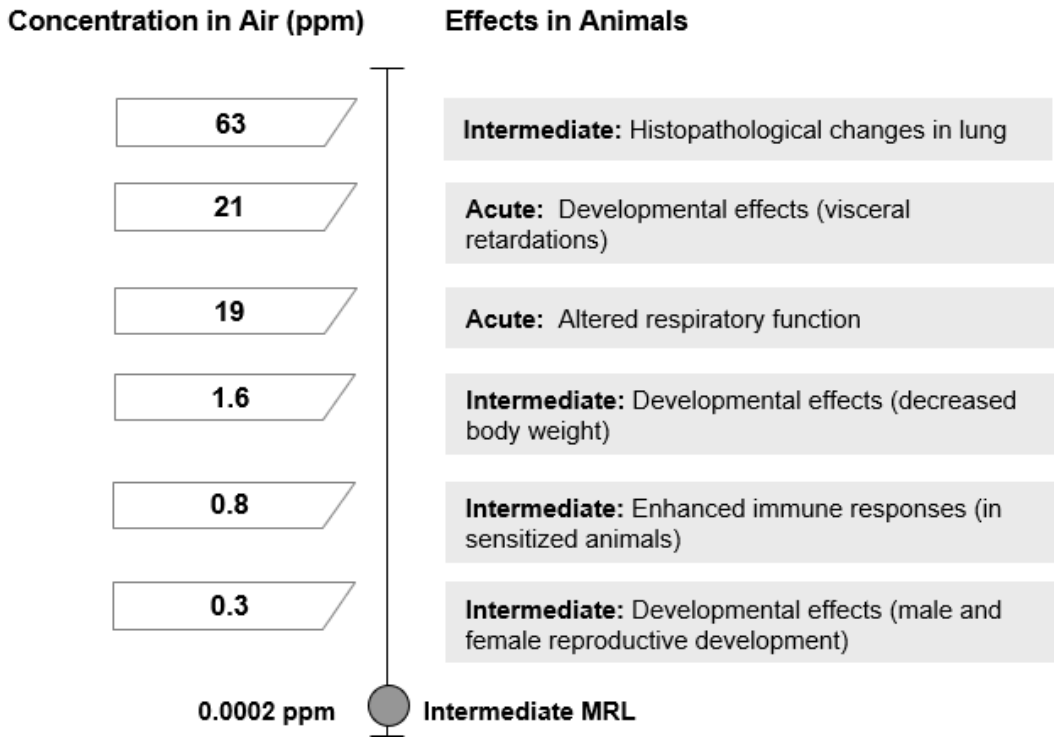
Metabolites considered as validated biomarkers of DEHP in biological samples include mono(2-ethylhexyl)phthalate (MEHP), MEHHP (mono-2-ethyl-5-hydroxyhexylphthalate), MEOHP (mono(2-ethyl-5-oxohexyl)phthalate), and MECPP (mono-2-ethyl-5-carboxypentylphthalate). Spot urine samples are preferred over other biological samples (e.g., blood or stools) due to ease of collection and analysis. However, urinary metabolite levels can only provide short-term exposure estimates, and they cannot 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 similar substances, called phthalates or phthalate esters. DEHP and other 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).

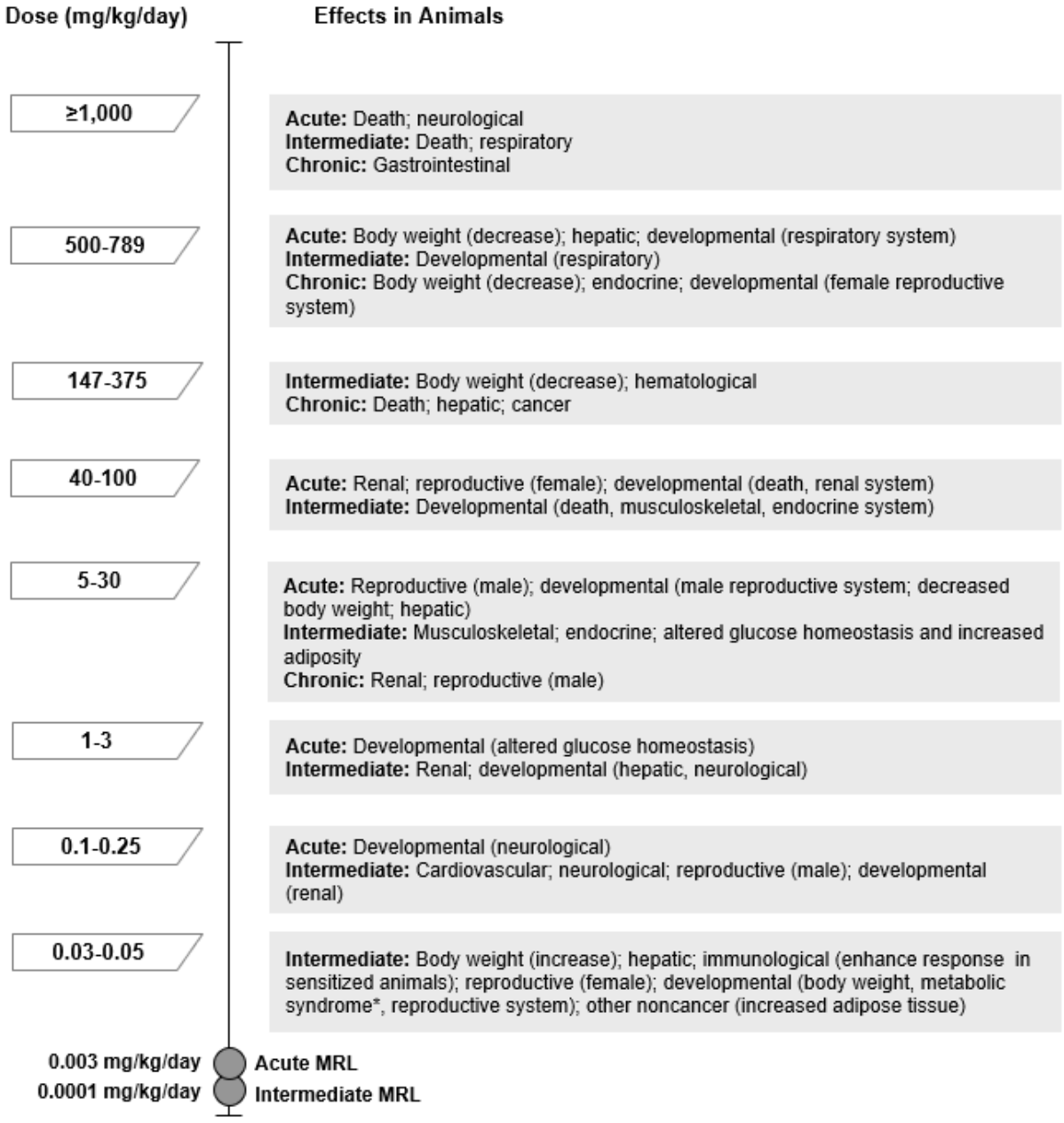
Limited data in animal studies indicate that health effects in animals following inhalation exposure include alterations in the immune system and the developing and mature reproductive systems at low concentrations (<1 ppm), with respiratory and other developmental effects at higher concentrations (Figure 1-1).

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



In oral animal studies, effects consistently reported at low doses (≤5 mg/kg/day) include altered development or function of several systems following *in utero* and/or early life exposure, altered immune responses, damage to the sexually mature male and female reproductive system, renal effects, and hepatic effects (Figure 1-2). Effects on body weight and the neurological, hematological, and non-reproductive endocrine systems were generally observed at higher DEHP doses.

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



*Observed effects included increased visceral fat and serum fasting glucose, insulin, and leptin.

1. RELEVANCE TO PUBLIC HEALTH

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

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

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). No consistent association between DEHP metabolites in urine and serum triglycerides or cholesterol levels in humans was observed in available cohort (Perng et al. 2017; Vafeiadi et al. 2018a) and cross-sectional (James-Todd et al. 2016a; Ko et al. 2019; Lin et al. 2016, 2020; Trasande and Attina 2015; Trasande et al. 2013a; Yaghjyan et al. 2015a, 2015b) studies.

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, nonpregnant rats and mice were 5 and 180 mg/kg/day, respectively (Sasaki et al. 2003; Zhang et al. 2017). 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, sinusoidal or vacuolar degeneration) were observed in some rodent studies, but LOAEL doses generally were ≥100 mg/kg/day in rats (Aydemir et al. 2018) or ≥300 mg/kg/day in mice (Wang et al. 2020). A couple of studies in rats reported hepatic lesions at much lower doses,

including vacuolar degeneration and inflammatory infiltration at doses of 0.05–5 mg/kg/day (Zhang et al. 2017, 2019).

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 (Chang et al. 2020; 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; 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 showed elevated serum urea when exposed to ≥200 mg/kg/day for 4–13 weeks (Aydemir et al. 2018; Myers 1992b), and mice showed elevated creatinine when exposed to 300 mg/kg/day for 35 days (Li et al. 2018). 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).

Immune Effects. Evidence for potential associations between DEHP exposure and risk of allergy and asthma in humans is mixed. Numerous epidemiological studies did not observe associations between DEHP exposure and measures of allergy or asthma in children or adults (Section 2.14). However, a few human epidemiological studies in children suggest an association between DEHP exposure and allergy (Ku et al. 2015; Podlecka et al. 2020; Wang et al. 2014) or asthma, wheeze, or airway inflammation (Franken et al. 2017; Gascon et al. 2015a; Kim et al. 2018e).

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 of 0.03 mg/kg/day or higher (Guo et al. 2012; Han et al. 2014a; Wang et al. 2018; Yang et al. 2008). Adjuvant effects were also observed in sensitized mice after exposure to air concentrations of 0.81 ppm, but not concentrations up to 0.11 ppm DEHP (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/or airway responsiveness. The human health relevance of findings from sensitized animals is uncertain in the absence of clear evidence that the immune system is a target of DEHP toxicity in humans or unsensitized animals.

Reproductive Effects. Cross-sectional studies suggest associations between levels of urinary DEHP metabolites in humans and decreased serum testosterone (Chang et al. 2015; Chen et al. 2017; Jurewicz et al. 2013; Wang et al. 2016) and reduced sperm motility and/or concentration (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Chang et al. 2017a; Minguez-Alarcon et al. 2018a) 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. Some human epidemiological studies suggest potential associations between maternal exposure to DEHP and preterm birth (Bloom et al. 2019a; Ferguson et al. 2014b, 2014c, 2019a; Gao et al. 2019; Meeker et al. 2009a; Zhang et al. 2020a), and a limited number of studies in women seeking *in vitro* fertilization reported decreased fertilization rates or reduced number and/or quality of oocytes and embryos with increased maternal DEHP exposure (Hauser et al. 2016; Machtinger et al. 2018).

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), and decreased oocyte fertilization, arrested zygote development, and decreased preimplantation embryos were observed at ≥0.2 mg/kg/day in a mating trial in mice (Parra-Forero et al. 2019). 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, post-implantation 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 (NTP 1988).

Developmental Effects. Human epidemiological studies suggest potential associations between maternal exposure to DEHP and male genital anomalies (Sathyanarayana et al. 2016a; 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 in males and females (Ferguson et al. 2014a; Watkins et al. 2014; Wolff et al. 2014), delayed mental and psychomotor development in young children (Balalian et al. 2019; Daniel et al. 2020; Kim et al. 2011; Olesen et al. 2018a; Polanska et al. 2014; Qian et al. 2019a; Téllez-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 also indicate the alteration of several additional organ systems with early life 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 (altered glucose homeostasis) and adrenal damage in young rats were 0.2 and 10 mg/kg/day, respectively (Christiansen et al. 2010; Fan et al. 2020). Other studies report reversible liver damage in rats and mice at maternal or early postnatal doses ≥3 mg/kg/day (Arcadi et al. 1998; Maranghi et al. 2010).

Neurobehavioral effects, including impaired reflexes and altered neurobehavior, were also observed in several studies of rat and mouse offspring following gestational and/or early postnatal exposure. The lowest maternal dose associated with neurodevelopmental effects was 0.2 mg/kg/day in mice (increased anxiety); however, another measure of anxiety in the same study did not observe evidence of increased anxiety until maternal doses of 750 mg/kg/day (Barakat et al. 2018). In other available studies, the lowest maternal doses associated with neurodevelopmental effects were 1 mg/kg/day in mice (Tanida et al. 2009) and 30 mg/kg/day in rats (Arcadi et al. 1998; Carbone et al. 2013).

Serious developmental effects (fetal death, teratogenicity) were not observed until much higher maternal doses. The lowest maternal doses associated with increased fetal death and teratogenic effects were 340 and 600 mg/kg/day, respectively, in rats (Camacho et al. 2020; Schilling et al. 2001), and 95 and 91 mg/kg/day, respectively, in mice (NTP 1988; Tyl et al. 1988).

Cancer Effects. One population-based study did not find an association between DEHP exposure and breast cancer (Morgan et al. 2017). Other epidemiology studies of cancer endpoints in humans exposed to DEHP are limited to case-control studies of breast cancer (Holmes et al. 2014; Lopez-Carrillo et al. 2010; Martinez-Nava et al. 2013; Merida-Ortega et al. 2016; Reeves et al. 2019), prostate cancer (Chuang et al. 2020), and thyroid cancer (Liu et al. 2020; Marotta et al. 2019; Miao et al. 2020) 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 in these case studies 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.

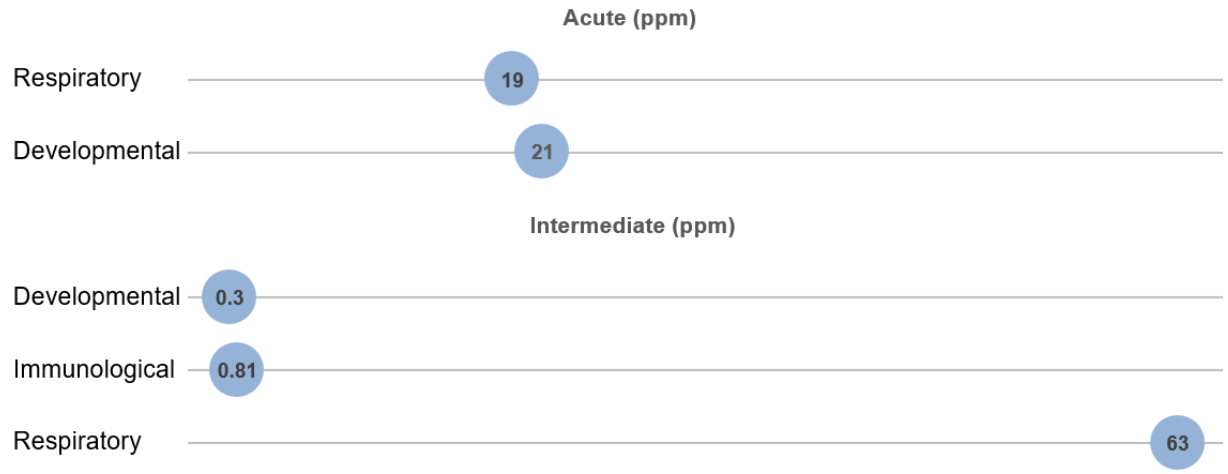
The inhalation database for animals was considered adequate for derivation of an intermediate-duration MRL, but inadequate for derivation of acute- or chronic-duration MRLs. As presented in Figure 1-3, the available inhalation data for DEHP from animal studies suggest that the immune and developing reproductive systems are sensitive targets of toxicity, with respiratory system damage observed at much higher concentrations.

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.

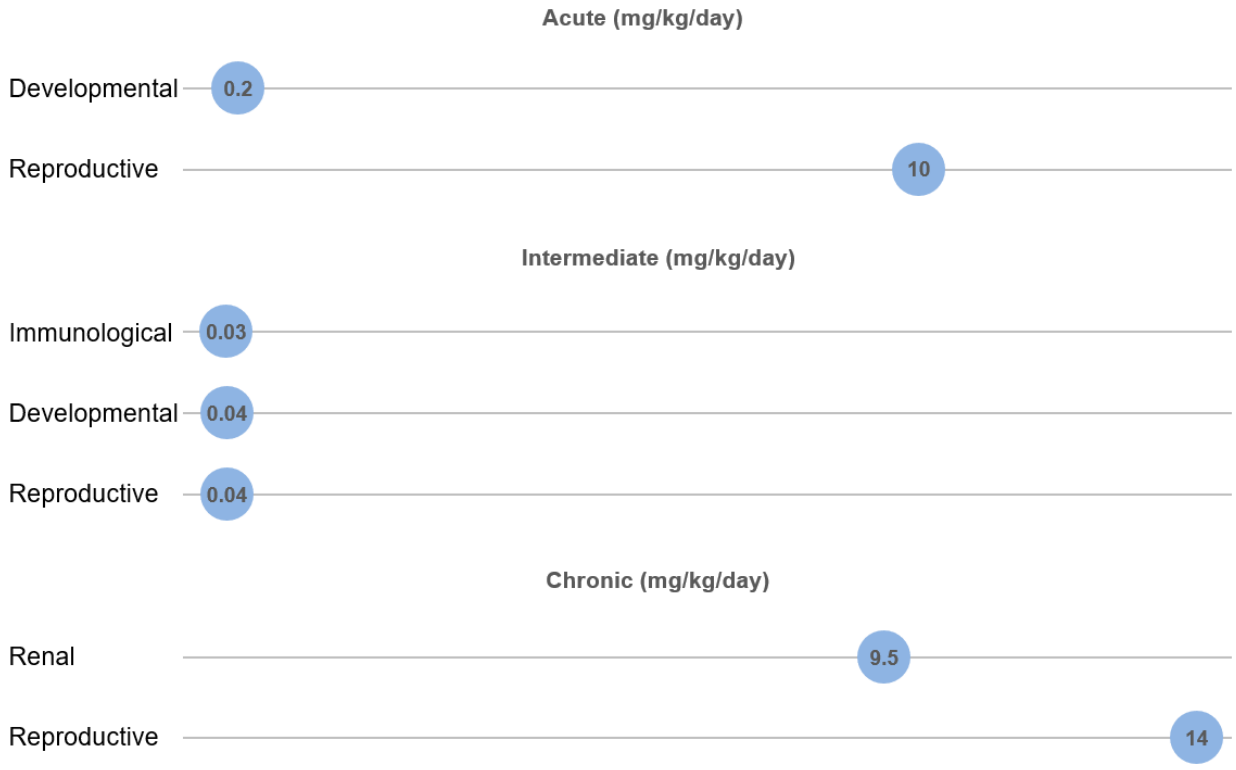


The oral database for animals was considered adequate for derivation of acute- and intermediate-duration oral MRLs for DEHP. The most sensitive targets in animals following oral exposure to DEHP included developmental effects (neurodevelopment, reproductive development, altered glucose homeostasis) and the adult immune, reproductive, and renal systems (Figure 1-4). 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. 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 intermediate oral MRL. No chronic oral MRL was developed.

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

The developing fetus/neonate and the immune, 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.



The MRL values are summarized in Table 1-1.

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

Exposure duration	MRL	Critical effect(s)	Point of departure/ human equivalent concentrations	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for derivation of an MRL; the intermediate-duration MRL should be protective of acute exposures.				
Intermediate	$2x10^{-4}$	Developmental effects (reproductive system)	LOAEL: 0.3 ($LOAEL_{HEC}$: 0.05)	300	Kurahashi et al. 2005; Ma et al. 2006
Chronic	Insufficient data for derivation of an MRL.				
Oral exposure (mg/kg/day)					
Acute	$3x10^{-3}$	Developmental effects (altered glucose homeostasis)	LOAEL: 1	300	Rajesh and Balasubramanian 2014
Intermediate	$1x10^{-4}$	Developmental effects (reproductive system)	LOAEL: 0.04	300	Zhang et al. 2015
Chronic	Insufficient data for derivation of an MRL.				

[a]See Appendix A for additional information.

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

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 and animal oral studies are presented in Table 2-2 and Figure 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 (SLOAELs) 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.

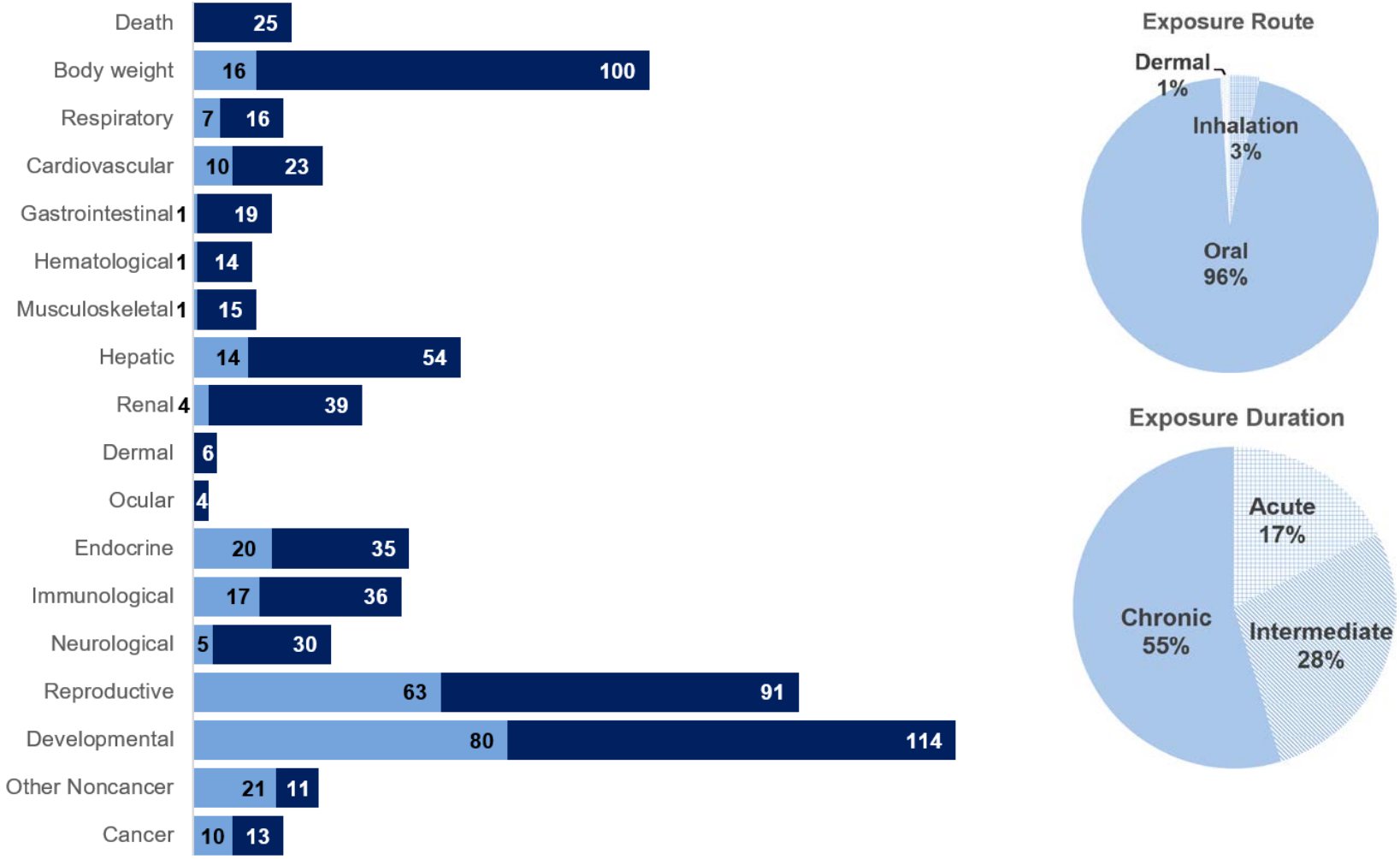
- **Immunological effects.** Human data regarding immunological effects following DEHP exposure are extremely limited. Results from studies evaluating potential associations between prenatal exposure and childhood risk of wheezing or increased IgE were inconsistent. However, some animal studies provide evidence that DEHP is an immune adjuvant in sensitized animals at low exposure levels. The human health relevance of findings from sensitized animals is uncertain in the absence of clear evidence that the immune system is a target of DEHP toxicity in humans or unsensitized animals.

- **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 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 the development of the reproductive system following early life exposure is a particularly sensitive target 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 466 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	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		Rapid shallow breathing (35% decrease in tidal volume, 15% increase in respiratory rate) during final 10 minutes of exposure
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]		250% increase in 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]		80% increase in plasma testosterone, 30% increase in relative seminal vesicle weight
Kurahashi et al. 2005									
6	Rat (Wistar) 10 F	20 days (PNDs 22–41) 6 hours/day 5 days/week (WB)	0, 0.3, 1.6	DX	Develop		0.3[c]		Vaginal opening and first estrus accelerated by 2-3 days at ≥0.3 ppm; 54% increase in serum estradiol and 167% increase in serum 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]		Vaginal opening and first estrus accelerated by 2–3 days at ≥0.3 ppm; irregular estrous cycles and ~10% decrease in PND 84 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, OW, IX	Bd wt	0.81			
					Hepatic	0.81			
					Immuno	0.11	0.81		Enhanced immune response to OVA challenge in sensitized animals (350% increase in OVA-specific IgG1)
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 an 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 x 6 hours/24 hours x 5 days/7days x 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 an 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); GD = gestational day; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immunotoxicity; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; LSE = levels of significant exposure; M = male(s); Musc/skel = musculoskeletal; (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; (WB) = whole-body

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

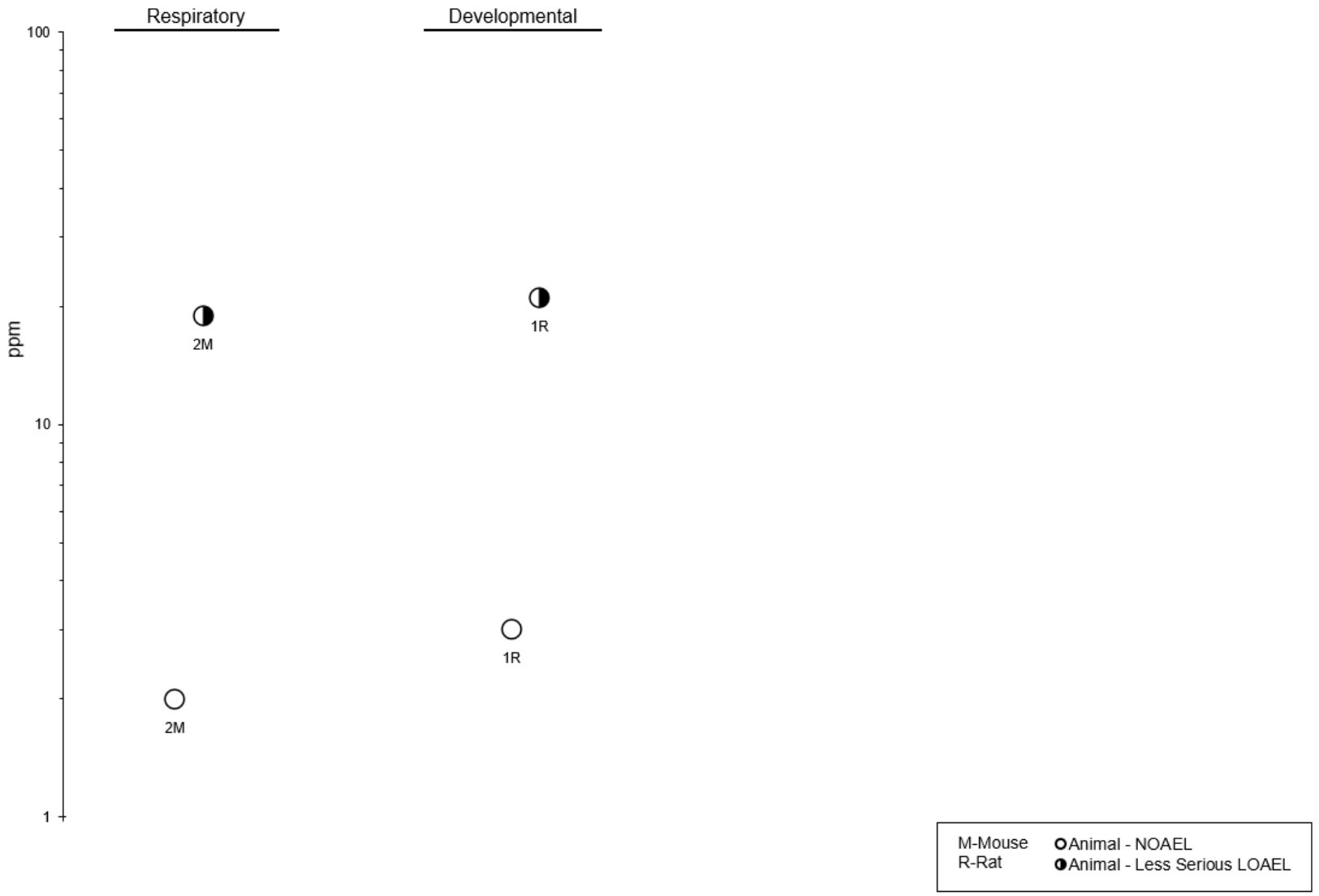


Figure 2-2. Levels of Significant Exposure to DEHP – Inhalation
Intermediate (15–364 days)

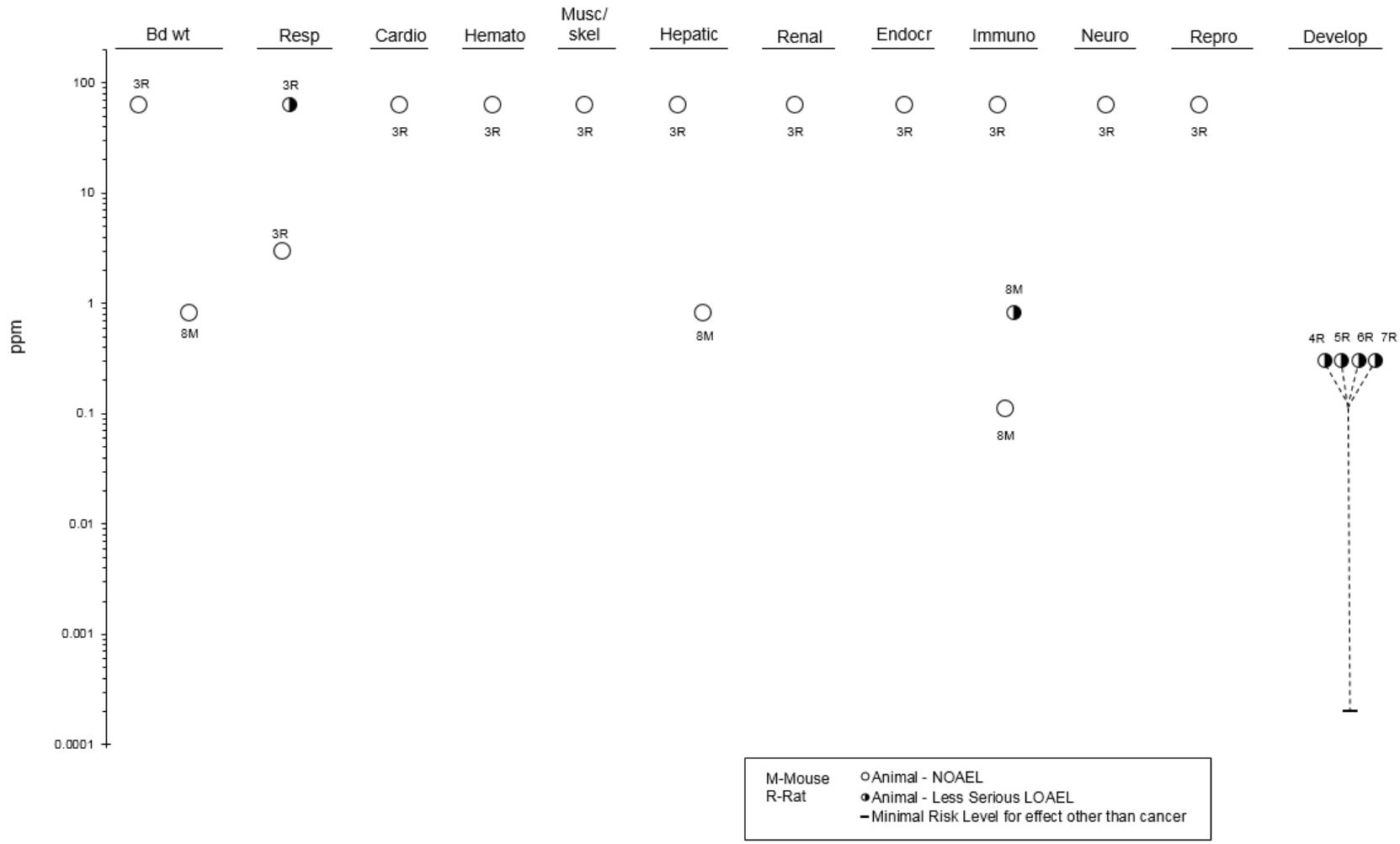


Table 2-2. Levels of Significant Exposure to DEHP – Oral

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	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									
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	Rat (Long-Evans) 10 M	14 days PNDs 21–34 (GO)	0, 1, 10, 100, 200	DX	Develop	10	100		45% reduction in basal and LH-stimulated testosterone production in Leydig cells
Akingbemi et al. 2001									
4	Rat (Long-Evans) 10 M	14 days PNDs 35–48 (GO)	0, 1, 10, 100, 200	DX	Develop	1	10		40% reduction in basal and LH-stimulated testosterone production in Leydig cells
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
5	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									
6	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									
7	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									

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
8	Rat (Sprague-Dawley) 6 M	5 days PNDs 3–7 (G)	0, 60, 300, 600	DX	Develop		60	600	LOAEL: 16% decrease in absolute testes weight, mitotic alterations in gonocytes; >20% decrease in absolute and relative testes weight and polynucleated gonocytes at ≥300 mg/kg/day; increased liver weight[b] at ≥300 mg/kg/day Serious LOAEL: 21% decrease in body weight, Sertoli cell apoptosis
Camacho et al. 2020 [Vehicle was Intralipid 20%.]									
9	Rat (Sprague-Dawley) 8–10 F	10 days GD 12– PND 0 (GO)	0, 10, 100, 750	BW, DX	Bd wt	100		750	103% decrease in maternal weight gain during exposure period (dams lost weight)
					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									
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									

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
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			
Dostal et al. 1987									
12	Rat (Sprague-Dawley) 6–10 M	5 days PNDs 86–90 (GO)		BI, OW	Renal	2,000			
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 (Sprague-Dawley) 6–8 F	5 days GDs 14–18 (GO)	0, 100, 300, 600, 900	DX	Develop		100	300	21% decrease in fetal testicular testosterone production; ≥67% decrease in fetal testosterone production at ≥300 mg/kg/day
Furr et al. 2014; Hannas et al. 2011									
19	Rat (Long-Evans) 19–38 M	14 days 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									
20	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									
21	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									
22	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									

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
23	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									
24	Rat (Wistar) 9–10 F	9 days GDs 6–15 (GO)	0, 40, 200, 1,000	BW, CS, OW, RX, DX	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	900	20% decreased in fetal testicular testosterone production; 80% decrease in fetal testosterone production at 900 mg/kg/day
Howdeshell et al. 2008									
26	Rat (Sprague-Dawley) 6 M	10 days (G)	0, 40, 400	CS, BW, OW	Bd wt	400			
					Renal		40		11% increase in kidney weight (castrated rats without testosterone supplementation)
					Repro	400			
Kim et al. 2018b [Hershberger assay; castrated rats with and without testosterone supplementation]									

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
27	Rat (Sprague-Dawley) 8 F	7 days GDs 13–19 (GO)	0, 10, 100	DX	Develop		10	100	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									
28	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									
29	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]									
30	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									
31	Rat (Long-Evans) 8 M	14 days (GO)	0, 10, 750	BC, RX	Bd wt	750			
					Repro		10		200 and 140% increase in Leydig cell number and proliferation,

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
									respectively (following EDS elimination of Leydig cells)
Li et al. 2012a									
32	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 were measured in adult (PND 60) offspring.]									
33	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									
34	Rat (Fischer-344) 8 F	Once (GO)	0, 150, 500, 1,500, 5,000	CS, NX	Neuro	1,500	5,000		Signs of general debilitation
Moser et al. 1995									
35	Rat (Fischer-344) 8 F	14 days (GO)	0, 50, 150, 500, 1,500	CS, NX	Neuro	1,500			
Moser et al. 1995									
36	Rat (Fischer-344) 10 F	10 days (GO)	0, 50, 100, 150, 200	CS, BW, NX	Bd wt	200			
					Neuro	200			
Moser et al. 2003									

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
37	Rat (Fischer-344) 5 M, 5 F	14 days (F)	M: 0, 670, 1,300, 2,700, 5,700, 12,000 F: 0, 730, 1,500, 3,000, 6,200, 12,000	LE	Death			12,000	2/5 males and 4/5 females died
NTP 1982									
38	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 (16–20% increase in blood glucose, 21–22% decrease in serum insulin); 12–21% decreased body weight and increased adipose tissue at ≥10 mg/kg/day in adult offspring
Rajesh and Balasubramanian 2014									
39	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									
40	Rat (Sprague-Dawley) 8–12 F	8 days GDs 12–19 (GO)	0, 50, 625	DX	Develop		50	625	28% decrease in fetal testosterone production; 85% decrease in fetal testosterone production at 625 mg/kg/day
Saillenfait et al. 2013									
41	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									

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 (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]									
43	Rat (Sprague-Dawley) 8 F	11 days GDs 11–21 (GO)	0, 10, 100, 500	DX	Develop		10	500	Effects at PNDs 13–63: 14–16% decrease in sperm concentration, viability, and motility; 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									
44	Rat (Sprague-Dawley) NS F	8 days GD 14–PND 0 (GO	0, 0.1, 10	DX	Develop	10			
Walker et al. 2020 [Reproductive function was assessed in adult male offspring.]									
45	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]									
46	Rat (Sprague-Dawley) 10 F	4 days (GO)	0, 20, 200, 2,000	BW, OW	Bd wt Repro	2,000 2,000			

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
Zacharewski et al. 1998 [mature ovariectomized rats]									
47	Rat (Sprague-Dawley) 6 M	14 days PNDs 22–35	0, 50, 150, 450	DX	Develop	50	150	450	Decreased absolute (-30%) and relative (-23%) testis weight, decreased thickness and vacuolization of the seminiferous epithelium at ≥150 mg/kg/day; severe vacuolization of seminiferous epithelium and lack of spermatids in tubules at 450 mg/kg/day
Zhang et al. 2018a									
48	Mouse (CD-1) NS F	10 days GD 11 – PND 0	0, 0.2, 500, 750 (micro-pipette)	DX	Develop		0.2		Increased anxiety (48% fewer entries into center of an open field); impaired memory, 26–38% fewer hippocampal pyramidal neurons, and altered histology of pyramidal neurons at ≥500 mg/kg/day
Barakat et al. 2018									
49	Mouse (CD-1) 9–20 F	10 days GDs 9–18	0, 0.0005, 0.001, 0.005, 0.5, 50, 500 (micro-pipette)	BC, DX, RX	Repro Develop	500 0.5	 50		Decreased fetal testes weight
Do et al. 2012									
50	Mouse (A/J) 10 M	2 weeks (F)	0, 12.3, 125	BW, FI, WI, HP, RX	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									
51	Mouse (C57BL/6) 4 M	5 days (G)	0, 4, 40, 400, 2000	BC	Other noncancer	400	2,000		Impaired glucose homeostasis (increased blood glucose with glucose challenge)

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
Lee et al. 2019a									
52	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									
53	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		Reversible liver lesions in PND 21 offspring (pyknotic nuclei, hepatocyte vacuolization)
Maranghi et al. 2010									
54	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									
55	Mouse (B6C3F1) 5 M, 5 F	14 days (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
NTP 1982									
56	Mouse (C57BL/6) 6 M	10 days (F)	0, 180, 360	BW, OW, IX	Bd wt	360			
					Immuno	360			
Sasaki et al. 2003									

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
57	Mouse (C57BL/6) 8–18 F	10 days GDs 7–16 (GO)	0, 5, 250, 500	CS, BW, RX, DX	Bd wt	500			
					Repro	5		250	Increased resorptions, 67% and 94% decrease in number of pups/litter at 250 and 500 mg/kg/day, respectively
					Develop	5		250	<50% fetal survival; increased total malformations, limb malformations, exencephaly; ~10% decrease in surviving female fetal weight
Ungewitter et al. 2017 [Females were mated with unexposed B6129S4 males.]									
58	Mouse (ICR) 8–10 F	14 days GDs 0–14 (GO)	0, 50, 200	BC	Repro		50		240% increase in serum progesterone
Zhang et al. 2020b									
59	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									
60	Rabbit (NS) 4–5 M	7 days (GO)	0, 2,000	LE	Death			2,000	50% died
Parmar et al. 1988									
61	Rabbit (NS) NS	Once (G)	NS	CS, BW	Death			33,900	LD_{50}
Shaffer et al. 1945									
INTERMEDIATE EXPOSURE									
62	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			

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
					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									
63	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									
64	Rat (Fischer-344) 24 M	60 days (F)	0, 17.5, 69.2, 284.1, 1,156.4	BW, FI, BC, OW, HP, 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									
65	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									
66	Rat	28 days PNDs 62–89	0, 1, 10, 100, 200	BC, BW, HP, RX	Bd wt	200			
					Repro	200			

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
	(Long-Evans) 10 M	(GO)							
Akingbemi et al. 2001									
67	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									
68	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									
69	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									
70	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, RX, 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

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
									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									
71	Rat (Long-Evans) 12 F	42 days GD 1–PND 21 (W)	0, 3, 30	BW, DX, RX	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									
72	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									
73	Rat				Bd wt	400			

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
	(Wistar) 6 M	4 weeks (GO)	0, 100, 200, 400	BW, BC, BI, HP, OW	Hepatic		100		Histopathological changes (increased congestion, mononuclear cell infiltration, sinusoidal degeneration), 18-21% increase in serum ALT and AST, 57% increase in absolute liver weight
					Renal		100		Histopathological changes (increased glomerular degeneration, congestion and mononuclear cell infiltration), 25% increase in absolute kidney weight; increased serum urea at ≥200 mg/kg/day
					Other noncancer		100		10% increase in serum glucose
Aydemir et al. 2018									
74	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 1986 [Female reproductive organs were not assessed.]									
75	Rat (Sprague-Dawley)	24 weeks (3-generation)	0.1, 0.58, 1.7, 5.9, 17, 57, 447, 659	BW, FI, OW, HP, RX, DX	Bd wt	57 M	447 M		10–19% decreased F1/F2 body weight; no change in food consumption

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 M, 17 F	6 weeks premating through 3 weeks post-weaning of 3rd litter (F)				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 ≥47 mg/kg/day and F1 pups at 659 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]

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 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									
77	Rat (Sprague-Dawley) 6 M	21 days PNDs 3–23 (G)	0, 60, 300, 600	DX	Develop		60	600	LOAEL: decreased seminiferous tubule diameter, 15–24% decrease in testis and seminal vesicle weight; decreased testicular tissue area, germinal cell depletion, 15% decrease in kidney weight and renal tubule degeneration Serious LOAEL: 27% decrease in body weight, developmental malformations in the lung parenchyma, hepatocellular hypertrophy and increased liver weight[b]
Camacho et al. 2020 [Vehicle was Intralipid 20%.]									
78	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
79	Rat (Wistar) 3 F	36 days GD 1–PND 15 (W)	0, 3, 30	DX, RX	Repro	30			
					Develop	3	30		Decreased testes weight and increased serum LH and FSH at PND 15
Carbone et al. 2012									
80	Rat (Wistar) 5 F	30 days PNDs 1–21 (via dam) PNDs 22–30 (W)	0, 30	DX	Develop	30			
Carbone et al. 2013									
81	Rat (Wistar) 5 F	45 days PNDs 1–21 (via dam) PNDs 22–45 (W)	0, 30	DX	Develop	30F	30 M		Increased anxiety-like behavior in elevated plus maze
Carbone et al. 2013									
82	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									
83	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 at ≥100 mg/kg/day; increased thickness of alveolar septa and increased interstitial lung tissue proportion at 750 mg/kg/day
Chen et al. 2010									
84	Rat	31 days			Bd wt	100			

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
	(Wistar) 8–16 F	GD 7–PND 16 (GO)	0, 3, 10, 30, 100	BI, BW, DX, RX	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									
85	Rat (Wistar) 8–16 F	31 days GD 7–PND 16 (GO)	0, 10, 30, 100, 300, 600, 900	BI, BW, DX, RX	Bd wt	900			
					Repro	900			
					Develop		10		Decreased AGD, increased nipple retention, decreased adrenal gland and LABC muscle weight at ≥10 mg/kg/day; decreased birth weight, mild external genital dysgenesis, decreased reproductive organ weights, and Leydig cell hyperplasia at ≥300 mg/kg/day
Christiansen et al. 2010									
86	Rat (Wistar) 8–10 M	4 weeks (G)	0, 1,000, 5,000, 10,000	LE, CS, BW, FI, WI, OW, HP, NX, RX	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

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
									of seminiferous tubules, and diffuse Leydig cell hyperplasia
Dalgaard et al. 2000									
87	Rat (Wistar) 10 M	9 weeks (GO)	0, 125, 250, 500, 1,000	CS, BW, FI, WI, OW, HP, NX	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									
88	Rat (Wistar) 10–12 F	42 days GD 1–PND 21 (GO)	0, 20, 100, 500	BW, DX, RX	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									
89	Rat (Wistar) 20 F	4 weeks GD 0–PND 7 (GO)	0, 30, 300, 750	DX	Develop		30		Decreased total T4, increased TSH levels, and altered ultrastructure of thyroid follicular cells at PND 7
Dong et al. 2019									

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
90	Rat (Wistar) 20 F	5 weeks GD 0–PND 14 (GO)	0, 30, 300, 750	DX	Develop		30		Decreased total T4, increased TSH levels, and altered ultrastructure of thyroid follicular cells at PND 14
Dong et al. 2019									
91	Rat (Wistar) 20 F	6 weeks GD 0–PND 21 (GO)	0, 30, 300, 750	DX	Develop		30		Altered ultrastructure of thyroid follicular cells at PND 21; decreased T4 and increased TSH at ≥300 mg/kg/day
Dong et al. 2019									
92	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									
93	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									

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
94	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 ≥142 mg/kg/day; decreased absolute and relative 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

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
95	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, RX	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									
96	Rat (Sprague-Dawley) 15 M	9 weeks (GO) PNDs 42–105	0, 0.03, 0.1, 0.3, 1	BW, OW, RX	Bd wt	1			
					Repro	0.03	0.1		167% increase in percent sperm with bent tails
Hsu et al. 2016									
97	Rat (Sprague-Dawley) 9–10 M, 9–10 F	13 weeks PNDs 6–96 (direct) (GO)	0, 0.3, 3, 30, 150	CS, BW, FI, BC, BI, HE, OW, GN, HP, DX	Bd wt	150			
					Hemato	150			
					Hepatic	150			Increased absolute and relative liver weight at 150 mg/kg/day[b]
					Renal	30	150		≥10% increase in relative kidney weight
					Endocr	30 M	150 M		Increased thyroid cell proliferation in females at ≥30 mg/kg/day and males at 150 mg/kg/day; thyroid hyperplasia and hypertrophy in both sexes at 150 mg/kg/day
						3 F	30 F		
					Repro	150 M			16–17% decreased in absolute and relative left ovary weight
						3 F	30 F		
					Develop	150			
Kim et al. 2018c, 2018d									

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
98	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									
99	Rat (Long-Evans) 8 M	21 days (GO)	0, 10, 750	BC, RX	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									
100	Rat (Long-Evans) 8 M	35 days (GO)	0, 10, 750	BC, RX	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									
101	Rat (Long-Evans) 2–6 F	19 days GDs 2–20 (GO)	0, 10, 100, 750	BW, DX, RX	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									

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 (Long-Evans) 11–13 F	31 days GD 12.5–PND 21.5 (GO)	0, 10, 750	BW, DX, RX	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									
103	Rat (Wistar) 10–12 F	42 days GD 0–PND 21 (GO)	0, 1.25, 6.25	BC, BW, RX	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									
104	Rat (Wistar) 12 F	4 weeks PNDs 22–49 (direct) (GO)	0, 250, 500, 1,000	DX	Develop		250		Increased serum GH at ≥250 mg/kg/day; longer estrous cycle, increased hypothalamic GH, increased serum progesterone, and decreased serum FSH, LH, and testosterone at ≥500 mg/kg/day; accelerated vaginal opening at 1,000 mg/kg/day
Liu et al. 2018a									
105	Rat (Sprague-Dawley) 6 M	30 days (GO)	0, 500	BW, FI, NX	Bd wt	500			
					Neuro		500		Increased anxiety
Liu et al. 2018b									

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
106	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									
107	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									
108	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

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
									neutrophils, and myeloid/erythroid ratio
					Musc/skel	1,857.6			
					Hepatic	1,724			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
						301.8 F	918.4 F		Increased kidney weight and BUN
					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			
					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									

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
109	Rat (Sprague-Dawley) 12–14 F	5 weeks GD 8–PND 21 (GO)	0, 30, 300	CS, BC, BW, OW, RX, DX	Bd wt	300			
					Cardio	30	300		13% decrease in relative heart weight
					Hepatic	300			
					Repro	300			
					Develop	30	300		Males: 10% decrease in AGI and increased multinucleated gonocytes (PND 3); increased incidences of hemorrhagic testes (PND 8); females: delayed vaginal opening
Nardelli et al. 2017									
110	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									
111	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									

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
112	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									
113	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									
114	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									
115	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									
116	Rat (Fischer-344) 10 M, 10 F	13 weeks (F)		CS, HP	Resp Cardio Gastro Musc/skel	3,000 3,000 3,000 3,000			

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
			M: 0, 150, 300, 620, 1,300, 2,600 F: 0, 180, 340, 700, 1,400, 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									
117	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									
118	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									
119	Rat (Wistar) 3 F	3 weeks PNDs 1–21 (GO)	0, 1, 10, 100	DX	Develop		1	10	LOAEL: 5–9% decrease in body weight from PND 9 to 22 Serious LOAEL: ≥10% decrease body weight from PNDs 9–12 at ≥10 mg/kg/day; 10% increase in fasting blood glucose levels observed at 100 mg/kg/day
Parsanathan et al. 2019									
120	Rat (Sprague-Dawley) 12 F	16 days (GO)	0, 37.5, 75, 150, 300	BI, BW, HP, OW, IX	Bd wt	300			
					Immuno	300			
Piepenbrink 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
121	Rat (Sprague-Dawley) 12–13 F	16 days GDs 6–21 (GO)	0, 37.5, 75, 150, 300	DX, RX	Repro	300			
					Develop		37.5		Increased AGD
Piepenbrink et al. 2005									
122	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			
					Repro	3.7 M	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
						419.3 F			
Poon et al. 1997									

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	Rat (Wistar) 6 F	6 weeks GD 9–PND 21 (GO)	0, 10, 100	DX	Develop		10		13% decrease in body weight; altered glucose homeostasis; decreased serum testosterone and estradiol; increased serum ALT (116%), AST (200%), ALP (34%), urea (117%), and creatinine (50%)
Rajagopal et al. 2019a [Endpoints were assessed in male PND 80 offspring.]									
124	Rat (Wistar) 6 M	30 days (GO)	0, 10, 100	BC, BI	Other noncancer		10		Altered glucose metabolism/ homeostasis
Rajesh et al. 2013									
125	Rat (Sprague-Dawley) 4 M, 4 F	5 months (F)	0, 100, 300	NX	Neuro		100		Impaired spatial learning
Ran et al. 2019									
126	Rat (Wistar) 10 M, 10 F	~19 weeks (2-generation) (F)	0, 130, 380, 1,040	BW, CS, DX, FI, HP, RX, OW	Death			1,040	3/9 F1 males and 2/9 F1 females died
					Bd wt	380 F			Decreased F0 and F1 body weight and food consumption at 1,040 mg/kg/day
						1,040 M			
					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 fertility, pups/dam, post-implantation loss, decreased reproductive organ weight, testicular lesions

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
					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									
127	Rat (Wistar) 25 M, 25 F	19 weeks (2-generation) ~10 weeks premating–PND 21 (F)	0, 113, 340, 1,088	LE, CS, BW, FI, OW, HP, RX, NX	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
					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	1,088 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

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
						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									
128	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									
129	Rat (Wistar) 12 F	4 weeks PNDs 15–43 (GO)	0, 0.2, 1, 5	CS, DX	Develop	0.2	1		20-30% increase in serum IGF-1 and serum and hypothalamic GnRH at 1 mg/kg/day; increased hypothalamic IGF-1, accelerated vaginal opening, and clinical signs of toxicity (lassitude, anorexia, hair loss and yellowing) at 5 mg/kg/day
Shao et al. 2019									

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
130	Rat (Wistar) 10 M, 10F	28 days (GO)	0, 5, 50, 500	BW, BC, BI	Bd wt		5		10% increase in body weight
					Endocr	50	500		Increased serum total T3 and T4, increased hypothalamic thyrotropin-releasing hormone
Sun et al. 2018									
131	Rat (Wistar) 5 F	3 weeks PNDs 1–21 (GO)	0, 7.5, 75	CS, BW, FI, DX	Bd wt	75			
					Develop		7.5		Effects in offspring at PNDs 90–92: Impaired glucose homeostasis and decreased serum triglycerides at ≥7.5 mg/kg/day; decreased serum at 75 mg/kg/day
Venturelli et al. 2015									
132	Rat (Wistar) 15 M	30 days PNDs 22–52 (GO)	0, 7.5, 75	DX	Develop	7.5	75		30% increase in fasting serum glucose
Venturelli et al. 2015									
133	Rat (Wistar) 7–8 F	4 weeks GD 13–PND 21 (GO)	0, 7, 70, 700	BW, OW, RX, DX	Bd wt	700			
					Repro	700			
					Develop	7	70	700	LOAEL: Decreased insulin secretion in pancreatic islet cells in males; delayed vaginal opening in females Serious LOAEL: Hypospadias; additional effects at this dose included >10% increase in body weight postweaning in both sexes, reduced AGI in males, delayed preputial separation, altered glucose homeostasis, increased serum cholesterol in males

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
					Other noncancer	700			
Venturelli et al. 2019									
134	Rat (Sprague-Dawley) 4 M	15 days 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									
135	Rat (Sprague-Dawley) 12 F	5 weeks GD 7–PND 21 (GO)	0, 0.01, 0.1, 1	DX	Develop	0.01	0.1		Decrease in absolute (52%) and relative (46%) epididymal weight in adult offspring
Wang et al. 2017a [Male offspring sacrificed on PND 196.]									
136	Rat (Wistar) 6–7 F	6 weeks GD 0–PND 21 (G)	0, 30, 300	DX	Develop		30		Enhanced immune response to OVA challenge in sensitized offspring
Wang et al. 2018 [OVA-sensitized offspring evaluated on PNDs 14, 21, and 28.]									
137	Rat (Sprague-Dawley) 6 M	30 days (W)	0, 300, 1,000, 3,000	BW, BC, OW, HP	Bd Wt		300		20% increase in body weight gain
					Gastro	3,000			
					Hepatic		300		Decreased serum cholesterol at ≥300 mg/kg/day; mild steatosis at ≥1,000 mg/kg/day; 21% increase in relative liver weight and increased serum ALT, ALP, and AST at 3,000 mg/kg/day
					Immuno		300		Increased IL-12 and TNF-α at ≥300 mg/kg/day; increased IFN-γ and IL-2 at 3,000 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
					Repro		300		Mild localized necrotic degeneration of seminiferous tubules and interstitial edema at ≥300 mg/kg/day; 60% decrease in serum testosterone at 3,000 mg/kg/day
Wang et al. 2020									
138	Rat (Wistar) 6 M	30 days (W)	0, 300, 1,000, 3,000	BW, BC, OW, HP	Bd Wt	3,000			
					Gastro	3,000			
					Hepatic	300	1,000		Slight centrilobular steatosis at ≥1,000 mg/kg/day; decreased serum cholesterol at 3,000 mg/kg/day
					Immuno	3,000			
					Repro	3,000			
Wang et al. 2020									
139	Rat (Wistar) 10 F	42 days GD 0–PND 21 (GO)	0, 0.25, 6.25	BW, DX, RX	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									
140	Rat (Wistar) 10 M, 10 F	28 days (GO)	0, 5, 50, 500	BW, FI, WI BC, OW	Bd wt	500			
					Hepatic	500			Increased relative liver weight at 500 mg/kg/day[b]
					Other noncancer	5	50		Altered glucose homeostasis; increased serum leptin
Xu et al. 2018									
141	Rat (Wistar)	30 days (G)	0, 0.7, 70	HP, BI, IX	Immuno		0.7		Enhanced immune response to OVA challenge in sensitized

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
	8 M								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									
142	Rat (Sprague-Dawley) 6 M	30 days (GO)	0, 250, 500, 750	LE, CS, BW, BC, OW, HP	Bd wt	750			
					Hepatic	250	500		Vacuolation, hepatic sinusoidal dilation, and reduction in hepatocyte number at ≥500 mg/kg/day; Increased liver weight and hepatocellular hypertrophy at ≥250 mg/kg/day[b]
					Endocr		250		Increased number of thyroid follicular epithelial cells at ≥250 mg/kg/day; decreased serum TT4, FT4, and TT3 at ≥500 mg/kg/day; decreased serum FT3 and TRH and follicular cavity diameter and altered thyroid ultrastructure at 750 mg/kg/day
Ye et al. 2017									
143	Rat (Sprague-Dawley) 10 M	15 weeks (GO)	0, 0.05, 5, 500	BW, BC, OW, HP	Bd wt	500			
					Hepatic		0.05		Vacuolar degeneration and inflammatory infiltration at ≥0.05 mg/kg/day; 26% increase in relative liver weight and 145% increase in serum ALP at ≥5 mg/kg/day; increased serum ALT (100%) and AST (70%) and central necrosis at 500 mg/kg/day
					Other noncancer	0.05	5		Altered glucose homeostasis
Zhang et al. 2017									

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
144	Rat (Sprague-Dawley) 8 M	31 days (GO)	0, 500	CS, BW, FI, BC, OW, HP	Bd wt	500			
					Endocr		500		Decreased free T4 and TSH; microscopic and ultrastructural changes in thyroid follicular cells
Zhang et al. 2018b									
145	Rat (Wistar) 10 M, 10 F	8 weeks (GO)	0, 5, 50, 500	BW, BC, HP	Bd wt	500			
					Hepatic		5		Disordered hepatocyte cords and vacuolar degeneration at ≥5 mg/kg/day; increased serum cholesterol and HDL at 500 mg/kg/day
					Other noncancer		5		Increased volume of adipocytes at ≥5 mg/kg/day; increased number of adipocytes at 500 mg/kg/day
Zhang et al. 2019, 2020c									
146	Rat (Wistar) 10 M, 10 F	8 weeks (GO)	0, 5, 50, 500	BW, BC, HP	Bd wt	50	500		>10% increase in body weight
					Hepatic	50	500		30% in increase cholesterol, 95% increase in HDL, 26% increase in LDL
					Other noncancer	5	50		Irregular adipocytes and macrophage infiltration in adipose tissue, increased serum leptin and decreased adiponectin at ≥50 mg/kg/day; increased number and volume of adipocytes at 500 mg/kg/day
Zhou et al. 2019									
147	Mouse (C57BL/6J x FVB) 6 F	9 weeks 2 weeks pre-mating to PND 21 (F)	0, 0.003, 0.03, 0.3, 3.3, 10, 33, 100	LE, CS, BW, FI, RX, DX	Bd wt	100			
					Repro	100			
					Develop	100			

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
Bastos Sales et al. 2018 [Some endpoints (locomotor activity, object recognition, and glucose homeostasis at weeks 27–40) were only assessed at 33 mg/kg/day.]									
148	Mouse (CD-1) 10 B	10 weeks 2 weeks premating – PND 21 (W)	0, 0.034, 0.34	BW, OW, HP, RX	Repro	0.34			
Cha et al. 2018									
149	Mouse (CD-1) 12 M	8 weeks (GO)	0, 1, 10, 100	BW, OW, HP	Bd wt	100			
					Musc/ Skel	1	10		25% decrease in trabecular bone mineral density, 17% decrease in bone volume fraction, reduced osteoblastogenesis and mineralization of bone marrow stromal cells; reduced trabecular bone thickness and cell number at 100 mg/kg/day
Chiu et al. 2018c									
150	Mouse (C57/BL6) 8 M	6 weeks (G)	0, 0.1, 1, 10	BC, BI, HP, OF	Cardio		0.1		13% increase in systolic blood pressure, thickening of interventricular septum and ventricular wall; increased heart rate at ≥1 mg/kg/day
Deng et al. 2019									
151	Mouse (ICR) 10 M	3 weeks (IN)	0, 0.18, 1.8, 18, 180	CS, BW, BC, BI, OW, OF	Bd wt	180			
					Cardio	18	180		10% increased heart rate, 29% increased mean blood pressure
					Hepatic	0.18	1.8		Increased total cholesterol at 1.8 mg/kg/day; decreased HDL cholesterol at ≥18 mg/kg/day; increased triglycerides, LDL cholesterol, ALT, and ALP at 180 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
					Other noncancer	18	180		60% increase in blood glucose
Ding et al. 2019									
152	Mouse (ICR) 6 F	28 days 7 days premating – PND 0 (G)	0, 0.2	DX	Develop		0.2		15% increase in body weight, increased white adipose tissue, and metabolic syndrome (reduced energy expenditure, abnormal glucose metabolism, and altered lipid profile) in male offspring
Fan et al. 2020 [Offspring were evaluated at PNW 12.]									
153	Mouse (ICR) 10 M	3 weeks (GO)	0, 0.18, 1.8, 18, 180	BW, BI, OW, NX	Bd wt	180			
					Neuro		0.18		Impaired learning and memory and reduced swim speed at ≥0.18 mg/kg/day; decreased anxiety at ≥1.8 mg/kg/day; decreased locomotor activity at 18 mg/kg/day
					Repro	18	180		15% decrease in relative testes weight
Feng et al. 2020									
154	Mouse (C57Bl/6J) 6–7 F	19 days GD1–19 (GO)	0, 0.05, 500	FI, RX, DX	Repro	0.05		500	100% litter loss
					Develop		0.05		Metabolic syndrome in PNW 9 offspring: increases in serum leptin (11–13%) and insulin (22-26%), fasting glucose levels (16%), and visceral fat weight (24–37%)
Gu et al. 2016									
155	Mouse (BALB/c) 8 M	52 days (G)	0, 0.03, 0.3, 3	BC, HP, IX	Immuno		0.03		Enhanced immune response to OVA challenge in sensitized animals (80% increase in serum total IgE); enhanced responses in

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
									non-sensitized animals at 3 mg/kg/day
Guo et al. 2012									
156	Mouse (BALB/c) 4 M, 4 F	28 days (GO)	0, 0.03, 0.3, 3	IX	Immuno		0.03		Enhanced humoral immune response to OVA challenge in sensitized animals (45–75% increase in OVA-specific IgE and IgG)
Han et al. 2014a									
157	Mouse (CD-1) 8 F	30 days (GO)	0, 0.02, 0.2, 20, 200	BW, OW, RX	Bd wt	200			
					Repro	20	200		Increased percentage of days spent in estrus
Hannon et al. 2014									
158	Mouse (A/J) 10 M	4 weeks (F)	0, 12.3, 125	BW, FI, WI, HP	Bd wt	125			
					Repro		12.3		Sertoli cell vacuolation and germ cell sloughing in seminiferous tubules
Kitaoka et al. 2013									
159	Mouse (Cr1:CD-1) 20 M, 20 F	18 weeks (F)	0, 13, 130, 390	BW, BC, OW, HP, DX, RX	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]									

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
160	Mouse (C57BL/6) 17 M	35 days (G)	0, 1, 10, 100, 300	BW, BC, BI, OW, HP	Bd Wt	300			
					Cardio	1	10		≥10% increase in relative heart weight at ≥1 mg/kg/day; increased lipid droplets in cardiac papillary muscle cells at ≥100 mg/kg/day
					Hepatic		1		Increased serum ALT and triglycerides (≥1 mg/kg/day), cholinesterase (≥10 mg/kg/day), and cholesterol at (≥100 mg/kg/day)
					Renal	100	300		43% increase in serum creatinine
					Endocr	10	100		20% increase in serum T4
					Other noncancer	100	300		68% increase in blood glucose
Li et al. 2018									
161	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

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
					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 7,899 F	2,579 M		Decreased testes weight at ≥2,579 mg/kg/day; testicular atrophy and decreased spermatogenesis at 6,922 mg/kg/day
Myers 1992a									
162	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	CS, HP	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			

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
NTP 1982									
163	Mouse (CD-1) 28–29 F	18 days GDs 0–17 (F)	0, 19, 48, 95	BW, FI, DX, RX	Bd wt	95			
					Repro	48	95		19% decrease in live pups/litter
					Develop	48		95	11% decrease in postnatal viability from PND 1 to 4
NTP 1988									
164	Mouse (CD-1) 6 F	30 days (IN)	0, 0.02, 0.2, 2	RX	Repro	0.02	0.2		Increased unfertilized oocyte rate and percent of zygotes with fragmentation, arrested zygote development, and decreased preimplantation embryos
Parra-Forero et al. 2019 [Females mated to untreated males; uterine contents evaluated at 24, 48, 74, 84, or 96 hours post-mating.]									
165	Mouse (CD-1) 7–10 F	42 days GD 0–PND 21 (F)	0, 0.05, 5, 500	OW, RX, DX	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									
166	Mouse (NC/Nga) 12 M	4 weeks 1 day/week (GO)	0, 0.0475, 0.095, 19	BC, CS, HP, IX	Immuno	19			
Sadakane et al. 2014 [mite-sensitized mice]									
167	Mouse (C57BL/6) 6 M	20 days (F)	0, 180, 360	BW, OW, IX	Bd wt	360			
					Immuno	360			
Sasaki et al. 2003									

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
168	Mouse (C3H/N) 15 F	8 weeks 7 weeks premating GD1 (F)	0, 0.05, 5, 500	BW, CS, FI, RX	Bd wt		0.05		~18% 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									
169	Mouse (C3H/N) 15 F	8 weeks 7 weeks premating–GD 1 (F)	0, 0.05, 5, 500	BW, CS, FI, RX, DX	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									
170	Mouse (ICR) 12–17 F	18 days GDs 0–17 (GO)	0, 50, 200	LE, BW, FI, RX, DX	Bd wt	200			
					Repro	200			
					Develop			50	≥10% decrease in fetal weight, 4% decrease in crown-rump length
Shen et al. 2017									

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
171	Mouse (ICR) 7–12 F	18 days GDs 1–18 (F)	0, 85, 170, 341, 683, 1,707	BW, FI, RX, DX	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									
172	Mouse (CD-1) 10 M, 10 F	17 weeks 4 weeks premating–PNW 9 (F)	0, 20.62, 60.42, 180.77	BW, FI, RX, DX, NX	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 TWAs across sex and generation.]									
173	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									

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
174	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									
175	Mouse (CD-1) 24–25 F	17 days GDs 0–17 (F)	0, 44, 91, 191, 292	BW, CS, FI, WI, OW, GN, RX	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;

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
									decreased fetal weight at ≥191 mg/kg/day
Tyl et al. 1988									
176	Mouse (BALB/c) 6 M	30 days (W)	0, 300, 1,000, 3,000	BW, BC, OW, HP	Bd Wt	3,000			
					Gastro	3,000			
					Hepatic	300	1,000		Increased serum ALP at ≥1,000 mg/kg/day; mild steatosis at 3,000 mg/kg/day
					Immuno	3,000			
					Repro	300	1,000		33% decrease in serum testosterone, slight localized degeneration of germ cells
Wang et al. 2020									
177	Mouse (C57BL/6J) 6 M	30 days (W)	0, 300, 1000, 3000	BW, BC, OW, HP	Bd Wt	3,000			
					Gastro	3,000			
					Hepatic		300		Mild inflammatory cell infiltrates at ≥300 mg/kg/day; 11% increase in relative liver weight at 3,000 mg/kg/day
					Immuno		300		Increased IL-1-α at ≥300 mg/kg/day; increased IL-6 and MCP-1 at 3,000 mg/kg/day
					Repro	1,000	3,000		Slight seminiferous tubule atrophy
Wang et al. 2020									
178	Mouse (Sv/129) 15 M	24 weeks (F)	0, 2,400	LE	Death			2,400	100% mortality between weeks 12 and 16
Ward 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
179	Mouse (C57BL/6) 9 M	45 days (G)	0, 0.1, 1, 10	CS, BW, BC, BI, HP, OF	Cardio		0.1		Increased mean and systolic blood pressure, thickened aortic wall, and hypertrophied and disordered aortic smooth muscle cells at ≥0.1 mg/kg/day; increased diastolic blood pressure at ≥1 mg/kg/day
					Renal	0.1	1		Glomerular damage, increased inflammatory cell infiltration
					Repro	10			
Xie et al. 2019									
180	Mouse (ICR) 7–15 M	28 days (GO)	0, 4, 400	BW, HE BC, OW, HP	Bd Wt	400			
					Hemato	400			
					Hepatic	400			Increased absolute liver weight and hepatocellular hypertrophy at 400 mg/kg/day[b]
					Renal	4	400		10% increase in absolute kidney weight
					Endocr	4	400		145% Increase in absolute adrenal gland weight
					Immuno	400			
					Neuro	400			
					Repro	4	400		24% increase in absolute testis weight; 16% increase in absolute prostate weight
Xu et al. 2019									

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
181	Mouse (CD-1) 5 F	20 days GDs 0.5–18.5 (NS)	0, 0.04	BC, DX	Repro		0.04		25% decrease in maternal serum estradiol
					Develop		0.04[d]		Delayed meiotic progression of germ cells in GD 17.5 F1 fetuses (cells in leptotene and zygotene stages increased by 22 and 31%, respectively); accelerated folliculogenesis in F1 and F2 PND 21 offspring (20% increase in secondary follicles)
Zhang et al. 2015									
182	Guinea pig (NS) 4–5 M	15 days (GO)	0, 2,000	LE	Death			2,000	40% mortality
Parmar et al. 1988									
183	Rabbit (NS) NS M	15 days (GO)	0, 2,000	LE	Death			2,000	100% mortality
Parmar et al. 1988									
CHRONIC EXPOSURE									
184	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]									
185	Rat (Sherman) 32 M, 32 F	2 years (F)	0, 20, 65, 200	BC, BW, HP, OW, RX	Bd wt	200			
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hemato	200			

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
					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			
Carpenter et al. 1953 [combined chronic and reproductive study; high-dose F1 animals maintained for 1 year]									
186	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.]									
187	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 and Kupffer cells at 789 mg/kg/day
						182 F	939 F		Increased cytoplasmic eosinophilia and Kupffer cells
					Renal	36	147		Increased kidney weight at ≥147 mg/kg/day; increased

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
									severity of 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									
188	Rat (Sprague-Dawley) 7–18 M	102 weeks (F)	0, 14, 140, 1,400	CS, EA, HP	Repro		14		"Inhibition" of spermatogenesis and general tubule atrophy (magnitude not reported)
Ganning et al. 1991									
189	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
190	Rat (Fischer-344) 50 M, 50 F	2 years (F)	M: 0, 322, 674 F: 0, 394, 774	BW, FI, HP, GN	Bd wt	774			
					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									
191	Rat (Fischer-344) NS M	365 days (F)	0, 930	BW, FI, OW HP, BI	Bd wt	930			
Marsman 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
192	Rat (Wistar) NS	2 years (F)	0, 2,000	HP	Repro			2,000	Testicular atrophy
Price et al. 1987									
193	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.]									
194	Rat (Fischer-344) 10–14 M	108 weeks (F)	0, 1,600	BW, HP, OW	Resp	1,600			
					Gastro		1,600		Pseudoductular lesions and altered acinar cell foci in the pancreas
					Renal	1,600			
					Cancer			1,600	CEL: hepatocellular carcinoma, pancreatic islet-cell adenoma
Rao et al. 1990									
195	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
196	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		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									
197	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									

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
198	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			
					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

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
199	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			
Carpenter et al. 1953 [Female reproductive organs were not assessed.]									
200	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			
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
201	Ferret (albino) 7 M	14 months (F)	0, 1,200	BI, BW, EA, OW, HP	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 an 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 an MRL of 0.003 mg/kg/day ($3x10^{-3}$ mg/kg/day).
[d]Used to derive an 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 an MRL of 0.0001 mg/kg/day ($1x10^{-4}$ mg/kg/day).

AGD = anogenital distance; AGI = anogenital index; ALP = alkaline phosphatase; ALT= alanine aminotransferase; AST = aspartate transaminase; B = both males and females (number per sex not reported); BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; 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; FT3 = free triiodothyronine; FT4 = free thyroxine; (G) = gavage; Gastro = gastrointestinal; GD = gestational day; GH = growth hormone; GN = gross necropsy; GnRH = gonadotropin-releasing hormone; (GO) = gavage in oil; HDL = high density lipoprotein; HE = hematology; Hemato = hematological; HP = histopathology; IFN-γ = interferon gamma; IGF-1 = insulin-like growth factor-1; IL = interleukin; Immuno = immunological; (IN) = ingestion; IX = immunotoxicity; LABC = levator ani/bulbocavernosus; LDL = low density lipoprotein; 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); MCP-1 = monocyte chemoattractant protein-1; Musc/skel = musculoskeletal; Neuro = neurological; NX = neurotoxicity; 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; RX = reproductive toxicity; T3 = triiodothyronine; T4 = thyroxine; TNF-α = tumor necrosis factor-alpha; TRH = thyrotropin-releasing hormone; TSH = thyroid stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyroxine; 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)

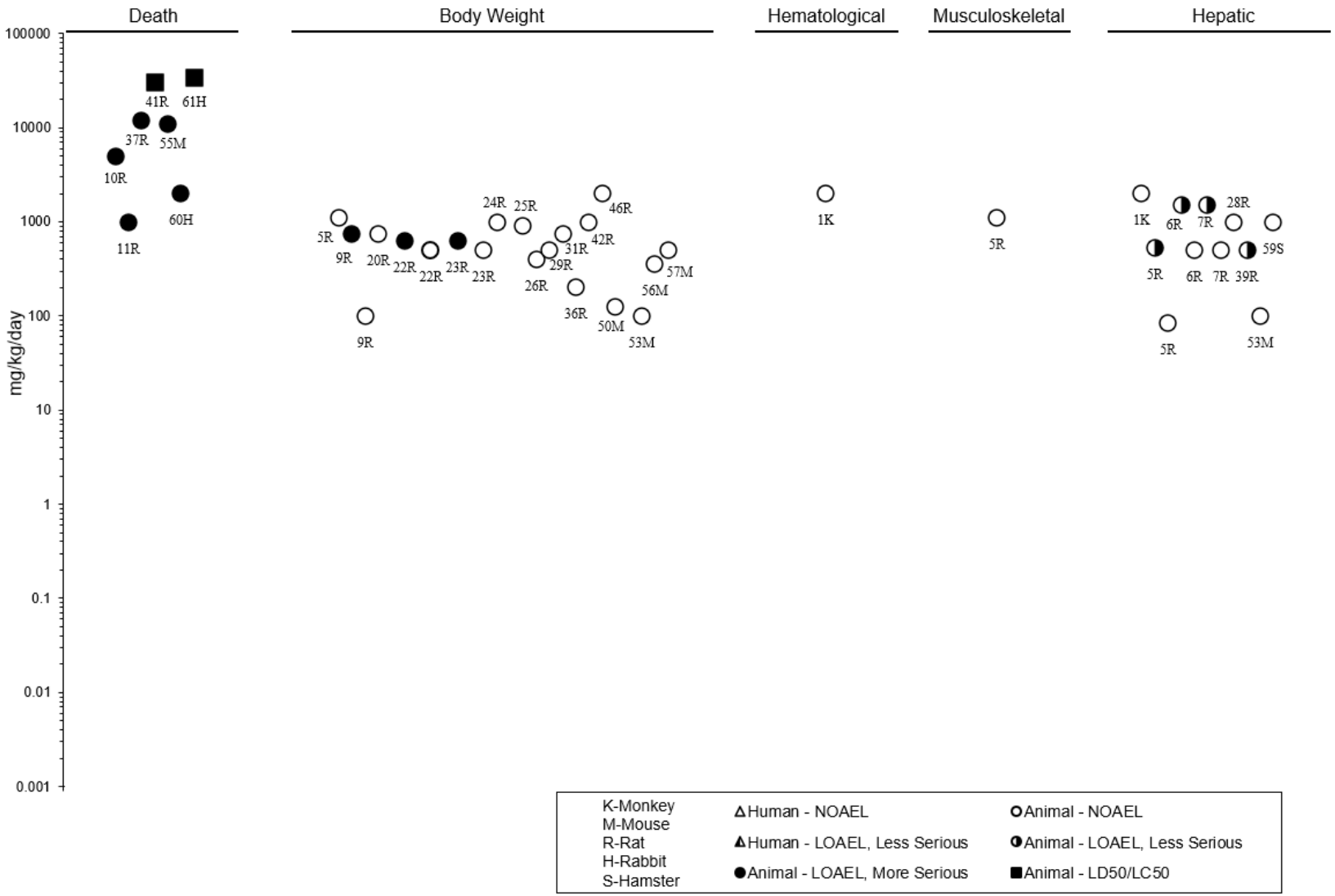


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Acute (≤14 days)

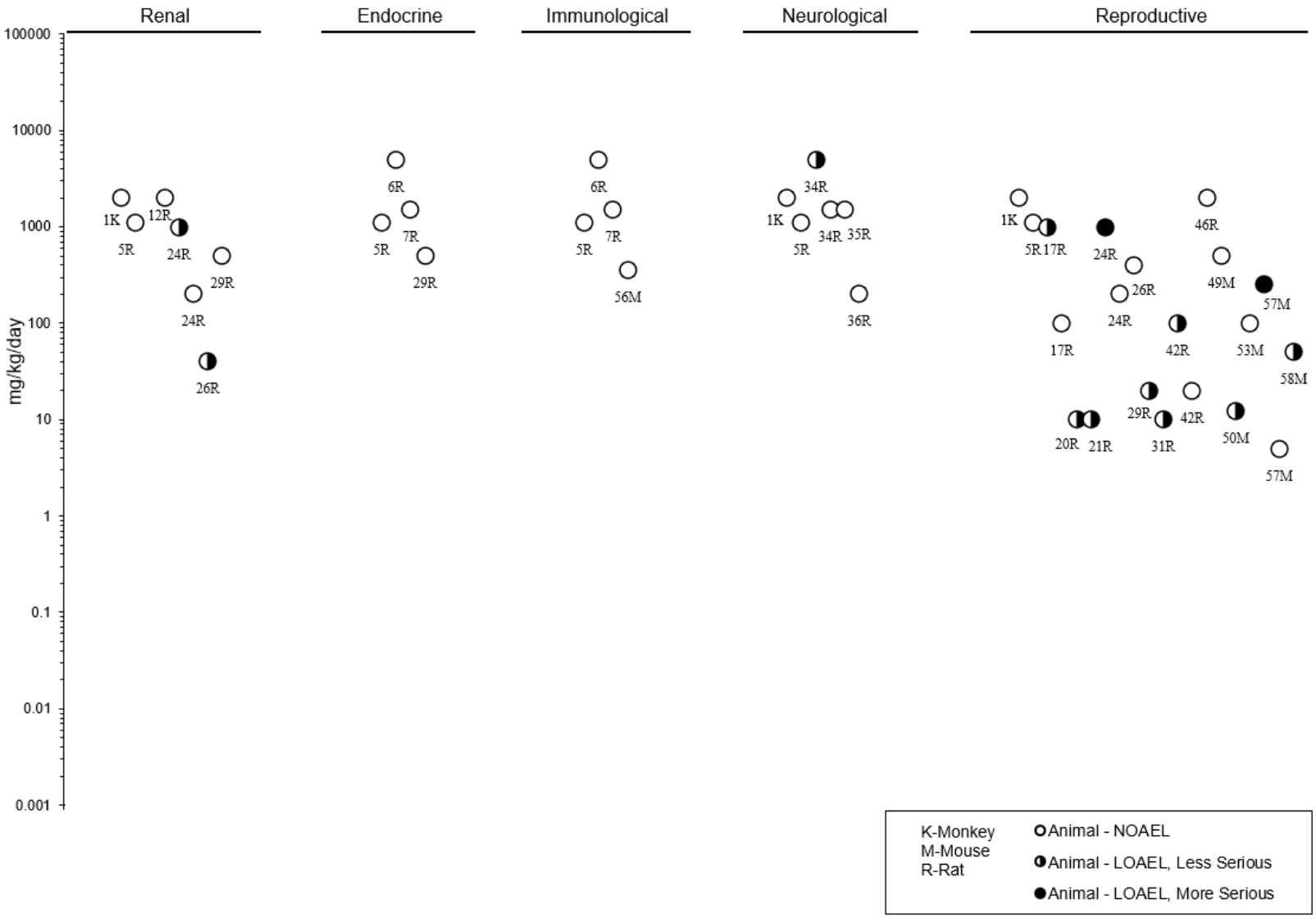


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Acute (≤14 days)

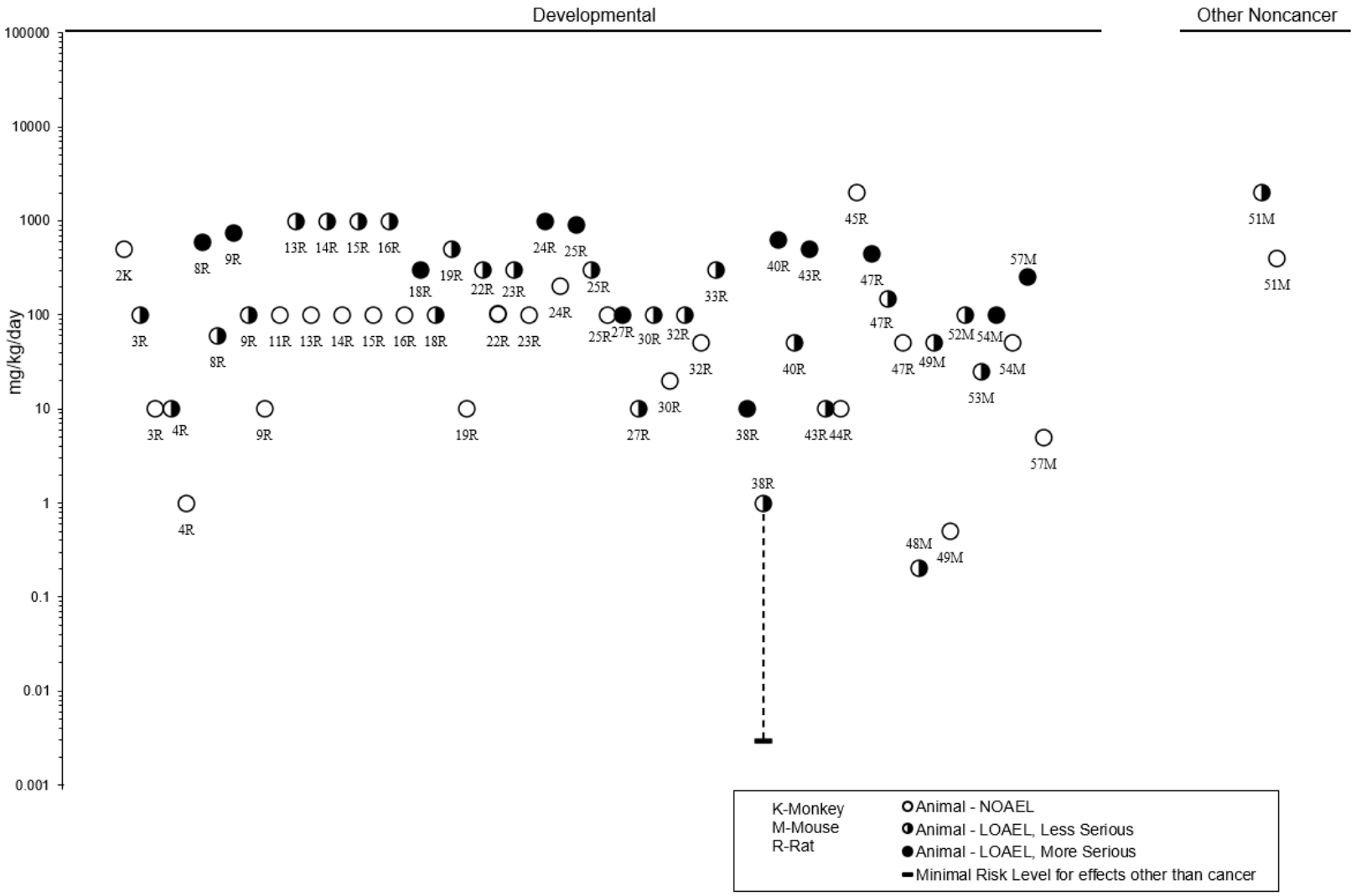


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

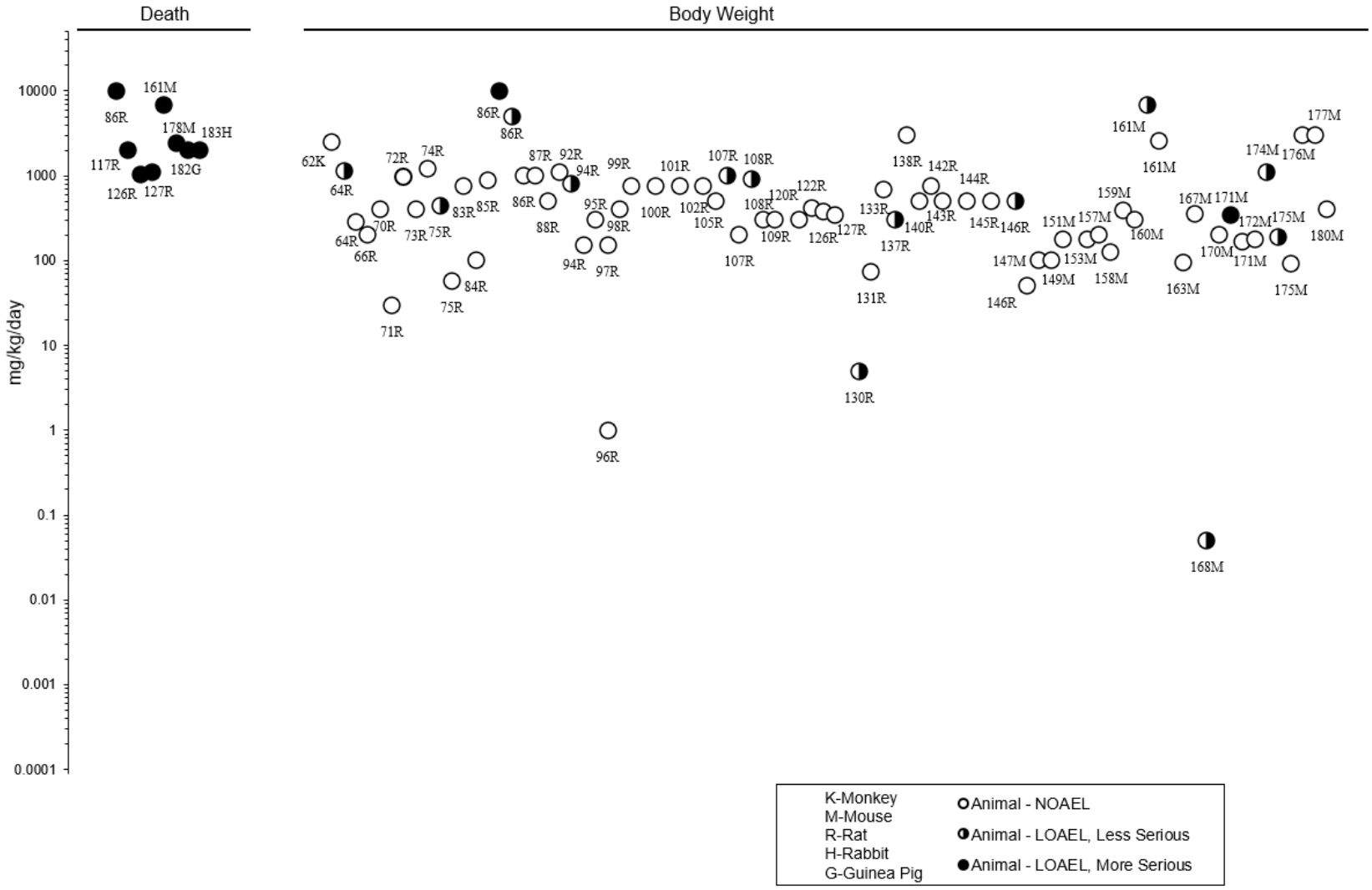


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

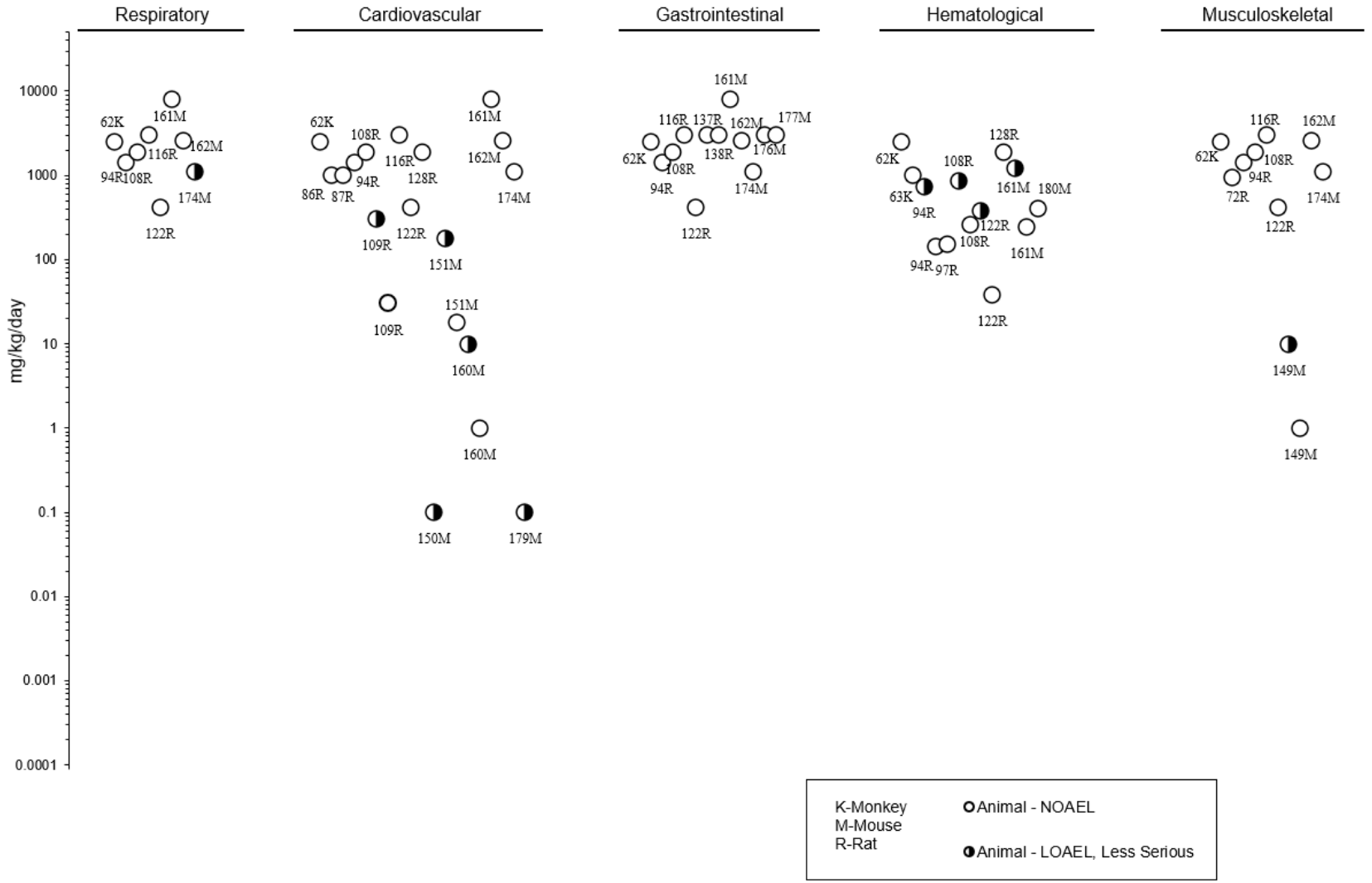


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

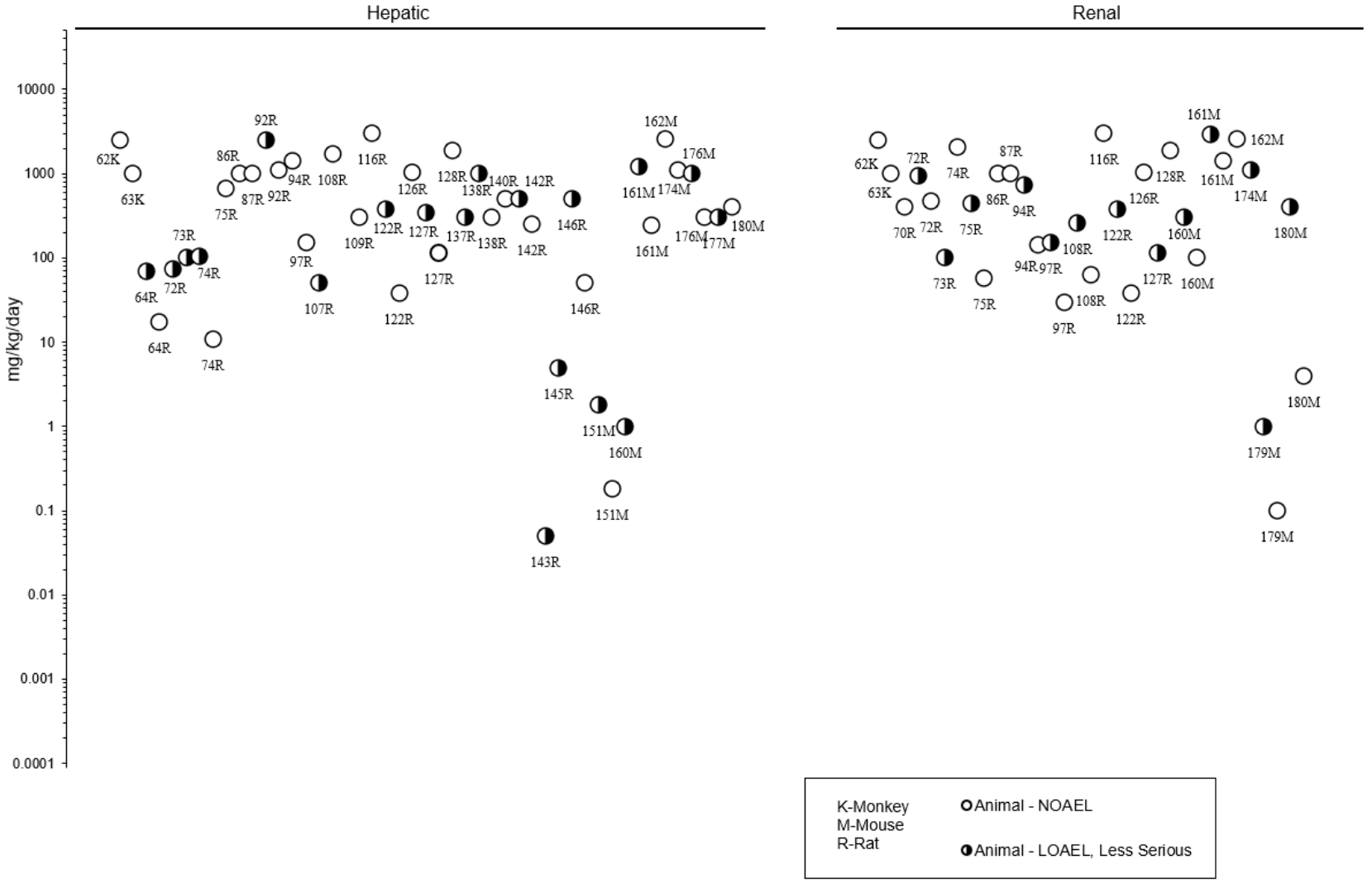


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

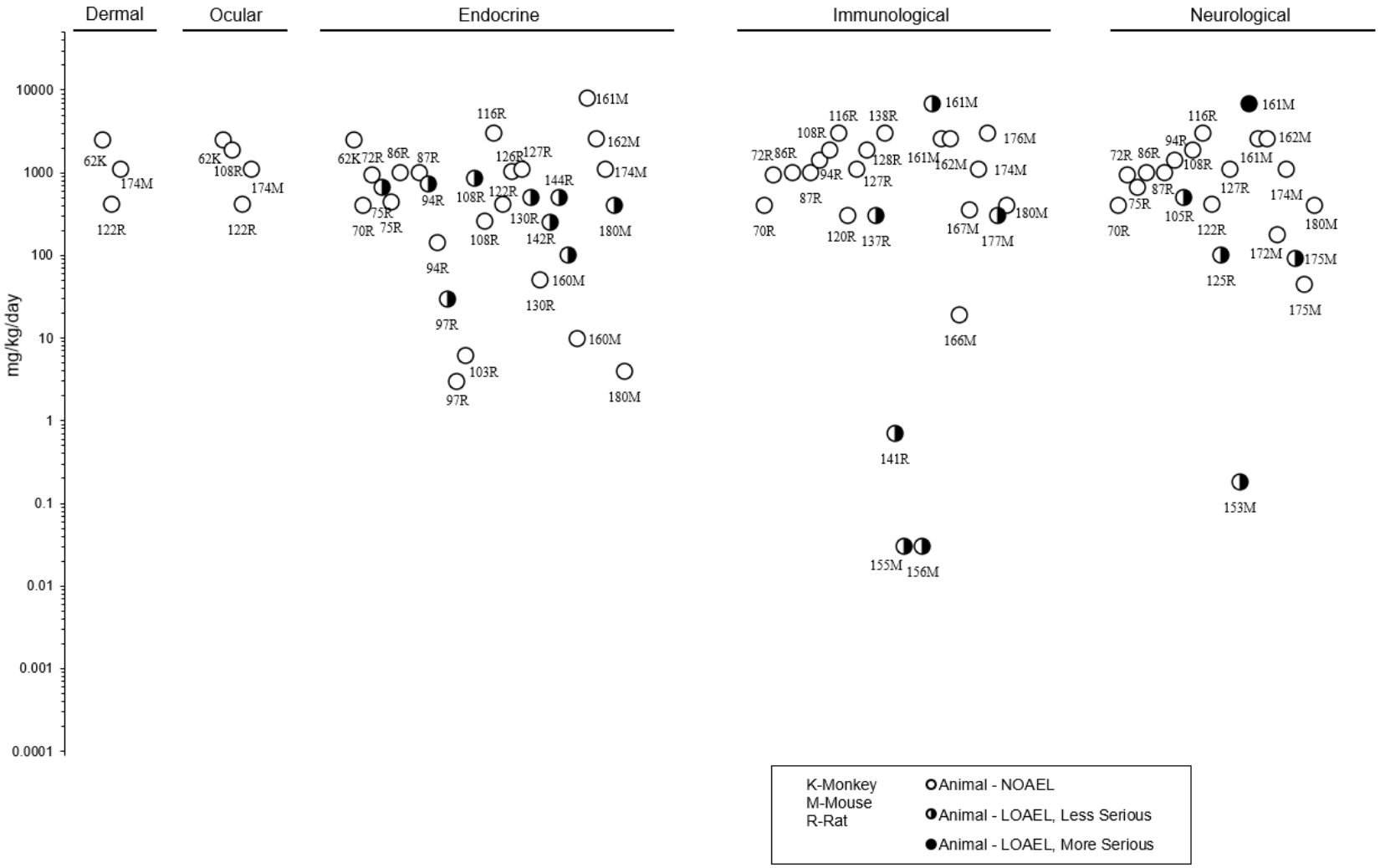


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

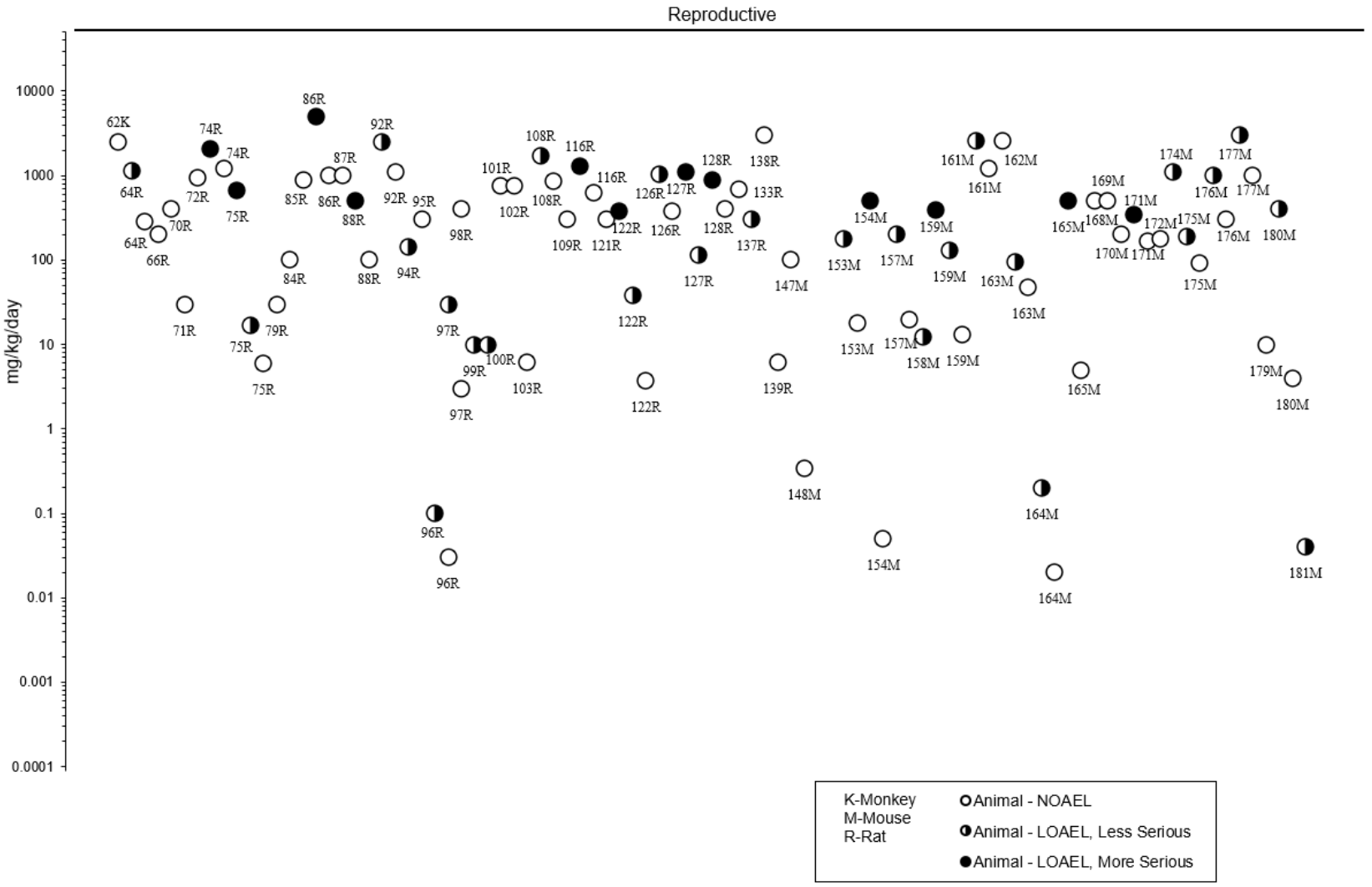


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

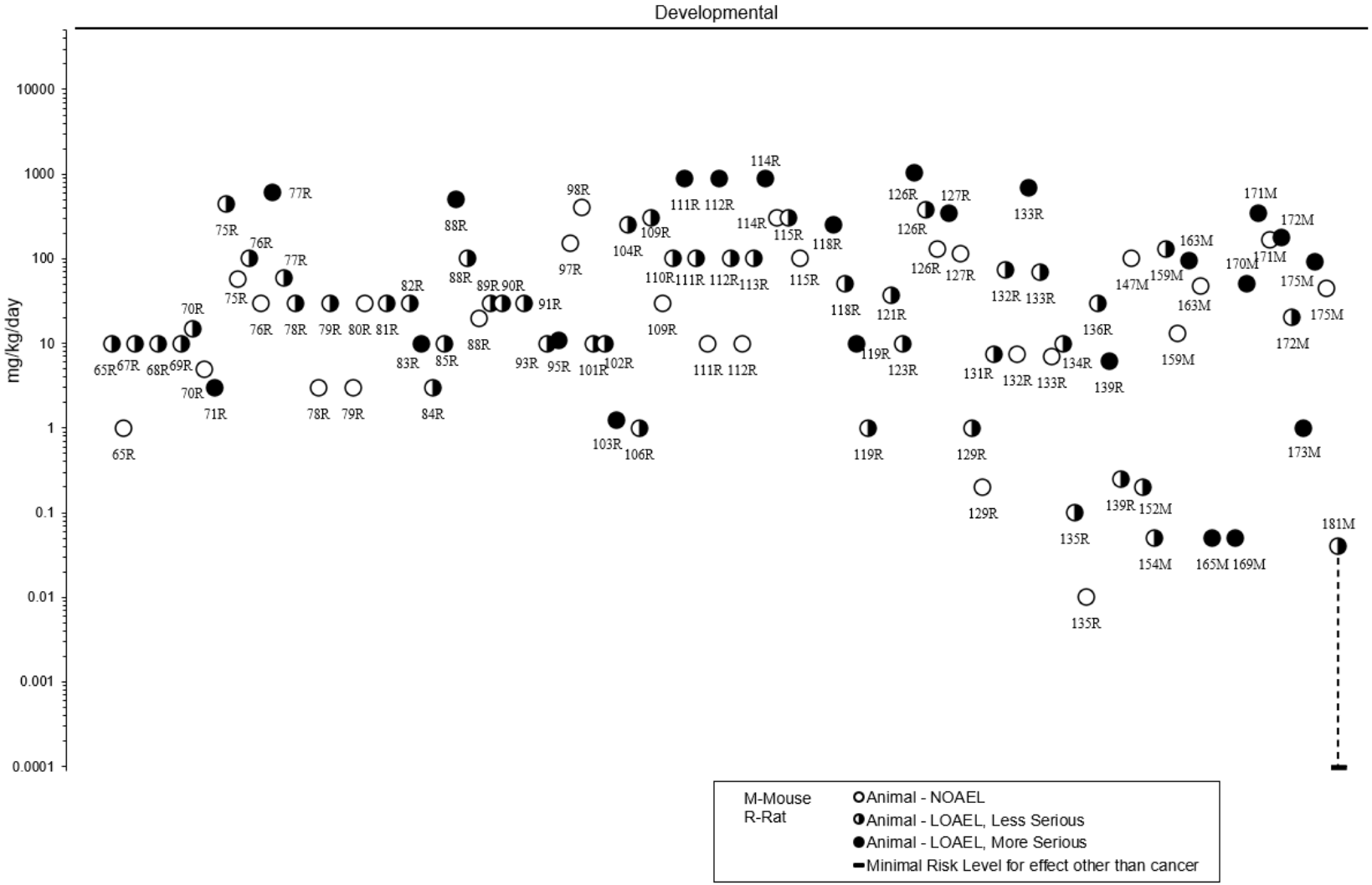


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Intermediate (15-364 days)

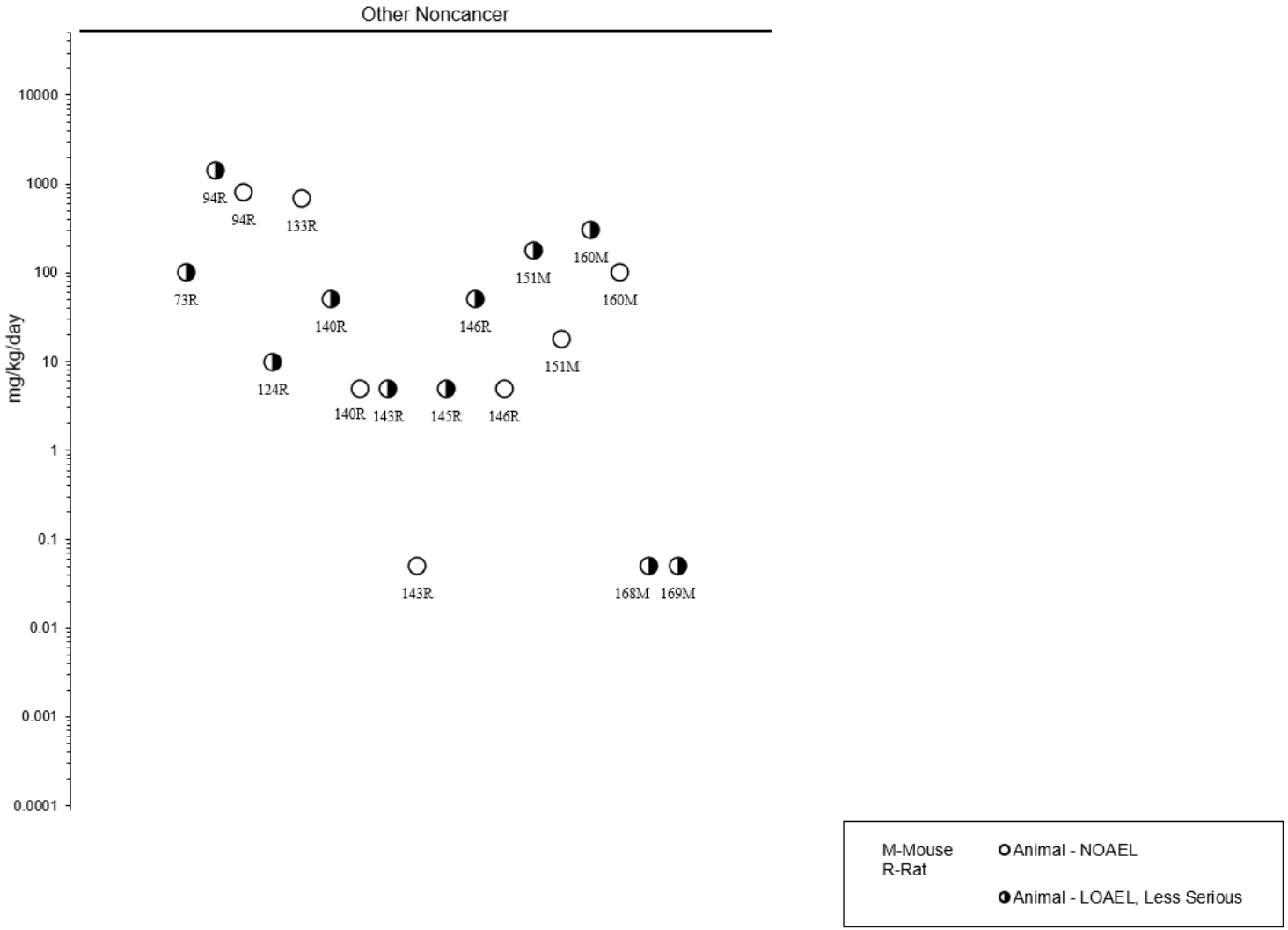


Figure 2-3. Levels of Significant Exposure to DEHP – Oral

Chronic (≥365 days)

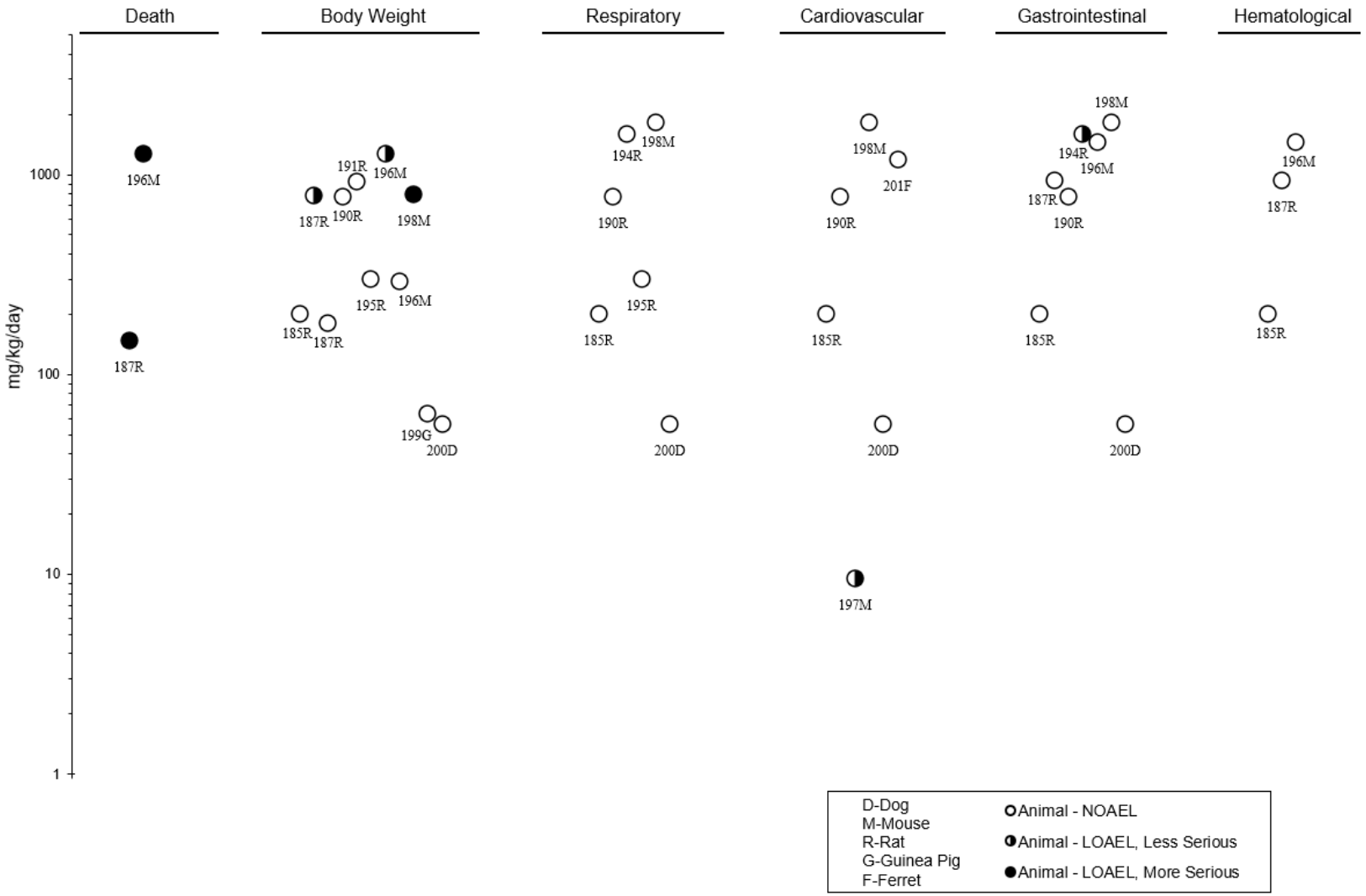


Figure 2-3. Levels of Significant Exposure to DEHP – Oral
Chronic (≥365 days)

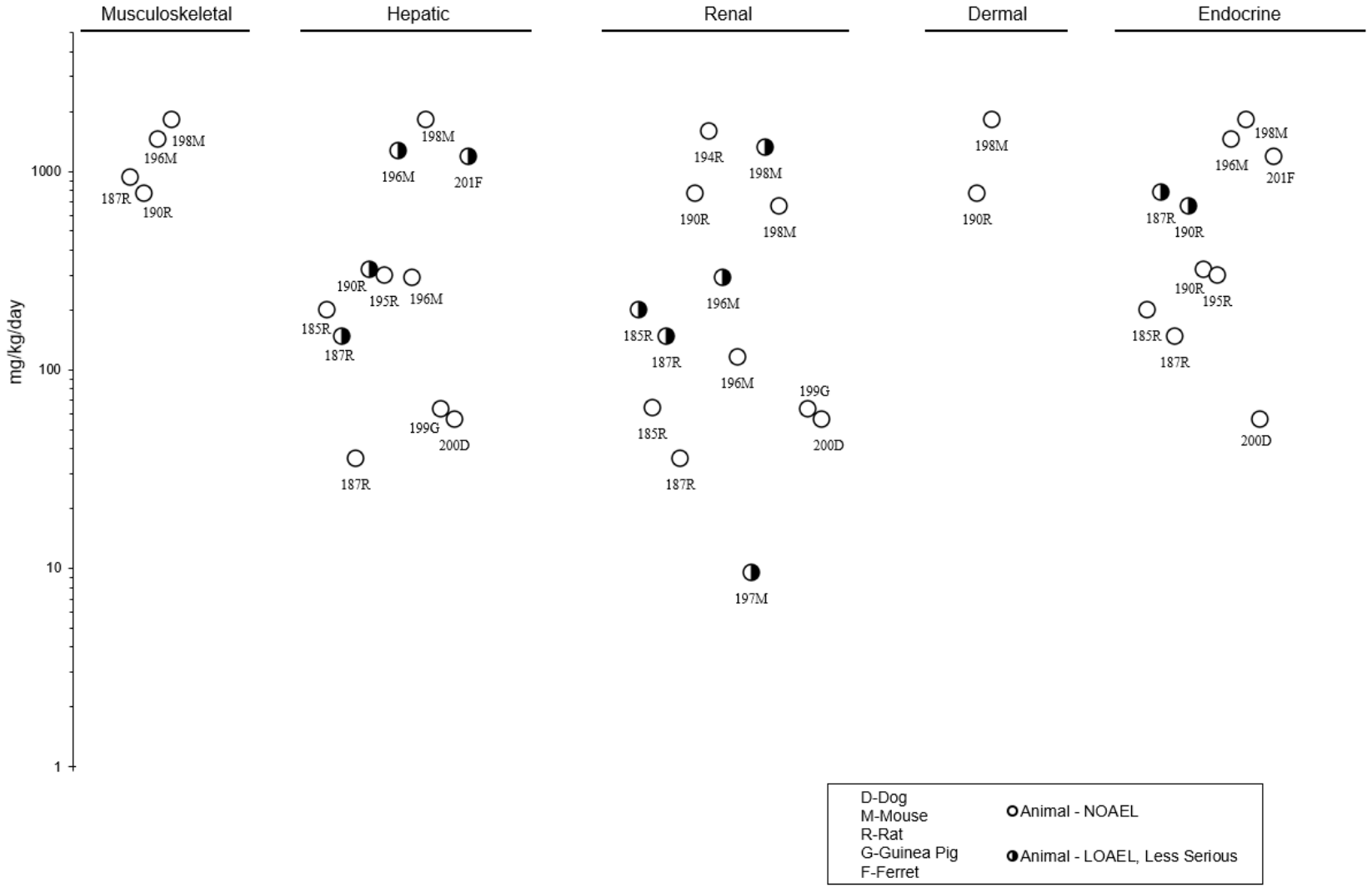
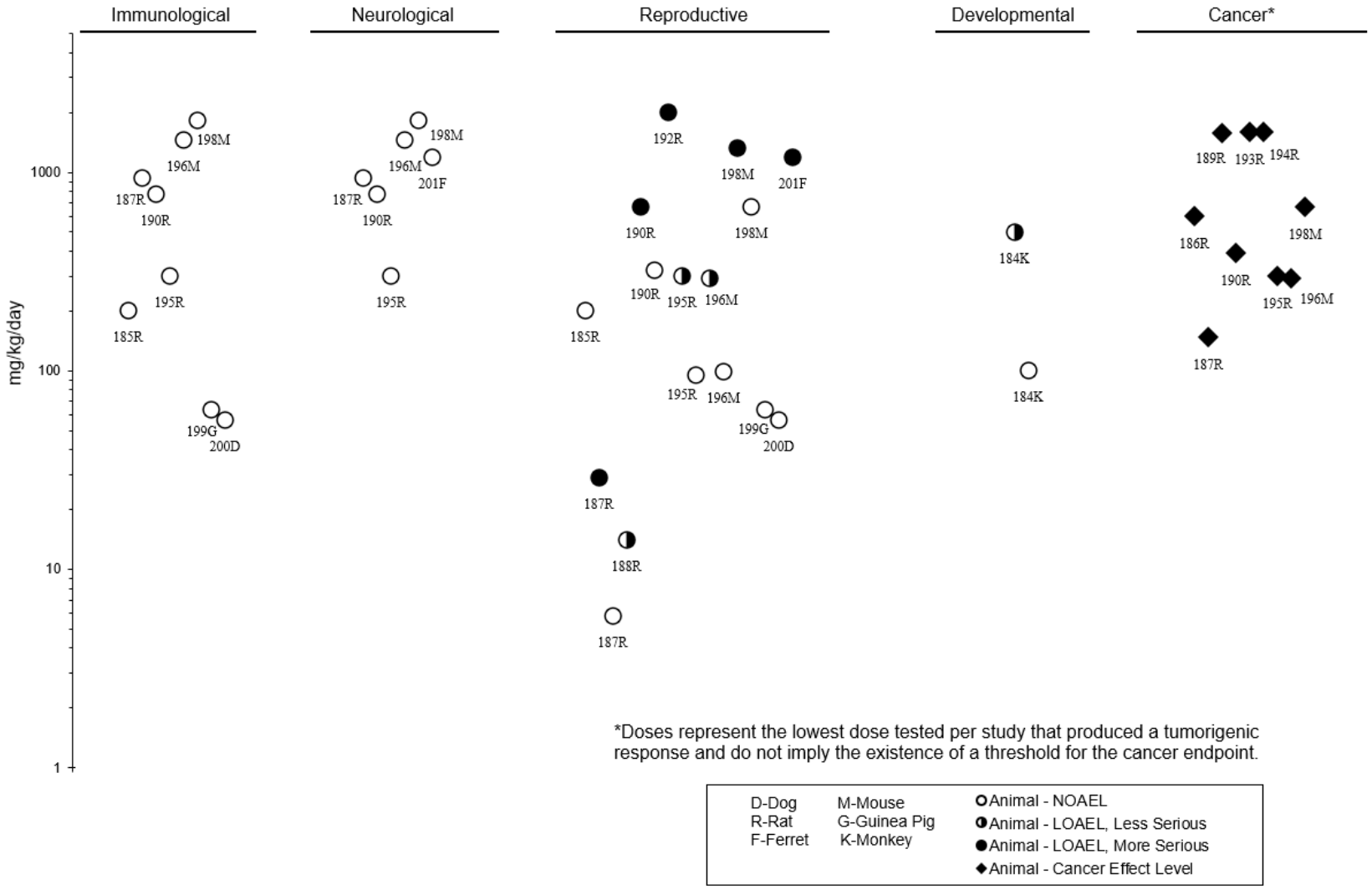


Figure 2-3. Levels of Significant Exposure to DEHP – Oral

Chronic (≥365 days)



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.

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. 1988); 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 20 mL/kg (19,700 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 25 mL/kg (24,600 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 2-3; these include a cohort study (Teitelbaum et al. 2012) where exposure was measured approximately 1 year prior to anthropometric measurements; 2 cohort studies where exposure was measured in pregnant women during the first trimester and body weights were measured at first and second trimester visits (Bellavia et al. 2017) or at delivery and 1 year postpartum (Perng et al. 2020); and 16 cross-sectional or case-control studies that measured exposure and outcome at the same time. Eleven 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 development.

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Bellavia et al. 2017 Cohort/cross-sectional, 347 pregnant women with full-term births, United States (Boston)	Gestational BWG or BMI	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	IQR: 0.2–0.8 µmol/L (SG-adj)	↔
Buser et al. 2014 Cross-sectional, children and adolescents (age 6–19 years) and nonpregnant, nonlactating adults (age >19 years), subject number not reported, United States	**Obesity (BMI ≥30) in adults**	**ΣDEHP**	GM (SE): 0.18 (0.01) µmol/mL	↑
		MEHP	GM (SE): 2.01 (0.10) ng/mL	↔
		MEHHP	15.86 (0.85)	↑
		MEOHP	9.16 (0.47)	↑
		MECPP	24.30 (1.20)	↑
	Overweight (BMI 25–29.9) in adults	ΣDEHP, MEHP, MEHHP, MEOHP, MECPP	See above	↔
	Obesity or overweight in children and adolescents	ΣDEHP	GM (SE): 0.24 (0.01) µmol/mL	↔
		MEHP	GM (SE): 2.18 (0.11) ng/mL	↔
		MEHHP	21.03 (1.25)	↔
		MEOHP	12.92 (0.72)	↔
		MECPP	34.79 (1.66)	↔
Dirtu et al. 2013 Case-control, 152 obese and 43 non-obese individuals, Belgium	**WC in controls**	ΣDEHP	IQR: 27–53 ng/mL	↔
		MEHP	2–5	↔
		MEHHP	9–19	↔
		MEOHP	3–9	↓
		MECPP	12–20	↓

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
	WC in cases	ΣDEHP	30–61	↔
		MEHP	2–5	↔
		MEHHP	10–25	↔
		MEOHP	4–11	↔
		MECPP	12–22	↔
Hatch et al. 2008 Cross-sectional, 2,118 females and 2,251 males (age 6–80 years), United States (NHANES)	**BMI (females)**	**MEHP**	Ages 6–11: GM (SD): 5.4 (2.8) µg/g Cr	↔
			Ages 12–19: 3.8 (2.9)	↔
			Ages 20–59: 4.0 (2.9)	↔
			Ages 60–80: 3.3 (2.9)	↓
		MEHHP	Ages 6–11: 39.6 (2.5)	↔
			Ages 12–19: 21.1 (2.6)	↔
			Ages 20–59: 18.3 (2.8)	↔
			Ages 60–80: 18.4 (2.7)	↔
		MEOHP	Ages 6–11: 27.5 (2.4)	↔
			Ages 12–19: 15.0 (2.4)	↔
			Ages 20–59: 12.5 (2.7)	↔
			Ages 60–80:12.4 (2.6)	↔
	WC (females)	**MEHP**	Ages 6–11: see above	↔
			Ages 12–19: see above	↓
			Ages 20–59: see above	↔
			Ages 60–80: see above	↓
		MEHHP, MEOHP	All ages (see above)	↔
	BMI or WC (males)	MEHP	Ages 6–11: 5.5 (3.1)	↔
			Ages 12–19: 2.7 (3.0)	↔
			Ages 20–59: 3.3 (3.2)	↔
			Ages 60–80: 2.5 (2.9)	↔

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEHHP	Ages 6–11: 39.1 (2.4)	↔
			Ages 12–19: 18.2 (2.8)	↔
			Ages 20–59: 16.6 (3.0)	↔
			Ages 60–80: 13.2 (2.9)	↔
		MEOHP	Ages 6–11: 26.6 (2.4)	↔
			Ages 12–19: 12.2 (2.8)	↔
			Ages 20–59: 10.6 (2.8)	↔
			Ages 60–80: 9.2 (2.7)	↔
Hou et al. 2015a, 2015b Cross-sectional, 270 children and adolescents (age 6.5–15 years) and 38 complainants involved in lawsuit regarding plasticizer-tainted foods (age 6.5–8 years), Taiwan	**BMI**	ΣDEHP	IQR: 100.74–237.19 ng/mL	↔
		MEHP	10.04–87.08	↔
		MEHHP	23.49–60.30	↑
		MEOHP	16.43–41.00	↔
		MECPP	31.70–77.63	↔
	Waist-to-hip (circumference) ratio	ΣDEHP, MEHP	See above	↔
		MEHHP, MEOHP, MECPP	See above	↑
	WC	ΣDEHP, MEHP, MEOHP, MECPP	See above	↔
		MEHHP	23.49–60.30	↑
James-Todd et al. 2016b Cross-sectional, 350 pregnant women with full-term births, United States (Boston)	BMI	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Median Q4: 2.09 µmol/L (SG-adj)	↔

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
James-Todd et al. 2016a Case-control, 965 cases with metabolic syndrome and 1,754 subjects without metabolic syndrome (age 20–80 years), United States (NHANES)	**Central obesity** (WC ≥102 cm in men or ≥88 cm in women)	**ΣDEHP** (MEHP, MEHHP, MEOHP)	Cases: GM (95% CI): 0.13 (0.12, 0.15) ng/mL Controls: 0.12 (0.10, 0.13)	↑
Kang et al. 2019 Cross-sectional, 4,752 adults (2,197 men, 2,555 women; age ≥19 years), Korea	**Obesity (BMI >30 kg/m^2) in women**	**ΣDEHP**	All subjects: GM (SE): 80.92 (1.42) µg/g Cr Normal/underweight: 76.81 (1.63) Overweight: 92.88 (2.64) Obese: 87.48 (6.65)	**All:** ↑ <50 yr: ↔ **≥50 yr:** ↑
		MEHHP	All subjects: 27.97 (0.54) Normal/underweight: 26.34 (0.61) Overweight: 32.69 (0.97) Obese: 31.02 (2.45)	**All:** ↑ <50 yr: ↔ **≥50 yr:** ↑
		MEOHP	All subjects: 20.08 (0.38) Normal/underweight: 19.17 (0.43) Overweight: 22.68 (0.68) Obese: 21.47 (1.75)	All: ↔ <50 yr: ↔ **≥50 yr:** ↑
		MECPP	All subjects: 31.69 (0.59) Normal/underweight: 30.19 (0.68) Overweight: 35.99 (1.09) Obese: 34.00 (2.53)	All: ↔ <50 yr: ↔ ≥50 yr: ↔
	Obesity (BMI >30 kg/m^2) in men	ΣDEHP	All subjects: 57.96 (1.06) Normal/underweight: 59.65 (1.32) Overweight: 55.78 (1.68) Obese: 55.80 (4.06)	All: ↔ <50 yr: ↔ ≥50 yr: ↔
		MEHHP	All subjects: 20.66 (0.42) Normal/underweight: 20.99 (0.52) Overweight: 20.12 (0.64) Obese: 20.85 (1.58)	All: ↔ <50 yr: ↔ ≥50 yr: ↔

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEOHP	All subjects: 13.76 (0.28) Normal/underweight: 14.27 (0.35) Overweight: 13.13 (0.44) Obese: 13.00 (1.04)	All: ↔ <50 yr: ↔ ≥50 yr: ↔
		MECPP	All subjects: 22.74 (0.40) Normal/underweight: 23.53 (0.50) Overweight: 21.83 (0.65) Obese: 21.24 (1.50)	All: ↔ <50 yr: ↔ ≥50 yr: ↔
Kim et al. 2018a Cross-sectional with nested case-control, 65 overweight girls (33 prepubertal, 32 pubertal) and 72 age-matched, non-overweight controls (35 prepubertal, 37 pubertal girls) (age 6–13 years), Korea	**Central obesity, BMI, WC, or percent body fat (prepubertal girls)**	MEHP	Overweight: GM (SE): 14.0 (2.9) µg/g Cr Control: 15.2 (2.5)	↔
		MEHHP	Overweight: 38.3 (15.6) Control: 41.5 (5.6)	↑
		MEOHP	Overweight: 29.7 (8.1) Control: 35.0 (4.5)	↔
		MECPP	Overweight: 82.8 (29.3) Control: 104.1 (1.7)	↔
	Central obesity, BMI, WC, or body fat (pubertal girls)	MEHP	Overweight: 13.2 (1.5) Control: 11.9 (1.4)	↔
		MEHHP	Overweight: 37.7 (5.8) Control: 37.7 (4.3)	↔
		MEOHP	Overweight: 29.7 (3.4) Control: 30.3 (3.5)	↔
		MECPP	Overweight: 90.9 (15.6) Control: 90.3 (14.4)	↔
Ko et al. 2019 Cross-sectional, 435 adults (388 men, 47 women; mean age 32.16 years), Taiwan	Abdominal obesity (WC ≥90 cm for men, ≥80 cm for women)	ΣDEHP	NR	↔
		MEHP	All: 25th–95th percentile: 0.269–2.789 µg/g Cr Men: 0.263–2.800 Women: 0.299–2.551	NR

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEHHP	All: 0.908–6.045 Men: 0.910–6.013 Women: 0.841–9.648	NR
		MEOHP	All: 0.486–2.603 Men: 0.479–2.636 Women: 0.505–2.509	NR
Li et al. 2020 Cross-sectional, 942 elderly adults (432 males, 510 females; age ≥60 years), China	**Obesity (BMI >28 kg/m^2)**	**ΣDEHP**	All: IQR: 4.45–15.32 µg/g Cr **Men:** 4.20–14.71 Women: 4.70–15.80	All: ↔ **Men:** ↑ Women: ↔
		MEHP	**All:** 0.15–1.73 Men: 0.16–1.82 Women: 0.14–1.64	**All:** ↑ Men: ↔ Women: ↔
		MEHHP	All: 1.44–4.23 **Men**: 1.32–3.97 Women: 1.53–4.51	All: ↔ **Men:** ↑ Women: ↔
		MEOHP	**All:** 1.27–3.78 **Men:** 1.23–3.39 **Women:** 1.33–4.13	**All:** ↑ **Men:** ↑ **Women:** ↑
	Central obesity (WC ≥85 cm men, WC ≥80 cm women)	**ΣDEHP**	See above	All: ↔ **Men:** ↑ Women: ↔
		MEHP	See above	**All:** ↑ Men: ↔ Women: ↔
		MEHHP	See above	All: ↔ Men: ↔ Women: ↔
		MEOHP	See above	All: ↔ **Men:** ↑ Women: ↔

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Lin et al. 2016 Cross-sectional, 793 students including 303 with and 486 without elevated blood pressure in childhood (mean age 21.28 years), Taiwan	**BMI**	**MEHP**	IQR: 1.7–38.99 µg/g Cr	↑
		MEHHP	15.86–43.16	↔
		MEOHP	10.18–26.56	↔
Lin et al. 2020 Cross-sectional, 792 adolescents and adults (age 12–30 years), Taiwan	**BMI**	**MEHP**	GM (95% CI): 6.1 (5.1, 7.3) µg/g Cr	↑
		MEHHP	27.9 (26.1, 30.0)	↔
		MEOHP	17.5 (16.4, 18.5)	↔
Perng et al. 2020 Cohort, 199 pregnant women (mean age 27.87 years), Mexico	**Maternal weight at delivery** (accounting for early pregnancy weight status and fetal growth)	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	IQR: 39.95–98.21 ng/mL	↓
	Rate of body weight loss during first year postpartum	**ΣDEHP**	See above	↓
Song et al. 2014 Cohort, 977 non-diabetic nurses (age 25–55 years) United States (NHANES)	BMI or weight gain	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	IQR: 115–870 nmol/L	↔
Stahlhut et al. 2007 Cross-sectional, 1,451 adult males (not taking insulin, oral hypoglycemic agents, or sex hormone agonists/antagonists), United States (NHANES)	**WC**	MEHP	Mean (SE): 11 (1.3) µg/g Cr	↔
		MEHHP	65.8 (7.9)	↑
		MEOHP	38.7 (4.5)	↑

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Teitelbaum et al. 2012 Cohort, 379 Hispanic and Black children (299 girls, 80 boys; age 6–8 years), United States (New York)	BMI or WC	ΣDEHP	Girls: median: 235.5 µg/g Cr Boys: median: 251.2 µg/g Cr	↔
		MEHP	Girls: 6.5; boys: 6.3	↔
		MEHHP	Girls: 72.0; boys: 75.7	↔
		MEOHP	Girls: 44.8; boys: 50.4	↔
		MECPP	Girls: 114.2; boys:114.6	↔
Wang et al. 2013 Cross-sectional, 259 students (age 8–15 years), including normal weight (n=124), overweight (n=53), and obese (n=82) subjects; China	**BMI or WC**	ΣDEHP	GM: 117.3 ng/mL	↔
		MEHP	21.3	↑
		MEHHP	16.1	↔
		MEOHP	22.9	↔
		MECPP	28.8	↔
Yaghjyan et al. 2015a, 2015b Cross-sectional, 6,005 women (age ≥18 years), United States (NHANES)	**BMI**	ΣDEHP	IQR: 19.59–58.66 µg/g Cr	↔
		MEHP	1.49–5.95	↑
		MEHHP	9.86–31.09	↔
		MEOHP	6.83–19.84	↔
		MECPP	17.16–49.78	↔
	WC	ΣDEHP, MEHP, MEHHP, MEOHP	See above	↔
		MECPP	See above	↑
Zhang et al. 2014 Cross-sectional, 246 girls (age 8–13 years), China	**Obesity**	**ΣDEHP**	8–10 years: range: 5.2–497.7 ng/mL 11–13 years: 1.3–864.4	↑
		MEHP	8–10 years: <LOD–92.2 11–13 years: <LOD–117.1	↔
		MEHHP	8–10 years: 3.2–290.0 11–13 years: 0.8–508.4	↑
		MEOHP	8–10 years: 1.2–115.5 11–13 years: <LOD–238.8	↑

Table 2-3. Selected Epidemiological Studies of DEHP Exposure and Body Weight Metrics

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
	Overweight	ΣDEHP, MEHP, MEHHP, MEOHP	All ages (see above)	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; BMI = body mass index; BWG = body weight gain; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; IQR = interquartile range; LOD = limit of detection; MECPP = mono(2-ethyl-5-carboxypentyl)phthalate; 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; Q4 = quartile four (of exposure); SD = standard deviation; SE = standard error; SG-adj = specific gravity adjusted; WC = waist circumference

Perng et al. (2020) observed an association between first trimester urinary ∑DEHP metabolite levels and decreased maternal weight at delivery (after accounting for early pregnancy weight status and fetal growth); however, rate of body weight loss over the first year postpartum was decreased with increased first trimester urinary ∑DEHP metabolite levels. In the other pregnancy cohort, 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 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 with DEHP urinary metabolite levels were reported for increased BMI in adults (Lin et al. 2016, 2020; Yaghjyan et al. 2015a, 2015b) and adolescents and children (Hou et al. 2015a, 2015b; Kim et al. 2018a; Lin et al. 2020; Wang et al. 2013), waist circumference in children (Hou et al. 2015a, 2015b; Kim et al. 2018a; Wang et al. 2013), and increased odds of obesity and/or central obesity in adults (Buser et al. 2014; James-Todd et al. 2016a; Kang et al. 2019; Li et al. 2020) or children (Kim et al. 2018a). 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. A few studies did not observe an association between anthropometric measurements and DEHP exposure in adults (Ko et al. 2019), pregnant women (James-Todd et al. 2016b), or children (Teitelbaum et al. 2012).

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. (2016a), 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 (Kang et al. 2019; Kim et al. 2018a; Li et al. 2020; Lin et al. 2016, 2020; 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. 2016a; 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, drinking water, 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. Numerous gavage studies in rodents did not report exposure-related changes in body weight in nonpregnant, adult rodents at acute doses ≤2,000 mg/kg/day or intermediate-duration doses ≤1,000 mg (Table 2-2). 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). In contrast, two intermediate-duration studies reported body weight increases ≥10% in Wistar rats exposed to doses ≥5 mg/kg/day for 4 weeks (Sun et

al. 2018) or 500 mg/kg/day for 8 weeks (Zhou et al. 2019). 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 several other rodent studies evaluating exposure during gestation and/or lactation at gavage doses ≤1,000 mg/kg/day (Table 2-2).

Drinking water studies in rodents. Wang et al. (2020) exposed Sprague-Dawley rats, Wistar rats, C57BL/6J mice, and BALB/c mice to DEHP in drinking water at doses up to 3,000 mg/kg/day for 30 days. Only Sprague-Dawley rats showed exposure-related changes in body weight, with a significant 16–20% increase in body weight gain during the exposure period at all doses tested (≥300 mg/kg/day).

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; Sasaki et al. 2003).

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 1986; 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 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. 2001). 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 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). Other 1- to 2-year studies in F344 rats reported reduced body weights only with concomitant reductions in food intake levels at dietary doses ≥322 mg/kg/day (Kluwe et al. 1982a; Marsman et al. 1988; NTP 1982). No dose-related body weight effects were noted in rats at chronic doses up to 300 mg/kg/day (Carpenter et al. 1953; Voss et al. 2005). 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 (NTP 1988; 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.

Additional dietary studies lacking food consumption data report decreased body weight following oral exposure to an acute dose of 3,850 mg/kg/day in mice (Muhlenkamp and Gill 1998), intermediate-duration doses of ≥2,100 mg/kg/day in rats or ≥1,300 mg/kg/day in mice (Agarwal et al. 1986; Mitchell et al. 1985; NTP 1982; Sasaki et al. 2003; Short et al. 1987), or chronic-duration doses of ≥140 mg/kg/day in rats (Ganning et al. 1991; Rao et al. 1990; Tamura et al. 1990). The potential contribution of food unpalatability precludes inclusion of body weight findings from these studies in the LSE table.

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 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). Studies in 3T3-L1 mouse adipocytes show that incubation with MEHP increased lipid accumulation, browning-like activation, production of reactive oxygen species (ROS) and altered expression of genes related to adipogenesis, adipocyte differentiation, and carbohydrate/glucose uptake (Hsu et al. 2019, 2020; Qi et al. 2019). Adipogenic processes were not demonstrated in human adipocytes exposed to DEHP (Schaedlich et al. 2018).

Wang et al. (2020) proposed that significant alterations in the gut microbiome following oral DEHP exposure may contribute to increased risk of obesity. Following a 30-day oral exposure, Sprague-Dawley rats, showed an increase in bacterial species *Fimicutes* and *Proteobacteria*, which are associated with obesity and diabetes. Sprague-Dawley rats also showed DEHP-associated weight gain. In contrast, Wistar rats and BALB/c and C57BL/6J mice did not have increased *Fimicutes* and *Proteobacteria* and showed normal 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. In contrast, a limited number of rodent studies reported elevated body weight following oral exposure; additional endpoints from these studies 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. Kolena et al. (2014) observed improved pulmonary function (ratio of forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC]) with higher urinary MEHP levels (median 5.94 ng/mL) in a study of 30 community service workers (mean age 46 years) with exposure to DEHP along with other air, liquid, or solid pollutants for an average of 7.9 years (men) and 5.6 years (women) during waste and recycle processing or loading; other DEHP metabolites were not evaluated. Similarly, Kolena et al. (2020) reported improved pulmonary function (FEV_1/FVC) with higher urinary MEHP, MEHHP, MEOHP, and MECPP levels in 32 male firefighters (mean age 38 years) with exposure to DEHP along with other air pollutants. Interpretation of studies with improved pulmonary function is limited by small sample size. No other studies evaluating lung function in workers following inhalation exposure to DEHP were identified.

Findings in general population studies are mixed. In a panel study with repeated urine samples and spirometry tests in 418 Korean adults >60 years old, increased DEHP metabolite (MEHHP and MEOHP) levels in urine were associated with poorer pulmonary function test scores (FEV_1/FVC and forced expiratory flow at 25–75% of FVC [$FEF_{25–75}$]) only in individuals with specific genetic polymorphisms in catalase (CAT), superoxide dismutase (SOD2) and myeloperoxidase (MPO) genes (GC-GC in CAT, TC-TC in SOD2, and Ag-AG in MPO) (Park et al. 2013). The study authors suggested that gene-environment interactions may alter the effect of DEHP exposure on lung function. A slight 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 interquartile increase in the sum of DEHP metabolites (MEHP, MEHHP, MEOHP) in the urine was associated with an approximate 1% reduction in

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 (1988–1994) (Hoppin et al. 2004). In a cohort study, no association was observed between lung function (FEV1, FVC, peak expiratory flow [PEF], or FEV_1/FVC) in 9-year-old children and urinary MEHP levels measured at 2, 5, or 9 years of age (Lin et al. 2018). In a cross-sectional study of asthmatic children, decreased FEV_1 was associated with urinary MEHHP levels; however, this association was no longer apparent when the analysis was adjusted for outdoor environment indicators (particulate matter, temperature, and relative humidity) (Kim et al. 2018e). No associations were observed with FEV_1/FVC, PEF, or $FEF_{25–75}$ and urinary DEHP metabolite levels.

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 (35% decrease in tidal volume associated with 15% increase in respiratory rate) was observed during lung function analysis of female mice during the last 10 minutes of a 60-minute exposure to DEHP at 19 ppm (Larsen et al. 2007). No alterations in lung function were reported 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 mg/kg/day (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 rat offspring exposed to DEHP at gavage doses of 750 mg/kg/day from GD 12 to PND 0 or PND 21(Chen et al. 2010). Lung alterations included increased thickness of alveolar septa and less airspace in the lung on PNDs 1 and 21, 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 either age following exposure to 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. 2014a; Larsen et al. 2007; Wang et al. 2018; 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 and a single cross-sectional

study of subclinical atherosclerosis. 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 three pregnancy cohort studies (one evaluated blood pressure in mothers, two evaluated blood pressure in offspring) and seven cross-sectional studies in the general population (Table 2-4). Four of the seven cross-sectional studies (James-Todd et al. 2016a; Shiue and Hristova 2014; Trasande and Attina 2015; Trasande et al. 2013a) used NHANES data and reported associations between DEHP urinary metabolite levels and increased blood pressure. The other three cross-sectional studies (Ko et al. 2019; Lin et al. 2016, 2020) did not observe associations between DEHP exposure and high blood pressure in Taiwan. 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 cohorts, no associations were observed between DEHP metabolite concentration in maternal urine and maternal blood pressure or pregnancy-induced hypertensive disorders (Werner et al. 2015) or in offspring blood pressure measured at 4–6 years of age (Vafeiadi et al. 2018a). In another cohort, an association between DEHP metabolite concentration in maternal urine and decreased systolic and diastolic blood pressure was observed in 10-year-old female offspring; no association was observed in male offspring (Sol et al. 2020).

One cross-sectional study evaluated the potential association between DEHP exposure and subclinical atherosclerosis in Taiwanese adolescents and young adults aged 12–30 (Lin et al. 2020). A positive association was observed between urinary MEHP levels and carotid intima-media thickness. No association was noted for urinary MEHHP or MEOHP.

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.

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
James-Todd et al. 2016a Cross-sectional, 965 cases of metabolic syndrome (464 men and 501 women) and 1,754 subjects without metabolic syndrome (924 men and 830 women) (age 20–80 years), United States (NHANES)	**BP**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	With metabolic syndrome: GM (95% CI): 0.13 (0.12, 0.15) Without metabolic syndrome: 0.12 (0.10, 0.13)	**All**: ↑ **Men**: ↑ Women:
Ko et al. 2019 Cross-sectional, 435 adults (388 men, 47 women; mean age 32.16 years), Taiwan	High BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg)	ΣDEHP	NR	↔
		MEHP	All: 25th–95th percentile: 0.269–2.789 µg/g Cr Men: 0.263–2.800 Women: 0.299–2.551	NR
		MEHHP	All: 0.908–6.045 Men: 0.910–6.013 Women: 0.841–9.648	NR
		MEOHP	All: 0.486–2.603 Men: 0.479–2.636 Women: 0.505–2.509	NR
Lin et al. 2016 Cross-sectional, 793 adult students including 303 with and 486 without elevated BP in childhood (mean age 21.28 years), Taiwan	Systolic BP	MEHP	IQR: 1.7–38.99 µg/g Cr	↔
		MEHHP	15.86–43.16	↔
		MEOHP	10.18–26.56	↔
Lin et al. 2020 Cross-sectional, 792 adolescents and adults (age 12–30 years), Taiwan	Systolic BP	MEHP	GM (95% CI): 6.1 (5.1, 7.3) µg/g Cr	↔
		MEHHP	27.9 (26.1, 30.0)	↔
		MEOHP	17.5 (16.4, 18.5)	↔

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Shiue and Hristova 2014 Cross-sectional, 20,293 adults (age ≥20 years) including 660 with high blood pressure and 4,578 with normal blood pressure, United States (NHANES)	**BP**	MEHP	Normal BP: Mean (SD): 4.15 (SD) 16.49 ng/mL High BP: 3.36 (6.62)	↔
		MEHHP	Normal BP: 27.75 (155.35) High BP: 25.03 (50.74)	↑
		MEOHP	Normal BP: 16.45 (97.03) High BP: 15.22 (25.48)	↑
		MECPP	Normal BP: 40.10 (249.63) High BP: 38.52 (64.13)	↑
		Shiue (2015a, 2015b) 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.		
Sol et al. 2020 Cohort, 1,064 mother-child pairs (538 boys, 526 girls; median age 9.7 years), Netherlands	Systolic and diastolic BP in boys	ΣDEHP (MECPP, MEHHP, MEOHP, MCMHP)	Maternal IQR (1st trimester): 90.0–328.6	↔
			2nd trimester: 54.1–184.2	↔
			3rd trimester: 74.7–227.5	↔
	Systolic and diastolic BP in girls	**ΣDEHP**	1st trimester: 88.8–298.6	↔
			2nd trimester: 48.7–174.3	↔
			3rd trimester: 81.4–272.8	↓

Table 2-4. Selected Epidemiological Studies of DEHP Exposure and Blood Pressure

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Trasande and Attina 2015 Cross-sectional, 1,329 children (age 8–19 years), United States (NHANES)	**Diastolic or systolic BP**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	IQR: 0.077–0.313 µM	↑
	BP >90th percentile for age/height z-score/sex	ΣDEHP	See above	↔
Trasande et al. 2013a Cross-sectional, 2,463 children and adolescents (age 6–19 years), United States (NHANES)	**Systolic BP**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	IQR: 0.166–0.704 M	↑
	Diastolic BP	ΣDEHP	See above	↔
	BP >90th percentile for age/height z-score/sex	ΣDEHP	See above	↔
Vafeiadi et al. 2018a Cohort, 260 mothers and their 500 children (279 boys, 221 girls; age 4–6 years), Greece	Systolic and diastolic BP	ΣDEHP (MEHP, MEHHP, MEOHP)	Maternal IQR (1st trimester): 0.1–0.2 µmol/g	↔
			Child: 0.2–0.5	↔
Werner et al. 2015 Cohort, 369 pregnant women (age ≥18 years), United States (Ohio)	Diastolic BP, systolic BP, or pregnancy-induced hypertensive disorder	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Average concentration from 16 and 26 weeks of gestation: 53–159 µg/g Cr	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; BP = blood pressure; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; IQR = interquartile range; MCMHP = mono-[(2-carboxymethyl)-hexyl] phthalate; 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; SD = standard deviation

There is limited evidence of altered cardiac function in mice following intermediate-duration oral exposure to DEHP. Two studies in mice reported elevated blood pressure after exposure to ≥0.1 mg/kg/day for 42–45 days (Deng et al. 2019; Xie et al. 2019). Deng et al. (2019) also reported elevated heart rate at 1 mg/kg/day (heart rate not assessed by Xie et al. 2019). These findings were accompanied by a significant thickening of the ventricular and aortic walls. Biochemical findings suggest that elevated blood pressure occurred due to activation of angiotensin converting enzyme (ACE), which inhibits the bradykinin-nitric oxide pathway. Another study reported elevated heart rate and mean blood pressure in mice orally exposed to 180 mg/kg/day for 3 weeks (Ding et al. 2019). Serum levels of cardiac troponin 1 and hypersensitive C-reactive protein were elevated at 18 and 180 mg/kg/day, respectively.

No changes in heart weight were observed; hearts were not examined for histopathological changes. Li et al. (2018) reported elevated relative heart weight and increased lipid droplets in cardiac papillary muscle cells in mice following a 35-day gavage exposure to ≥1 and ≥100 mg/kg/day, respectively. Cardiac function was not tested in this study, but metabonomic, gene expression, and enzyme activity analysis revealed that DEHP altered endogenous metabolites and metabolic pathways involved in fatty acid and glucose metabolism in cardiomyocytes at all doses.

Additional studies have reported elevated blood pressure in rodents following intermediate- or chronic-duration oral exposure to DEHP; however, findings were considered secondary to observed renal dysfunction, as discussed in Section 2.10 (Renal). 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. Wei et al. (2012) reported elevated blood pressure associated 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. 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).

In the majority of 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; Myers 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). However, relative heart weights were significantly decreased in rat dams following exposure to 300 mg/kg/day from GD 8 to PND 21 (Nardelli et al. 2017). 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).

Potential effects on human heart muscle contractility and rhythm were identified in *in vitro* and *ex vivo* 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). Exposure to MEHP produced electrophysiological changes in the isolated rat heart (increased action potential triangulation, altered action potential duration restitution curve), suggesting an increased risk of arrhythmia (Jaimes et al. 2019). 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. In general, available animal data do not indicate that the cardiovascular system is a sensitive target of DEHP toxicity. Evidence from animal studies suggests that altered blood pressure is likely secondary to renal toxicity following exposure to DEHP; however, one study (Xie et al. 2019) reported elevated blood pressure at doses below those associated with renal damage.

2.6 GASTROINTESTINAL

Human Studies. Wang et al. (2015) reported increased rates of nausea and vomiting 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). These effects may be secondary to neurotoxicity (see

Section 2.15), rather than a direct effect on the gastrointestinal symptom. No other 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; no other effects of exposure were noted (Shaffer et al. 1945).

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

In oral studies, pseudoductular lesions or altered acinar cell foci were observed in the pancreas of rats administered dietary DEHP at 1,600 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; Myers 1992b; NTP 1982; Poon et al. 1997; Wang et al. 2020), or 7,899 mg/kg/day in mice (Myers 1992a; NTP 1982; Toyosawa et al. 2001; Wang et al. 2020).

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. Where effects were reported, sex-related differences were generally observed with increased sensitivity in males. 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 for 13 weeks; doses ≤37.6 mg DEHP/kg/day were without hematological effect in males (Poon et al. 1997). No hematological effects were noted in similarly exposed female rats at doses up to 419.3 mg/kg/day (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 in males or females at ≤261.2 or 918.4 mg/kg/day, respectively (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 ≤154 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). No changes in comprehensive hematological evaluations were observed in Sprague-Dawley rats exposed to gavage doses up to 150 mg/kg/day on PNDs 6–96 (Kim et al. 2018c). In 28-day studies in mice, significantly reduced hemoglobin and hematocrit were observed in males and females at doses ≥1,209 and 2,888 mg/kg/day, respectively; no hematological changes were observed at oral doses ≤400 mg/kg/day (Myers 1992a; Xu et al. 2019). 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; where effects were observed, male rats were generally more sensitive than female rats.

2.8 MUSCULOSKELETAL

Human Studies. In a cohort study of 481 mother-child pairs, maternal urinary DEHP metabolite levels were associated with decreased skeletal muscle index (SMI) in 6-year-old girls, but not boys (Lee et al. 2020). No associations were observed between maternal urinary DEHP metabolite levels and percentage of skeletal muscle (% SM) or between child urinary DEHP metabolite levels and SMI or % SM. No additional 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).

One gavage study reported decreased bone mineral density and bone volume fraction coupled with reduced osteoblastogenesis and mineralization of bone marrow stromal cells in ICR mice exposed to ≥10 mg/kg/day for 8 weeks (Chiu et al. 2018c). Osteoblastogenesis was replaced by adipogenesis in bone marrow stromal cells. At 100 mg/kg/day, trabecular bone thickness and cell number were also reduced. No changes in cortical bone thickness or trabecular separation were observed. In other rodent studies, no adverse musculoskeletal 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. Epidemiological data for DEHP exposure and the musculoskeletal endpoint are limited to a single cohort study of mother-child pairs. Maternal urinary levels of DEHP were associated with a decrease in the SMI in 6-year-old girls, but not boys, and no association was found for child urinary levels

(Lee et al. 2020). An adult monkey study and most rodent studies indicate that the musculoskeletal system is not adversely affected from DEHP exposure. One mouse study (Chiu et al. 2018a, 2018b) indicated altered trabecular (but not cortical) bone density, volume, and thickness following exposure to DEHP.

2.9 HEPATIC

Overview. Human data on hepatic effects of DEHP are limited to evaluation of clinical chemistry parameters, including serum enzymes and lipid and cholesterol evaluation. 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 2-5. A positive association between hypertriglyceridemia and DEHP exposure was reported in a cross-sectional study of NHANES participants with and without metabolic syndrome (data from cases and non-cases were combined for regression analysis; James-Todd et al. 2016a), in a cohort study of 3–5- and 7–9-year-old children (Han et al. 2019), and in cord blood in

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference, study type, and population	Outcome evaluated	Metabolite[a]	Urine concentration	Result
Han et al. 2019 Cohort, 164 children (assessed at age 3–5 and 7–9 years), South Korea	**Triglycerides**	**ΣDEHP**	3–5 years: IQR: 258.18–595.69 µg/g Cr	↔
			7–9 years: 159.43–370.86	↑
		MEHP	3–5 years: 14.14–37.55	↔
			7–9 years: 10.35–31.76	↑
		MEHHP	3–5 years: 89.79–212.80	↔
			7–9 years: 58.19–127.45	↑
		MEOHP	**3–5 years: 54.92–134.51**	↑
			7–9 years: 33.33–74.17	↑
		MECPP	3–5 years: 75.08–190.57	↔
			7–9 years: 49.22–120.65	↑
	HDL cholesterol	**ΣDEHP**	**3–5 years**: see above	↓
			7–9 years: see above	↔
		MEHP, MEHHP, MEOHP, MECPP	3–5 years: see above	↔
			7–9 years: see above	↔
James-Todd et al. 2016a Cross-sectional, 965 cases of metabolic syndrome and 1,754 controls without metabolic syndrome (age 20–80 years), United States (NHANES)	**Triglycerides**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	Cases: GM (95% CI): 0.13 (0.12, 0.15) ng/mL Controls: 0.12 (0.10, 0.13)	↑
	Low HDL cholesterol	ΣDEHP	See above	↔
Kim et al. 2016a Cohort, 128 infants, Korea	**BMI or triglyceride in cord blood**	**ΣDEHP**	NR	↑
		MEHHP	Infant (first urine) IQR: 3.21–11.87 ng/mL	↑
		MEOHP	1.51–6.50	↑
	Total cholesterol in cord blood	ΣDEHP, MEHHP, or MEOHP	See above	↔

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference, study type, and population	Outcome evaluated	Metabolite[a]	Urine concentration	Result
Ko et al. 2019 Cross-sectional, 435 adults (388 men, 47 women; mean age 32.16 years), Taiwan	High triglycerides (≥150 mg/dL) or low HDL (male <40 mg/dL, female <50 mg/dL)	ΣDEHP	NR	↔
		MEHP	All: 25th–95th percentile: 0.269–2.789 µg/g Cr Men: 0.263–2.800 Women: 0.299–2.551	NR
		MEHHP	All: 0.908–6.045 Men: 0.910–6.013 Women: 0.841–9.648	NR
		MEOHP	All: 0.486–2.603 Men: 0.479–2.636 Women: 0.505–2.509	NR
Lin et al. 2020 Cross-sectional, 792 adolescents and adults (age 12–30 years), Taiwan	**HDL cholesterol**	**MEHP**	GM (95% CI): 6.1 (5.1, 7.3) µg/g Cr	↓
		MEHHP	27.9 (26.1, 30.0)	↔
		MEOHP	17.5 (16.4, 18.5)	↔
	Triglycerides or LDL cholesterol	MEHP, MEHHP, MEOHP	See above	↔
Lin et al. 2016 Cross-sectional, 793 students including 303 with and 486 without elevated blood pressure in childhood, (mean age 21.28 years), Taiwan	**HDL cholesterol**	**MEHP**	IQR: 1.7–38.99 µg/g Cr	↑
		MEHHP	15.86–43.16	↔
		MEOHP	10.18–26.56	↔
	Triglycerides or LDL cholesterol	MEHP, MEHHP, MEOHP	See above	↔

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference, study type, and population	Outcome evaluated	Metabolite[a]	Urine concentration	Result
Perng et al. 2017 Cohort, 240 mother-adolescent pairs (112 boys, 128 girls; age 8–14 years), participants in the Early Life Exposure in Mexico to Environmental Toxicants Project, Mexico	**LDL cholesterol**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	Maternal: Mean (SD): 0.3 (0.3 nmol/mL)	↔
			Child (boys): 1.7 (11.0)	↔
			Child (girls): 0.6 (0.6)	↓
	Total, or HDL cholesterol or triglycerides	ΣDEHP	Maternal: see above	↔
			Child (boys): see above	↔
			Child (girls): see above	↔
Trasande and Attina 2015 Cross-sectional, 1,329 children (age 6–19 years), United States (NHANES)	Triglycerides or HDL cholesterol	ΣDEHP	IQR: 0.077–0.313 µM	↔
Trasande et al. 2013a Cross-sectional, 2,463 children and adolescents (age 6–19 years), United States (NHANES)	Triglycerides or HDL cholesterol	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	IQR: 0.166–0.704 mol/L	↔
Vafeiadi et al. 2018a Cohort, 260 mothers and their 500 children (279 boys, 221 girls; age 4–6 years), Greece	**Total cholesterol**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	Maternal IQR (1st trimester): 0.1–0.2 µmol/g	↔
			Child: 0.2–0.5	All: ↔ Boys: ↔ **Girls:** ↑
	HDL cholesterol	ΣDEHP	Maternal: see above	↔
			Child: see above	↔

Table 2-5. Selected Epidemiological Studies of DEHP Exposure and Serum Lipid/Cholesterol Alterations

Reference, study type, and population	Outcome evaluated	Metabolite[a]	Urine concentration	Result
Yaghjyan et al. 2015a, 2015b Cross-sectional, 6,005 women (age ≥18 years), United States (NHANES)	Triglycerides or total, HDL, or LDL cholesterol	ΣDEHP	IQR: 19.59–58.66 µg/g Cr	↔
		MEHP	1.49–5.95	↔
		MEHHP	9.86–31.09	↔
		MEOHP	6.83–19.84	↔
		MECPP	17.16–49.78	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

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 = 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

an infant cohort (Kim et al. 2016a). However, no association between DEHP exposure and triglyceride levels were observed in another cohort (Perng et al. 2017) or in cross-sectional studies (Ko et al. 2019; Lin et al. 2016, 2020; Trasande and Attina 2015, Trasande et al. 2013a; Yaghjyan et al. 2015a, 2015b). A negative relationship between MEHP (but not MEHHP or MEOHP) in urine and high-density lipoprotein (HDL) cholesterol levels was observed in cross-sectional studies of young adults in Taiwan (Lin et al. 2020) and between the sum of DEHP metabolites and HDL levels in children at 3–5 years of age (but not 7–9 years of age) in a South Korean cohort (Han et al. 2019). However, no association was observed in additional studies of this endpoint (James-Todd et al. 2016a; Ko et al. 2019; Perng et al. 2017; Trasande and Attina 2015; Trasande et al. 2013a; Vafeiadi et al. 2018a; Yaghjyan et al. 2015a, 2015b). In a mother-child cohort, Vafeiadi et al. (2018a) observed increased total cholesterol in 4–6-year-old girls with increased urinary metabolites in girls (but not maternal levels); no changes were observed in boys. Total cholesterol in cord blood was not associated with maternal urinary DEHP metabolites (Kim et al. 2016a). Perng et al. (2017) observed decreased low-density lipoprotein (LDL) in 8–14-year-old girls with increased urinary metabolites in girls (but not maternal levels); no changes were observed in boys for LDL or in either sex for total cholesterol.

Available cross-sectional studies did not indicate an association between DEHP urinary metabolite levels and LDL (Yaghjyan et al. 2015a, 2015b) or total cholesterol levels (Lin et al. 2016, 2020; Yaghjyan et al. 2015a, 2015b).

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), most oral studies in rodents (Table 2-2) did not find exposure-related changes during microscopic examination of the liver following exposure to DEHP at acute 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).

A few intermediate-duration studies have reported exposure-related hepatic lesions other than hepatocellular hypertrophy in rats 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 1986). Because this finding was limited to a single animal at a low dose only, it is likely an incidental 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). Other studies in Wistar rats reported increased incidence of congestion, mononuclear cell infiltration, and sinusoidal degeneration following exposure to ≥100 mg/kg/day via gavage for 4 weeks (Aydemir et al. 2018), slight centrilobular steatosis following exposure to ≥1,000 mg/kg/day via drinking water for 30 days (Wang et al. 2020), and disordered hepatocyte cords and vacuolar degeneration at ≥5 mg/kg/day via gavage for 8 weeks (Zhang et al. 2019, 2020c). One study in Sprague-Dawley rats qualitatively reported vacuolar degeneration and inflammatory infiltration after exposure to ≥0.05 mg/kg/day for 15 weeks, which progressed to central necrosis at 500 mg/kg/day (Zhang et al. 2017). Effects reported in other intermediate-duration Sprague-Dawley rat studies were observed at much higher oral doses, including vacuolation, hepatic sinusoidal dilation, and reduction in hepatocyte number following exposure to ≥500 mg/kg/day for 30 days (Ye et al. 2017) and liver steatosis at ≥1,000 mg/kg/day for 30 days (Wang et al. 2020).

Similarly, a few intermediate-duration studies have reported exposure-related hepatic lesions other than hepatocellular hypertrophy in mice following oral DEHP exposure. In a 30-day drinking water study, liver steatosis was observed in BALB/c mice at 3,000 mg/kg/day, and mild inflammatory cell infiltrates were observed in C57BL/6J mice at ≥300 mg/kg/day (Wang et al. 2020). In a dietary study in mice, moderate focal coagulative necrosis was observed in the livers of B6C3F1 mice at doses ≥1,209 mg/kg/day for 13 weeks, but not at 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 and Kupffer cells 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 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). Small, but significant, increases in serum ALT and AST were observed in Wistar rats following exposure to ≥100 mg/kg/day for 4 weeks; larger increases were observed for ALT and AST (1.8- and 2.4-fold, respectively) were observed only at 400 mg/kg/day (Aydemir et al. 2018). Another study in Wistar rats

reported significant increases in serum ALT (~20–25%) following exposure to 300 or 1,000 mg/kg/day, but not at 3,000 mg/kg/day (Wang et al. 2020). In similarly exposed Sprague-Dawley rats, serum ALT, ALP, and AST were significantly increased by approximately 20–30% at 3,000 mg/kg/day (Wang et al. 2020). However, a 15-week study in Sprague-Dawley rats reported effects at much lower doses, with a 120–145% increase in serum ALP at doses ≥5 mg/kg/day and a 70–100% increase in serum AST and ALT at 500 mg/kg/day (Zhang et al. 2017). In other rat studies, no biologically relevant changes in hepatic serum enzyme levels have been reported following acute- or intermediate-duration oral exposure up to 1,858 mg/kg/day (Astill et al. 1986; Kim et al. 2018c; Myers 1992b; Nardelli et al. 2017; Poon et al. 1997) or chronic-duration oral exposure up to 939 mg/kg/day (David et al. 2000a). In C57BL/6J mice, a 35-day gavage study reported a 46–83% increase in serum ALT at ≥1 mg/kg/day (Li et al. 2018). In contrast, no exposure-related changes in serum ALT, AST, or ALP were observed in C57BL/6J mice following drinking water exposure to doses up to 3,000 ppm for 30 days (Wang et al. 2020). In similarly exposed BALB/c mice, serum ALP was significantly increased by approximately 30–40% following drinking water exposure to ≥1,000 mg/kg/day for 30 days (Wang et al. 2020). In ICR mice, a significant 23% increase in serum ALP and 54% increase in serum AST was observed following oral exposure to 180 mg/kg/day for 3 weeks, but not ≤18 mg/kg/day (Ding et al. 2019). In other mouse studies, 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/or triglyceride levels were seen in rats exposed to DEHP at doses >100 mg/kg/day (Astill et al. 1986; Barber et al. 1987; CMA 1986; Poon et al. 1997; Reddy et al. 1976; Wang et al. 2020). 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). In contrast, increased cholesterol and/or triglycerides were reported in rats exposed to 500 mg/kg/day for 8 weeks (Zhang et al. 2019, 2020c; Zhou et al. 2019) and mice exposed to ≥1.8 mg/kg/day for 3 weeks or ≥1 mg/kg/day for 35 days (Ding et al. 2019; Li et al. 2018). Ding et al. (2019) suggested that this finding was due to altered lipid metabolism associated with decreased hepatic lipase and lecithin-cholesterol acyltransferase levels. In a drinking water study, no changes in serum cholesterol or triglycerides were noted in mice exposed to doses up to 3,000 mg/kg/day for 30 days (Wang et al. 2020).

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, nonpregnant rats and mice were 5 and 180 mg/kg/day, respectively (Sasaki et al. 2003; Zhang et al. 2017). One gestational/lactation exposure study reported increased maternal liver weight in mice at 5 mg/kg/day (Pocar et al. 2012). A large number of 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 1986; 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 1986; 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. 1953).

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 described 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 gene expression, protein level, 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 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 (Turunen 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 deoxyribonucleic acid (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 2000).

Summary. Human data on hepatic effects of DEHP are limited but suggest that occupational exposure levels may be associated with increased serum liver enzyme levels and decreased plasma cholinesterase activity. In studies of general population exposures, urinary metabolite levels were generally not

consistently 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 $\mu g/m^3$ DEHP in the three factories), serum urea and creatinine levels did not differ from those in 104 unexposed workers (Wang et al. 2015).

There is some evidence of altered renal clinical chemistry in Taiwanese children exposed to foods contaminated with DEHP (duration of exposure time unknown). Tsai et al. (2016) reported higher urinary albumin/creatinine ratio (ACR) in a group of exposed Taiwanese children, compared to an unexposed group. ACR indicates elevated protein levels in the urine and is a biomarker for kidney disease. Exposed children also had a higher prevalence of microalbuminuria associated with the highest intake of contaminated foods (estimated to be >0.05 mg/kg/day), compared with unexposed children (Tsai et al. 2016; Wu et al. 2018). However, serum blood urea nitrogen (BUN) and creatinine levels in exposed children 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 also reported an association between higher levels of DEHP metabolites in urine and increasing urinary ACR. However, the odds of micro- or macroalbuminuria (ACR ≥30 mg/g) were not increased in children with higher levels of DEHP metabolites in urine (Trasande et al. 2014). In contrast, a cross-sectional study in Taiwanese children and adolescents (7–<18 years old; not among the children exposed to contaminated

food) did not find an association between urinary levels of DEHP metabolites and ACR, BUN, or odds of microalbuminuria (Chang et al. 2020). In Taiwanese adults, increased urinary DEHP metabolites were associated with increased serum BUN (Chang et al. 2020). Across the entire population, no association was observed between ACR or microalbumin and DEHP exposure. However, odds of microalbuminuria (microalbumin >1.9 mg/dL) were increased in individuals in the highest tertile of estimated DEHP intake (≥0.003 mg/kg/day), compared to the lowest (<0.001 mg/kg/day).

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 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). Additionally, Rao et al. (1990) did not observe histopathological changes in the rat kidney following exposure to 1,900 mg/kg/day for 108 weeks.

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 (Astill et al. 1986; Barber et al. 1987; CMA 1986; Dalgaard et al. 2000; NTP 1982), up to 3,000 mg/kg/day for up to 13 weeks (Dalgaard et al. 2000; Myers 1992b; NTP

1982; Poon et al. 1997; Shaffer et al. 1945), or up to 1,440 mg/kg/day for 17 weeks (Gray et al. 1977). However, a 4-week study in male rats reported increased glomerular degeneration, congestion, and mononuclear cell infiltration at gavage doses ≥100 mg/kg/day (Aydemir et al. 2018).

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 oral doses up to 2,600 mg/kg/day for 4–13 weeks (Myers 1992a; NTP 1982; Xu et al. 2019). 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). One intermediate-duration study in mice reported glomerular damage (consistent with hypertensive renal injury) and increased inflammatory cell infiltration at doses ≥1 mg/kg/day (Xie et al. 2019). 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). In a 4-week gavage study, serum urea was increased by approximately 50% at ≥200 mg/kg/day in male Wistar rats (Aydemir et al. 2018). 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; Kim et al. 2018c; 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). An intermediate-duration study in C57Bl/6 mice

reported a 43% increase in serum creatinine following exposure to 300 mg/kg/day for 35 days (Li et al. 2018). In other mouse studies, no exposure-related changes were observed in clinical chemistry measures 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- or chronic-duration rat studies at doses ≥100 mg/kg/day (Table 2-2) and in acute-duration studies following exposure to 1,000 mg/kg/day (Hellwig et al. 1997). In a Hershberger assay, absolute kidney weights were increased >10% at ≥40 mg/kg/day in castrated rats; no changes in kidney weights were observed in castrated rats supplemented with testosterone propionate at doses up to 400 mg/kg/day (Kim et al. 2018b). In other studies, kidney weight changes did not occur in other rat studies at acute-duration doses of 500–2,100 mg/kg/day (Astill et al. 1986; Dostal et al. 1987; 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) and absolute kidney weight (without a significant change in body weight) was increased in male mice exposed to 400 mg/kg/day for 28 days (Xu et al. 2019). However, no kidney weight changes occurred in other mouse studies following exposure 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. 1988). 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). Mitochondrial dysfunction and oxidative stress were suggested as possible mechanisms for DEHP-induced nephrotoxicity based on experiments in cultured embryonic human kidney cells (HEK-293 cells) (Ashari et al. 2020).

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).

A single dose of up to 20 mL/kg (19,700 mg/kg) DEHP was applied to rabbit skin for 24 hours using a modified FDA cuff test procedure. Despite this dose resulting in the death of 2/6 rabbits, there was no evidence of dermal injury 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 and cord blood glucocorticoids. Data regarding potential endocrine effects in animals following DEHP exposure were available from one inhalation study and numerous oral studies.

Epidemiology Studies—Thyroid Function. Effects of DEHP exposure on thyroid function (serum levels of triiodothyronine [T3], thyroxine [T4], and thyroid stimulating hormone [TSH]) have been evaluated in 19 epidemiological studies in which DEHP exposure was evaluated using urinary metabolite biomarkers (Table 2-6).

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Pregnant women				
Huang et al. 2018 Cohort/cross-sectional, 98 pregnant women referred for amniocentesis (mean age 35 years), Taiwan, China	TSH	ΣDEHP	GW 18: GM (95% CI): 21.64 (16.44, 28.25) ng/mL GW 26: 30.68 (24.51, 38.39) GW 39: 39.34 (31.60, 48.97)	↔
		MEHP	GW 18: 2.43 (1.67, 3.52) GW 26: 3.45 (2.43, 4.91) GW 39: 2.49 (1.60, 3.87)	↔
		MEHHP	GW 18: 2.67 (1.75, 4.08) GW 26: 5.33 (3.63, 7.82) GW 39: 9.69 (7.27, 12.91)	↔
		MEOHP	GW 18: 3.41 (2.45, 4.75) GW 26: 5.36 (4.06, 7.08) GW 39: 8.38 (6.68, 10.52)	↓
		MECPP	GW 18: 6.15 (4.37, 8.65) GW 26: 9.89 (7.95, 12.30) GW 39: 12.46 (10.03, 15.50)	↔
	TT3	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔
		MECPP	See above	↓
	TT4 and FT4	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
		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 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Huang et al. 2007 Cross-sectional, 76 pregnant women referred for amniocentesis (mean age 22.6 years), Taiwan, China	FT4 or TT4	MEHP	IQR: 31.4–121.0 µg/g Cr	↔
Johns et al. 2016 Case-control, 439 pregnant women (116 cases of preterm birth and 323 term birth controls), United States (Massachusetts)	**TSH**	ΣDEHP	GM (GSD): Median GW 9.71: 0.39 (3.16) µmol/L (SG-adj) Median GW 17.9: 0.38 (3.01) Median GW 26: 0.32 (3.04) Median GW 35.1: 0.42 (3.18)	↔
		MEHP	GM(GSD): Median GW 9.71: 10.6 (3.52) µg/L (SG-adj) Median GW 17.9: 10.9 (3.39 Median GW 26: 9.46 (3.28) Median GW 35.1: 9.83 (3.52)	↓
		MEHHP	Median GW 9.71: 34.7 (3.37) Median GW 17.9: 34.8 (3.10) Median GW 26: 27.2 (3.21) Median GW 35.1: 9.83 (3.33)	↔
		MEOHP	Median GW 9.71: 18.6 (3.28) Median GW 17.9: 18.3 (3.03) Median GW 26: 15.6 (3.19) Median GW 35.1: 20.9 (3.22)	↔
		MECPP	Median GW 9.71: 44.4 (3.35) Median GW 17.9: 42.6 (3.25) Median GW 26: 36.8 (3.31) Median GW 35.1: 49.3 (3.35)	↔
	TT3 and FT4	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
	TT4	ΣDEHP, MEHHP, MEOHP, or MECPP	See above	↔
		MEHP	See above	↑
		Repeated measures analysis with cases and controls combined.		
Johns et al. 2015 Cohort/cross-sectional, 106 pregnant women (age 18–40 years), Puerto Rico	**FT4**	**ΣDEHP**	NR	↓
		MEHP	GWs 16–20: IQR: 1.61–6.36 ng/mL (SG-adj) GWs 24–28: 1.69–6.73	NR
		MEHHP	GWs 16–20: 6.14–19.9 GWs 24–28: 7.28–16.9	NR
		MEOHP	GWs 16–20: 5.57–16.5 GWs 24–28: 6.22–14.8	NR
		MECPP	GWs 16–20: 12.7–31.4 GWs 24–28: 13.4–29.3	NR
	TSH and FT3	ΣDEHP	NR	↔
		Cross-sectional analysis (same day serum and urine samples) using visit 3 (GWs 24–28) data only; no significant association seen with visit 1 (GWs 16–20) data only or in longitudinal analysis.		
Kuo et al. 2015 Cohort, 148 mother-child pairs, Taiwan	TSH (cord blood)	MEHP	IQR: 8.19–19.34 µg/g Cr	↔
		MEHHP	14.84–33.81	↔
		MEOHP	14.68–31.59	↔
Villanger et al. 2020a, 2020b Cohort/cross-sectional with nested case-control, 1,072 pregnant women (534 cases of mothers of children with diagnosed ADHD, 538 random controls; mean age at delivery 30.24 years), Norway	TSH, FT3, TT3, FT4, TT4	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP, MCMHP)	GW 17: 20th–80th percentile: 0.17–0.41 µmol/L	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Yao et al. 2016 Cohort/Cross-sectional, 2,521 pregnant women (mean age 25 years), China	**TSH**	**MEHP or MEHHP**	NR	↑
		MEOHP	NR	↔
	TT3, TT4, or FT4	**MEHP or MEHHP**	NR	↓
		MEOHP	NR	↔
	No associations were observed between maternal DEHP metabolite levels and cord serum thyroid hormone levels.			
Other populations				
Al-Saleh et al. 2019a Cross-sectional, 599 male partners (mean age 37.86 years) of infertile couples, Saudi Arabia	**TSH**	ΣDEHP	IQR: 0.161–0.433 µmol/L	↔
		MEHP	IQR: 9.467–22.368 µg/L	↔
		MEHHP	5.889–20.496	↔
		MEOHP	9.875–28.432	↔
		MECPP	17.044–53.328	↔
Boas et al. 2010 Cross-sectional, 758 children (age 4–9 years), Denmark	TSH, TT3, TT4, FT3, or FT4	ΣDEHP	NR	↔
		MEHP	Males: IQR: 4.1–11 µg/g Cr Females: 4.1–12	↔
		MEHHP	Males: 33–84 Females: 36–81	↔
		MEOHP	Males: 17–42 Females: 18–41	↔
		MECPP	Males: 29–68 Females: 33–75	↔
	Cr-corrected analysis for all children (girls and boys combined); p>0.05 for all.			
Dirtu et al. 2013 Case-control, 152 obese individuals and 43 non-obese controls (age 19–59 years), Belgium	**TSH**	**ΣDEHP**	**Controls**: IQR: 27–53 ng/mL	↑
			Cases: 30–61	↔
		MEHP	Controls: 2–5	↔
			Cases: 2–5	↔
		MEHHP	Controls: 9–19	↔
			Cases: 10–25	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEOHP	**Controls:** 3–9	↑
			Cases: 4–11	↔
		MECPP	**Controls:** 12–20	↑
			Cases: 12–22	↔
	FT4	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	Controls: see above	↔
			Cases: see above	↔
		Gender-specific results also did not show any significant associations for DEHP metabolites.		
Huang et al. 2017 Cross-sectional, 279 adults (age ≥18 years, mean age 53.4 years) and 79 minors (age <18 years, mean age 12.6 years), Taiwan	**FT4 (adults)**	ΣDEHP	IQR: 0.16–0.36 µmol/g Cr	↔
		MEHP	IQR: 3.25–15.08 µg/g Cr	↓
		MEHHP	13.36–30.51	↔
		MEOHP	8.22–20.02	↓
		MECPP	16.43–38.73	↔
		MCMHP	0.33–7.16	↔
	TT4 (adults)	**ΣDEHP, MEHHP**	See above	↓
		MEHP, MEOHP, MECPP, or MCMHP	See above	↔
	TSH, TT3 (adults)	ΣDEHP, MEHP, MEHHP, MEOHP, MECPP, or MCMHP	See above	↔
	TT3 (minors)	ΣDEHP	IQR: 0.17–0.53 µmol/g Cr	↔
		MEHP	IQR: 2.38–12.17 µg/g Cr	↑
		MEHHP	14.45–44.11	↔
		MEOHP	9.42–27.98	↔
		MECPP	18.88–55.05	↔
		MCMHP	1.71–10.99	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
	TSH, FT4, TT4 (minors)	ΣDEHP, MEHP, MEHHP, MEOHP, MECPP, or MCMHP	See above	↔
Huang et al. 2020a Cross-sectional, 266 adults (age ≥18 years, mean age 53.6 years), Taiwan	**TT4**	**ΣDEHP**	GM (95% CI): 0.199 (0.180, 0.219) nmol/mL	↓
		MEHP	GM (95% CI): 3.689 (2.955, 4.604) ng/mL	↔
		MEHHP	15.90 (14.01, 18.04)	↓
		MEOHP	8.346 (7.128, 9.772)	↓
		MECPP	17.57 (15.11, 20.44)	↓
		MCMHP	1.524 (1.219, 1.906)	NR
	TSH, TT3, or FT4	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Huang et al. 2020b Cohort, 166 children and adolescents examined at 3 clinical visits over 4 years post-exposure to phthalate-tainted food (age 2–18 years, mean age at visit 1: 6.1 years, visit 2: 7.9 years, and visit 3: 9.8 years), Taiwan	**FT4**	**ΣDEHP**	Visit 1: IQR: 0.08–0.26 nmol/L Visit 2: 0.08–0.32 Visit 3: 0.06–0.23	↑
		MEHP	Visit 1: IQR: 1.77–9.98 ng/mL Visit 2: 3.83–13.7 Visit 3: 2.57–8.63	↔
		MEHHP	Visit 1: 11.4–38.84 Visit 2: 12.1–45.4 Visit 3: 7.79–35.5	↑
		MEOHP	Visit 1: 7.54–29.42 Visit 2: 7.66–29.4 Visit 3: 6.01–21.6	↑
	TSH, TT3, or TT4	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Kim et al. 2017a, 2017b Cross-sectional, 1,829 adolescents and adults (age ≥12 years), United States (NHANES)	**TSH**	MEHP	IQR: 0.780–5.30 ng/mL	↔
		MEHHP	9.10–46.6	↑
		MEOHP	5.20–25.6	↑
		MECPP	14.7–65.9	↑
	FT3, TT3	MEHP, MEHHP, MEOHP, MECPP	See above	↔
	FT4	MEHP or MECPP	See above	↔
		MEHHP or MEOHP	See above	↓
	TT4	MEHP	See above	↔
		MEHHP, MEOHP, or MECPP	See above	↓
Meeker and Ferguson 2011 Cross-sectional, 1,346 adults (age ≥20 years) and 329 adolescents (age 12–19 years), United States (NHANES)	**TSH**	MEHP	Adolescent: IQR: <LOD–4.5 µg/g Cr:	↔
			Adult: <LOD–5.20	↔
		MEHHP	Adolescent: 10.3–45.32	↔
			Adult: 9.84–37.0	↑
		MEOHP	Adolescent: 5.79–24.74	↔
			Adult: 5.43–20.5	↑
		MECPP	Adolescent: 16.7–64.8	↔
			Adult: 15.4–50.8	↑
	TT3	**MEHP or MECPP**	**Adolescent:** see above	↑
			Adult: see above	↔
		MEHHP	**Adolescent:** see above	↑
			Adult: see above	↓
		MEOHP	**Adolescent:** see above	↑
			Adult: see above	↓
	TT4	**MEHP, MEHHP, MEOHP, or MECPP**	Adolescent: see above	↔
			Adult: see above	↓

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
	FT3 and FT4	MEHP, MEHHP, MEOHP, or MECPP	Adolescent: see above	↔
			Adult: see above	↔
Meeker et al. 2007 Cross-sectional, 408 male partners of sub-fertile couples (age 18–55 years), United States (Massachusetts)	**TT3**	**MEHP**	IQR: 3.16–21.3 ng/mL (SG-adj)	↓
		MEHHP	23.4–113	↔
		MEOHP	16.3–71.3	↔
	TSH and FT4	MEHP, MEHHP, MEOHP	See above	↔
Morgenstern et al. 2017 Cohort/Cross-sectional, 181 mother-child pairs (99 girls, 82 boys; age 3 years) and 229 children (120 girls, 109 boys; age 3 years), United States (New York City)	**FT4 (children)**	**MEHP**	**Maternal:** 5.7 (4.7, 6.9)	↑
			Child: 3.2 (2.8, 3.7)	↔
		MEHHP	Maternal: 23.6 (19.6, 28.5)	↔
			Child: 32.8 (27.9, 38.5)	All: ↔ Boys: ↔ **Girls: ↓**
		MEOHP	Maternal: 19.7 (16.4, 23.7)	↔
			Child: 19.2 (16.4, 22.5)	All: ↔ Boys: ↔ **Girls: ↓**
		MECPP	Maternal: 41.6 (35.2, 49.2)	↔
			Child: 61.0 (52.9, 70.3)	↔
	TSH (children)	MEHP, MEHHP, MEOHP, MECPP	Maternal: see above	↔
			Child: see above	↔
Park et al. 2017 Cross-sectional, 6,003 adults (2,638 men, 3,365 women; age ≥20 years), Korea	**TSH**	ΣDEHP	Total: IQR: 31.54–89.41 µg/L	↔
			Men: 34.17–90.02	↔
			Women: 29.64–88.74	↔
		MEHHP	Total: 10.72–32.14	↔
			Men: 11.63–32.73	↔
			Women: 9.850–31.71	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEOHP	**Total:** 7.670–22.35	↑
			Men: 8.050–22.16	↔
			Women: 7.289–22.58	↔
		MECPP	Total: 12.84–34.77	↔
			Men: 13.53–34.63	↔
			Women: 11.97–35.40	↔
	TT3	ΣDEHP, MEHHP, MEOHP, or MECPP	Total: see above	↔
			Men: see above	↔
			Women: see above	↔
	TT4	**ΣDEHP or MEHHP**	**Total:** see above	↓
			Men: see above	↓
			Women: see above	↔
		MEOHP or MECPP	Total: see above	↔
			Men: see above	↔
			Women: see above	↔
Souter et al. 2020a, 2020b Cross-sectional, 558 sub-fertile women seeking fertility treatment (median age 34.0 years), United States (Massachusetts)	**FT3**	**ΣDEHP**	NR	↓
		MEHP	IQR: <LOD–4.30 µg/L	↔
		MEHHP	3.50–23.6	↔
		MEOHP	2.30–15.2	↔
		MECPP	6.30–38.2	↑
	TT3, FT4	**ΣDEHP**	NR	↓
		MEHP, MEHHP, MEOHP, or MECPP	See above	↔
	TT4	**ΣDEHP**	NR	↓
		MEHHP	See above	↓
		MEHP, MEOHP, or MECPP	See above	↔

Table 2-6. Summary of Epidemiological Studies of DEHP Exposure and Thyroid Hormone Levels

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
	TSH	ΣDEHP	NR	↔
		MEHP, MEHHP, MEOHP, or MECPP	See above	NR
Weng et al. 2017 Cohort/Cross-sectional, 189 children (92 boys, 97 girls; age 9–10 years), Taiwan	**FT3**	**ΣDEHP**	33rd–66th percentile (adjusted for Cr): 25.34–49.92 µg/L	↑ **(all, boys)** ↔ girls
		MEHP	2.74–6.42	↔
		MEHHP	13.04–25.93	↑ **(all, boys)** ↔ (girls)
		MEOHP	9.15–17.95	↔ (all, girls) ↑ **(boys)**
	FT4	ΣDEHP, MEHP, or MEHHP	See above	↔
		MEOHP	See above	↔ (all, boys) ↑ **(girls)**

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; FT3 = free triiodothyronine; FT4 = free thyroxine; GM = geometric mean; GSD = geometric standard deviation; GW = gestation week; IQR = interquartile range; LOD = limit of detection; MCMHP = mono-[(2-carboxymethyl)-hexyl] phthalate; 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; SG-adj = specific gravity adjusted; TSH = thyroid stimulating hormone; TT3 = total triiodothyronine; TT4 = total thyroxine

Six 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 large study (n=1,072 women) (Villanger et al. 2020a), the sum of DEHP metabolite levels were not associated with TSH or free or total T3 or T4 in maternal serum during gestation week 17; potential associations with individual metabolites were not evaluated. In a smaller 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 106 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). In pregnancy cohorts, no associations were observed between maternal urinary DEHP metabolite levels and cord serum thyroid hormone levels (Huang et al. 2018; Kuo et al. 2015; Yao et al. 2016). However, Morgenstern et al. (2017) reported an association between maternal third trimester urinary MEHP levels and increased free T4 serum levels in 3-year-old children; no association was observed with TSH levels in children. Other studies in pregnant women did not evaluate cord or child serum thyroid levels.

Findings in cross-sectional studies of other populations were also inconsistent. Some studies reported associations between DEHP urinary metabolite levels and increased serum TSH in adults and adolescents (Dirtu et al. 2013; Kim et al. 2017a; Meeker and Ferguson 2011; Park et al. 2017), while others did not observed this association in adults (Al-Saleh et al. 2019a; Huang et al. 2017, 2020a; Meeker et al. 2007; Souter et al. 2020a), children or adolescents (Boas et al. 2010; Huang et al. 2017, 2020b; Meeker and Ferguson 2011; Morgenstern et al. 2017), or obese individuals (Dirtu et al. 2013). Similarly, DEHP urinary metabolite levels were associated with decreased free or total T3 in adults in some studies (Meeker et al. 2007; Souter et al. 2020a, 2020b), but increased total or free T3 in children or adolescents

in other studies (Huang et al. 2017; Meeker and Ferguson 2011; Weng et al. 2017). No changes in free or total T3 were associated with DEHP exposure in other studies in adults, adolescents, and children (Boas et al. 2010; Huang et al. 2017, 2020a, 2020b; Kim et al. 2017a, 2017b; Park et al. 2017). DEHP urinary metabolite levels were associated with decreased free and/or total T4 in adults, adolescents, and/or children (Huang et al. 2017, 2020a, 2020b; Kim et al. 2017a, 2017b; Meeker and Ferguson 2011; Park et al. 2017; Souter et al. 2020a; Weng et al. 2017) in some studies; other studies did not observe this association in adults (Dirtu et al. 2013; Meeker et al. 2007) or adolescents or children (Boas et al. 2010; Huang et al. 2017; Meeker and Ferguson 2011).

Animal Studies—Thyroid/Parathyroid Gland. A limited number of animal studies were found in the literature that evaluated the function of the thyroid gland; findings were inconsistent between studies. Increased serum total T3 and total T4 and hypothalamic thyrotropin-releasing hormone (TRH) were observed in adult Wistar rats exposed to 500 mg/kg/day for 4 weeks, but not ≤50 mg/kg/day (Sun et al. 2018). No changes were observed in free T3, free T4, or TSH. In contrast, free T4 and TSH levels were decreased in adult Sprague-Dawley rats exposed to 500 mg/kg/day for 31 days, with no change in free T3 or TRH (Zhang et al. 2018b). These findings were accompanied by microscopic and ultrastructural changes in the thyroid follicular cells, including cellular hypertrophy. Similarly, in weanling Sprague-Dawley rats exposed to DEHP for 30 days, changes in thyroid hormone levels included decreased serum total T3 and free and total T4 at ≥500 mg/kg/day and decreased free T3 and TRH at 750 mg/kg/day (Ye et al. 2017). Histological and ultrastructural changes in thyroid follicular cells were observed at ≥250 and 750 mg/kg/day, respectively. Following gestational and lactational exposure, decreased serum total T4 and increased serum TSH were observed in PND 7 and 14 Wistar rat offspring at maternal doses ≥30 mg/kg/day (Dong et al. 2019). When exposure continued through PND 21, serum thyroid hormone changes were only observed at ≥300 mg/kg/day. Ultrastructural changes in thyroid follicular cells were observed at ≥30 mg/kg/day at all timepoints. However, in a second rat developmental study, there were no changes in serum thyroid hormones in PND 21 or 63 offspring born to Sprague-Dawley dams exposed to DEHP at doses up to 400 mg/kg/day from GD 6 to PND 20 (Kobayashi et al. 2006). In adult C57BL/6 male mice, an increase in serum T4 was also observed after exposure to ≥100 mg/kg/day for 35 days; no other thyroid hormones were evaluated, and this finding was not observed at ≤10 mg/kg/day (Li et al. 2018). In adult ICR mice, no changes in serum T3 or T4 were observed following a 28-day exposure to doses up to 400 mg/kg/day (Xu et al. 2019).

One gavage study reported thyroid hyperplasia and hypertrophy in Sprague-Dawley rats exposed to 150 mg/kg/day for 13 weeks starting on PND 6 (Kim et al. 2018c). Increases in thyroid cell proliferation

were also observed in males and females at 150 and ≥30 mg/kg/day, respectively. The relative contributions of developmental and post-sexual maturation exposure on thyroid histology in this study are unknown. No changes in thyroid/parathyroid weight were observed. No changes in thyroid/parathyroid weight or histology were observed in any other 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 (Dong et al. 2017; Kim et al. 2018c, 2019a; Li et al. 2020; 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 (Miodovnik et al. 2014). DEHP was shown to be a thyroid receptor antagonist, and it inhibited the binding of T3 to the purified thyroid hormone receptor (Miodovnik et al. 2014) and T4 to integrin $\alpha_v\beta_3$, a plasma membrane bound thyroid hormone receptor (Li et al. 2020). DEHP can also increase the metabolism of thyroid hormones and interfere with thyroid hormone binding proteins (Kim et al. 2019a). Dong et al. (2017) analyzed gene and protein expression in the thyroid, pituitary, and hypothalamus of rats exposed chronically to DEHP and the results suggested a disruption of the hypothalamus-pituitary-thyroid axis through altered TSH/TSH receptor signaling. Altered expression of the TSH receptor in the hypothalamus and the TRH receptor in the pituitary were also observed in the DEHP-exposed rats (Ye et al. 2017; Zhang et al. 2018b). Kim et al. (2018c, 2019a) also observed thyroid cell proliferation and gene expression changes consistent with altered thyroid hormone regulation following *in vivo* or *in vitro* exposure. Ye et al. (2017) also proposed that observed oxidative stress and altered expression of enzymes in the liver may contribute to the downregulation of thyroid hormones.

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 1,600 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; Myers 1992b; NTP 1982; Poon et al. 1997), or 7,899 mg/kg/day in mice (Myers 1992a; NTP 1982; Toyosawa et al. 2001).

Epidemiology Studies—Adrenal Function. One pregnancy cohort study with 553 mother-child pairs evaluated potential associations between maternal DEHP exposure and cord blood cortisol and cortisone levels (Sun et al. 2018). Increased first and third trimester urinary MEHP levels were associated with increased cortisone cord levels in girl infants only. No association between cord blood cortisone levels were observed in either sex for MECPP, MEHHP, MEOHP, or ΣDEHP levels during any trimester. Increased third trimester urinary MEHP, MEHHP, MEOHP, and ΣDEHP levels were associated with increased cord blood cortisol levels in female infants. In contrast, increased third trimester urinary MECPP, MEHHP, and MEOHP levels were associated with decreased cord blood cortisol levels in male infants. No associations between cord blood cortisol and first or second trimester DEHP urinary metabolite levels. No other studies evaluating adrenal function and DEHP exposure in humans were identified.

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; Xu et al. 2019) 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). No change in adrenal gland weight was observed in male Wistar rats exposed to DEHP on PNDs 1–21 (via dam) or PNDs 22–52 (direct) at doses up to 75 mg/kg/day (Venturelli et al. 2015), or from GD 13 to PND 21 (via dam) at doses up to 700 mg/kg/day (Venturelli et al. 2019).

In contrast, *increased* relative adrenal gland 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. Increased absolute adrenal gland weight (without a change in body weight) was also reported in male mice following gavage exposure to 400 mg/kg/day for 28 days (Xu et al. 2019). 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 (Lee et al. 2017; 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). DEHP was shown to down-regulate the expression of

estrogen receptor (ER) α and β in primary cultures of rat anterior pituitary cells, which may be related to altered pituitary cell growth (Perez et al. 2020).

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 (e.g., cross-sectional design, small sample size, lack of consistent control for potential confounders). There were no consistent alterations in thyroid function following DEHP exposure from the limited number of available animal studies. 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 in sensitized animals. 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 2-7. In a cohort study that examined the risk for asthma symptoms and wheezing, 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.

Table 2-7. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Araki et al. 2020 Cross-sectional, 128 children (68 boys, 60 girls; age 7–12 years), Japan	Wheeze, rhinoconjunctivitis, or eczema	ΣDEHP (MEHP, MEOHP, MECPP)	IQR: 179–512 nmol/g Cr	↔
Ashley-Martin et al. 2015 Cohort, 1,137 children (maternal urine evaluated), Canada	IgE in cord blood	ΣDEHP	NR	↔
		MEHP	IgE ≥0.5 ku/L: GM (GSD): 2.6 (2.7) ng/mL IgE <0.5 ku/L: 2.6 (2.5)	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
	IL-33 and TSLP in cord blood	ΣDEHP	NR	↔
		MEHP	IL-33 and TSLP ≥80th percentile: 2.5 (2.6) IL-33 and TSLP <80th percentile: 2.7 (2.5)	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
Bekö et al. 2015 Case-control, 200 cases, children (age 3–5 years) with at least two conditions (asthma, allergic rhinoconjunctivitis, or eczema), and 300 controls, Denmark	**IgE sensitization**	MEHP	Cases: IgE-: Median: 3.7 ng/mL; IgE+: 4.01 Controls: 5.18	↔
		MEHHP	Cases: IgE-: 31.7; IgE+: 33.2 Controls: 33.5	↔
		MEOHP	Cases: IgE-: 13.3; IgE+: 16.0 Controls: 17.5	↔
		MECPP	Cases: IgE-: 29.9; IgE+: 31.5 Controls: 36.6	↑
		IgE sensitization was associated with MECPP only among asthma patients; no associations between DEHP metabolites among controls or among cases with rhinoconjunctivitis and atopic dermatitis.		

Table 2-7. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Bertelsen et al. 2013 Cross-sectional, 623 children (age 10 years), Norway	Asthma	ΣDEHP (MEP, MEHHP, MEOHP, MECPP)	IQR: 0.58–1.18 µmol/L (SG-adj)	↔
Franken et al. 2017 Cross-sectional, 418 adolescents (mean age 14.8 years), Belgium	**Asthma**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	IQR: 0.07–0.22 µmol/L (SG-adj)	↑
Gascon et al. 2015a Cohort, 391 children, allergy outcomes determined at age 6 and 14 months and 4 and 7 years, maternal urine evaluated, Spain	**Wheeze or asthma (age 7 years)**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	IQR: 69.5–147.9 µg/g Cr	↑
	Eczema (age 7 years) or atopy (age 4 years)	ΣDEHP	See above	↔
Hoppin et al. 2013 Cross-sectional, 2,325 children (age ≥6 years) and adults (age ≥18 years), United States (NHANES)	Allergic symptoms	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Children: IQR: 54.15–230.02 ng/mL (survey-weighted) Adults: 33.21–160.81	↔
Hsu et al. 2012 Cross-sectional, 101 children (mean age 7 years), Taiwan	Asthma, rhinitis, or eczema	MEHP	IQR: 5.7–20.0 µg/g Cr	↔
Johnk et al. 2020 Cohort, 552 mother-child pairs (age 5 years), maternal urine evaluated, Denmark	Wheeze, asthma, eczema, or rhinitis in children	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	IQR: 9.4–34.6 ng/mL	↔

Table 2-7. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Just et al. 2012 Cohort, 244 children, fractional exhaled NO concentrations (FeNO; a marker of airway inflammation) measured at age 4.9–9.1 years (maternal urine evaluated), United States (New York)	FeNO	MEHHP	GM (95% CI): 42 (36, 49) ng/mL	↔
Kim et al. 2018e Cross-sectional 56 children with asthma; age 6–16 years, Korea	**FeNO**	**MEHHP**	IQR: 35.2–85.7 µg/g Cr	↑
		MEOHP	27.2–60.6	↑
Ku et al. 2015 Cohort, 171 children evaluated for asthma symptoms (age 8 years; maternal and child urine evaluated), Taiwan	Wheezing or asthma	ΣDEHP (MEHP, MEHHP)	Maternal: GM (95% CI): 50.22 (42.22, 59.72) µg/g Cr	↔
	Serum IgE (in allergic children)	ΣDEHP	Maternal: see above	↔
			Child (5 years): NR	↔
		MEHP	Maternal: 16.90 (14.49, 19.72)	↑
			Child (5 years): GM: 11.9 µg/g Cr	↑
	Serum IgE (in non-allergic and all children)	ΣDEHP or MEHP	Maternal: see above	↔
			Child (5 years): see above	↔
Lin et al. 2018 Cohort, 191 children (115 with allergic disease, 76 without allergic disease), children assessed for allergy at mean age 9.2 years (urine collected at age 2, 5, and 9 years), Taiwan	Asthma, allergic rhinitis, atopic dermatitis, elevated IgE, or serum IgE	MEHP	Child (2 years): GM: 38.3 µg/g Cr	↔
			5 years: 14.8	↔
			9 years: 3.7	↔
		Metabolite concentrations were estimated from graphically presented data using GrabIt! software.		

Table 2-7. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Podlecka et al. 2020 Cohort, 145 mother-child pairs, children assessed for allergy at age 9 years, Poland Maternal and 2-year-old urine levels obtained from previous publication (Polanska et al. 2014)	**Food allergy**	MEHP	Maternal: median (range): 0.2 (0.02–3.5) ng/mL Child (2 years): 0.02 (0.02–176) Child (9 years): 3.04 (NR)	↔
		MEHHP	Maternal: 2.0 (0.05–256) Child (2 years): 2.1 (0.05–190) Child (9 years): 20.34 (NR)	↔
		MEOHP	Maternal: 1.3 (0.05–132) Child (2 years): 1.2 (0.05–283) Child (9 years): 8.03 (NR)	↑
	Atopic dermatitis	MEHP or MEOHP	See above	↔
		MEHHP	See above	↑
	Allergic rhinitis, or Asthma and Wheezing	MEHP, MEHHP, or MEOHP	See above	↔
Stelmach et al. 2015 Cohort, 147 children (age 2 years), maternal and child urine evaluated, Poland	Atopic dermatitis or food allergy	ΣDEHP	Maternal: IQR: 1.73–37.75 µg/g Cr Child (2 years): 1.81–9.11	↔
		MEHP	Maternal: 0.04–0.64 Child: 0.02–0.02	↔
		MEHHP	Maternal: 0.11–20.57 Child: 1.09–5.37	↔
		MEOHP	Maternal: 0.69–6.54 Child: 0.48–2.79	↔
Strassle et al. 2018 Cross-sectional, 1,091 adults age ≥18 years (mean age 44.5 years), United States (NHANES)	Wheeze, asthma, rhinitis, or hay fever	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	IQR: 34.30–177.10 ng/mL	↔
		Wheeze was associated with increased ΣDEHP individuals with high exposure to house dust endotoxin (≥25 EU/mg)		

Table 2-7. Selected Epidemiological Studies of DEHP Exposure and Allergy, Asthma, and Atopy

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Wang et al. 2014 Cohort/Cross-sectional, 483 children (244 boys and 239 girls), atopic disorders determined at ages 2 and 5 years, (child's urine evaluated at ages 2 and 5 years), Taiwan	**Serum IgE**	**MEHP**	GM (SE): 16.01 (1.12) µg/g Cr	**All:** ↑ **Boys:** ↑ Girls: ↔
	Atopic dermatitis	MEHP	See above	↔
Whyatt et al. 2014 Cohort, 300 children, asthma determined when children were age 5, 6, 7, 9, and 11 years (maternal urine evaluated), United States (New York)	Current and/or history of asthma symptoms	MEHHP	IQR: 10.6–50.0 ng/mL	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; FeNO = fractional exhaled NO concentration; GM = geometric mean; GSD = geometric standard deviation; IgE = immunoglobulin E; IL-33 = interleukin 33; IQR = interquartile range; 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; SE = standard error; SG-adj = specific gravity adjusted; TSLP = thymic stromal lymphopoietin

However, DEHP metabolites were not associated with asthma symptoms or wheezing in children in the other cohort studies (Johnk et al. 2020; Ku et al. 2015; Lin et al. 2018; Podlecka et al. 2020; Whyatt et al. 2014). Maternal urinary MEHHP levels during pregnancy were not associated with a change in fractional exhaled nitric oxide (FeNO, 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. In a cross-sectional study, Franken et al. (2017) reported increased risk of asthma in adolescents with an interquartile increase in the sum of DEHP urinary metabolites. No associations were observed between DEHP exposure and asthma symptoms or wheezing in cross-sectional studies in children (Araki et al. 2020; Bertelsen et al. 2013; Hsu et al. 2012) or adults (Strassle et al. 2018). However, urinary MEHHP and MEOHP levels were associated with FeNo levels in a cross-sectional analysis of children and adolescents with asthma (Kim et al. 2018e).

One cohort study reports increased risk of food allergy at age 9 years with increased maternal or child urinary levels of MEOHP (but not MEHP or MEHHP) and increased risk of atopic dermatitis at age 9 years with increased maternal or child urinary levels of MEHHP (but not MEHP or MEOHP) (Podlecka et al. 2020). No association with allergic rhinitis was observed. In other studies, no associations between DEHP urinary metabolites and food allergy, eczema, atopy, rhinitis, hay fever, and/or general allergic symptoms were observed in cohort studies in children (Gascon et al. 2015a; Johnk et al. 2020; Lin et al. 2018; Stelmach et al. 2015; Wang et al. 2014) or cross-sectional studies in children (Araki et al. 2020; Hoppin et al. 2013; Hsu et al. 2012) or adults (Strassle et al. 2018). 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).

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 associated with higher serum IgE in children 8 years of age that were diagnosed with allergic symptoms (Ku et al. 2015). No association was observed in non-allergic children, or when allergic and non-allergic children were combined. In another cohort of 9-year-old children, serum IgE levels were not associated with urinary MEHP levels measured at 2, 5, or 9 years of age; no other DEHP metabolites were evaluated (Lin et al. 2018). A cross-sectional study of children 3–5 years of age did not find an association between the children's MEHP, MEHHP, or MEOHP urinary levels and IgE sensitization (Bekö et al. 2015), although urinary MECPP was associated with IgE sensitization.

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.

One cross-sectional study evaluated potential associations between DEHP exposure and markers of autoimmunity in adult women (Souter et al. 2020a). Urinary DEHP metabolite levels were not associated with thyroid peroxidase or thyroglobulin antibodies.

Animal Studies—Immune Function. Several animal studies have reported adjuvant effects of low levels of DEHP exposure in rodents sensitized to OVA. In these studies, OVA-sensitized rodents were exposed to DEHP prior to an OVA challenge. Immune responses were measured in treated animals and compared with responses in OVA-sensitized controls. The human health relevance of findings in these sensitized animals is uncertain in the absence of clear evidence that the immune system is a target of DEHP toxicity in humans or unsensitized animals.

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. This study did not evaluate non-sensitized animals.

Enhanced immune responses in OVA-sensitized rodents were also observed following oral exposure to DEHP. The lowest oral dose associated with an altered immune response was 0.03 mg/kg/day based on increased OVA-specific IgE and IgG after 28 days (Han et al. 2014a) or total serum IgE after 52 days of exposure (Guo et al. 2012). More consistent evidence for enhanced immune responses was observed in these studies at 3 mg/kg/day, including increased cytokine production, germinal center formation in splenic lymphoid nodules, altered T-cell subpopulations, increased eosinophils in BAL fluid, and airway remodeling. Yang et al. (2008) reported similar enhancements in the immune response of OVA-sensitized mice after DEHP exposure to ≥0.7 mg/kg/day (lowest dose tested) for 30 days.

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. Similarly, a limited number of endpoints were altered in non-sensitized animals exposed to 3 mg/kg/day for 52 days, including elevated anti-OVA-IgE levels and lung tissue IFN-γ (Guo et al. 2012). Han et al. (2014a) did not evaluate non-sensitized animals.

Developmental exposure to DEHP also enhanced immune responses in OVA-sensitized rats following gestational and lactational exposure to oral doses ≥30 mg/kg/day (lowest dose tested) (Wang et al. 2018). Immune changes following OVA challenge were increased, including OVA-specific serum IgE and IgG1, cytokine production, and follicular helper cell population. Wang et al. (2018) also 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. Increases in eosinophils in BAL fluid and airway responsiveness were observed at maternal doses ≥30 mg/kg/day. No exposure-related findings were observed in 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. Cytokine levels were elevated in non-sensitized, non-challenged Sprague-Dawley rats and C57BL/6J mice following drinking water exposure to doses ≥300 mg/kg/day for 30 days (Wang et al. 2020). In Sprague-Dawley rats, levels of IL-12, TNF-α, IFN-γ, and IL-2 were elevated; in C57BL/6J mice, levels of IL-1, IL-6, and monocyte chemoattractant protein-1 (MCP-1) were elevated. No changes in cytokine levels were observed in similarly exposed Wistar rats or BALB/c mice at doses up to 3,000 mg/kg/day.

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; Xu et al. 2019), or chronic-duration studies at doses up to 1,821 mg/kg/day (Kluwe et al. 1982a, 1982b, 1985; 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). Increased thymus weight was reported in one mouse study following a 28-day exposure to DEHP at 400 mg/kg/day; however, the relevance of this finding in the absence of histopathological changes is unclear (Xu et al. 2019). In other rodent studies, 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 a large number of 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. 2014a, 2019). These cells synthesize excesses

of IL-21 and IL-4, which result in increased secretion of allergy-related IgE and IgG1. DEHP increased the expression of signaling lymphocytic activation molecule-associated protein (SAP) and transcription factors Bcl-6 and c-Maf in T follicular helper cells (Han et al. 2014a, 2019). 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). One cohort evaluated depression in elderly subjects and five cross-sectional studies evaluated various 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 adults (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).

In a cohort of 535 elderly adults (mean age of 73 years), urinary MEHHP, MEOHP, MECPP, and ΣDEHP levels were associated with an increased score on the Korean version of the Short Form Geriatric Depression Scale, evaluated 1–3 times over a 2-year period (Lee et al. 2018). In a cross-sectional study, an analysis of 5,560 adult (20–80 years of age) NHANES (2011–2012) participants also observed an association between risk of depression and increased concentrations of MECPP in urine, but not other DEHP metabolites (Shiue 2015c). 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. In other cross-sectional studies, 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).

Wang et al. (2015) reported clinical symptoms of neurotoxicity (i.e., headache, fatigue, dizziness, muscle weakness, nausea, and vomiting) 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 rats 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. However, Liu et al. (2018b) reported elevated anxiety in rats in the elevated plus maze and open field testing following a 30-day exposure to 500 mg/kg/day; no changes in overall motor activity were observed. In the Morris water maze, rats exposed to ≥100 mg/kg/day for

5 months showed impaired spatial learning in the Morris water maze; no changes in swimming speed or spatial memory were observed at doses up to 500 mg/kg/day (Ran et al. 2019).

Similarly, a limited number of studies evaluated neurological function in adult mice after oral exposure to DEHP. No changes in exploratory behavior were observed in F0 mice from a 1-generation study after 3 weeks of exposure to doses up to 180.77 mg/kg/day (behavior assessed 1 week prior to mating) (Tanaka 2002). In contrast, another 3-week study in mice reported decreased swimming speed in the Morris water maze at ≥0.18 mg/kg/day and decreased total distance travelled in an open field at ≥18 mg/kg/day (Feng et al. 2020). Observed changes in motor activity did not appear to be secondary to anxiety since time spent in the center of the open field was increased at ≥1.8 mg/kg/day. There was also evidence of impaired learning and memory in the Morris water maze at ≥0.18 mg/kg/day (Feng et al. 2020); however, it is unclear if some or all of the observed effect was secondary to observed swimming impairments. At much higher doses (≥6,922 mg/kg/day), clinical signs of neurotoxicity were reported in mice exposed to DEHP 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 numerous 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 in adults are extremely limited. There is limited evidence of altered neurobehavior in rats and mice following exposure to low oral doses of DEHP.

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 after sexual maturation are below. Several studies evaluating potential mechanisms of reproductive toxicity are also discussed.

Epidemiology Studies—Male Reproductive Effects. Data following inhalation exposure are limited to three small occupational studies in PVC workers evaluating serum hormone levels (Table 2-8) or sperm parameters (see Table 2-9). A study from China reported decreased free testosterone levels with increasing urinary MEHP levels in male workers (n=74); no other metabolites were evaluated and no associations were observed with serum estradiol, luteinizing hormone (LH), or follicle stimulating hormone (FSH) (Pan et al. 2006). A similar study in Taiwan (n=82) did not observe associations between DEHP urinary metabolites and total testosterone, estradiol, LH, FSH, inhibin B, or sex hormone-binding globulin (SHBG); free testosterone was not evaluated (Fong et al. 2015). In another Taiwanese study including 47 PVC workers and 15 controls, decreased sperm motility was associated with increased urinary MEHP, MEHHP, and MEOHP levels; no association was observed for sperm concentration or morphology (Huang et al. 2014a).

Cross-sectional studies evaluating potential associations between serum reproductive hormone and non-occupational DEHP exposure are presented in Table 2-8. Seven of the 15 studies examining serum testosterone levels in men have indicated associations between decreasing total and/or free testosterone levels and increasing urinary MEHP levels (Table 2-8). The association was seen in studies of men recruited from the general population (Chen et al. 2017; Joensen et al. 2012; Woodward et al. 2020) as well as among male partners of sub-fertile couples (Chang et al. 2017a, 2017b; Jurewicz et al. 2013; Meeker et al. 2009b; Wang et al. 2016). Of these studies, only Chang et al. (2017a, 2017b) observed an association between decreased testosterone and other DEHP metabolites (MEHHP, MEOHP, and MECPP). Woodward et al. (2020) reported decreasing total and free testosterone with increasing ΣDEHP metabolites in men ≥60 years old, but not younger men. One study (Chang et al. 2015) reported increased total and free testosterone with increasing serum MEHP metabolites in male partners of sub-fertile couples.

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Occupationally exposed populations				
Fong et al. 2015 Occupational, 82 male PVC production workers (mean age 38 years), Taiwan	TT, E2, SHBG, LH, FSH, or Inhibin B	MEHP	IQR: 11.5–36.0 µg/g Cr	↔
		MEOHP	38.8–111.3	↔
Pan et al. 2006 Occupational, 74 exposed male PVC workers (mean age 33.5 years) and 63 unexposed male construction workers (mean age 34.3 years), China	**FT** E2, LH, or FSH	**MEHP**	Exposed: IQR: 209.6–1,884.4 µg/g Cr Unexposed: 3.7–9.9	↓
		MEHP	See above	↔
General population studies				
Axelsson et al. 2015 Cross-sectional, 314 men (age 17–20 years), Sweden	TT, FT, E2, SHBG, LH or FSH	MEHP	Range: 0.01–19 nmol/mmol Cr	↔
		MEHHP	0.5–340	↔
		MEOHP	0.2–200	↔
		MECPP	0.3–110	↔
Chang et al. 2019a, 2019b Cross-sectional, 207 elderly men (mean age 62.5 years) diagnosed with benign prostatic hyperplasia and prostatic enlargement, Taiwan	**E2**	**MEHP**	IQR: 1.42–5.50 ng/mL	↑
		MEHHP	2.99–13.1	↑
		MEOHP	2.39–8.95	↑
		MECPP	4.69–16.1	↑
	E1	MEHP, MEHHP, or MECPP	See above	↔
		MEOHP	See above	↑
	LH, FSH, SHBG, Inhibin B, TT, or FT	MEHP, MEHHP, MEOHP, or MECPP	See above	↔

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Chen et al. 2017 Cross-sectional, 313 males age 12–30 years (and 473 females), Taiwan	**TT (male adults age ≥22–30 years)**	**MEHP**	Total (male and female, all ages) Mean (SD): 5.05 (12.86) µg/g Cr	↓
		MEHHP	26.70 (2.53)	↔
		MEOHP	16.65 (2.51)	↔
	TT (male adolescents age 12–<22 years)	MEHP, MEHHP, or MEOHP	See above	↔
Joensen et al. 2012	**TT, FT, or FSH**	**MEHP**	IQR: 0.4–18 ng/mL	↓
Cross-sectional, 881 men (age ~18–22 years), Denmark	E2, SHBG, LH, or Inhibin-B	MEHP	See above	↔
Jönsson et al. 2005 Cross-sectional, 234 men (age 18–21 years), Sweden	TT, E2, SHBG, LH, FSH, or Inhibin B	MEHP	IQR: <LOD–5.1 nmol/mmol Cr	↔
Meeker and Ferguson 2014 Cross-sectional, 867 males (age 12–80 years), United States (NHANES)	TT	ΣDEHP	NR	↔
		MEHP	12–20 years: IQR: 0.73–2.79 ng/dl 20–<40 years: 0.97–3.08 40–<60 years: 0.68–1.94 60–80 years: 0.58–2.09	↔
		MEHHP	12–20 years: 4.83–11.9 20–<40 years: 4.85–11.3 40–<60 years: 4.58–11.4 60–80 years: 5.08–11.8	↔
		MEOHP	12–20 years: 3.04–7.41 20–<40 years: 2.77–7.06 40–<60 years: 2.89–5.92 60–80 years: 3.42–7.92	↔

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MECPP	12–20 years: 7.97–21.6 20–<40 years: 6.95–17.7 40–<60 years: 7.65–15.9 60–80 years: 8.45–19.7	↔
Woodward et al. 2020 Cross-sectional, 1,420 adult men (488 age 20–39 years, 457 age 40–59 years, 475 age ≥60 years), United States (NHANES)	**TT, E2, FT**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	All ages: IQR: 0.04–0.13 µmol/L	↔
			20–39 years: 0.04–0.12	↔
			40–59 years: 0.04–0.15	↔
			≥60 years: 0.04–0.13	↓
	SHBG	ΣDEHP	All ages and age groups: see above	↔
Populations recruited from fertility clinics				
Al-Saleh et al. 2019a Cross-sectional, 599 male partners (mean age 37.86 years) of infertile couples, Saudi Arabia	**FSH**	**ΣDEHP**	IQR: 0.161–0.433 µmol/L	↓
		MEHP	IQR: 9.467–22.368 µg/L	↔
		MEHHP	5.889–20.496	↓
		MEOHP	9.875–28.432	↓
		MECPP	17.044–53.328	↓
	Prolactin	**ΣDEHP or MEOHP**	See above	↓
		MEHP, MEHHP, or MECPP	See above	↔
	LH, E2, or TT	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
	WHO-diagnosed infertility in 47.7% of men, based on sperm concentration, motility, and morphology (≤15 million/mL, 32% and 4%, respectively).			

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]		Result
Chang et al. 2015 Case-control, 176 men (age 25–45 years) including infertile men (n=141) and fertile men (n=35), Taiwan	**TT or FT**	ΣDEHP	Fertile Infertile 1 Infertile 2	GM (GSD): 0.11 (0.07) µmol/g Cr 0.12 (0.06) 0.14 (0.15)	↔
		MEHP	Fertile Infertile 1 Infertile 2	GM (GSD): 3.21 (0.30) µg/g Cr 4.11 (0.28) 4.52 (0.33)	↑
		MEHHP	Fertile Infertile 1 Infertile 2	8.30 (0.79) 9.94 (0.70) 10.1 (0.78)	↔
		MEOHP	Fertile Infertile 1 Infertile 2	6.14 (0.72) 5.85 (0.39) 5.66 (0.38)	↔
		MECPP	Fertile Infertile 1 Infertile 2	9.15 (1.01) 11.9 (0.83) 12.4 (0.85)	↔
	SHBG	ΣDEHP, MEHP, MEHHP, or MECPP	See above		↔
		MEOHP	See above		↑
	E2, LH, FSH, Inhibin B, or INSL3	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above		↔

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).

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Chang et al. 2017a, 2017b Cross-sectional, 253 male partners of sub-fertile couples from infertility clinics (124 men with normal semen quality, mean age 33.3 years; 129 men with abnormal semen quality, mean age 35.4 years) and 37 male partners of fertile couples (mean age 32.7 years), Taiwan	**TT**	**MEHP**	All men: IQR: 3.19–7.42 ng/mL	↓
		MEHHP	8.01–18.6	↓
		MEOHP	5.12–12.5	↓
		MECPP	10.1–23.4	↓
	E2	**MEHP, MEHHP, MEOHP, or MECPP**	See above	↑
	SHBG	MEHP	See above	↔
		MEHHP, MEOHP, or MECPP	See above	↑
	INSL3	**MEHP**	See above	↓
		MEHHP, MEOHP, or MECPP	See above	↔
	LH, FSH, or Inhibin B	MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Jurewicz et al. 2013 Cross-sectional, 269 men (mean age 32 years) attending infertility clinic, Poland	**TT**	**MEHP**	Range: 0.5–399.3 µg/g Cr	↓
		MEOHP	1.2–131.0	↔
	E2 or FSH	MEHP or MEOHP	See above	↔

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Mendiola et al. 2012 Cross-sectional, 850 men (425 male partners of pregnant women who conceived without assistance; 425 male partners of infertile couples), mean age 32.2 and 36 years, respectively, United States (California, Massachusetts, Minnesota, Missouri, New York, Iowa)	**FT**	**MEHP**	10^{th}–90^{th} percentile: 0.9–39.2 ng/mL	↓
		MEHHP	5.4–170	↓
		MEOHP	3.2–110	↓
	E2	**MEHP**	See above	↓
		MEHHP or MEOHP	See above	↔
	SHBG	MEHP	See above	↔
		MEHHP or MEOHP	See above	↑
	TT, LH, or FSH	MEHP, MEHHP, or MEOHP	See above	↔
	Among fertile men (Mendiola et al. 2011), a positive association was seen between MEHP and SHBG, but not for other metabolites or hormones. Among infertile men, negative associations were seen between SG-adjusted MEHP and total testosterone and estradiol levels (Meeker et al. 2009b).			
Pan et al. 2015 Cross-sectional,1,066 male partners of infertile couples (mean age 29.1 years), China	**E2 or INSL3**	**MEHP**	IQR: 2.4–8.7 ng/mL	↓
	TT, SHBG, LH, or FSH	MEHP	2.4–8.7	↔

Table 2-8. Summary of Epidemiological Studies of DEHP Exposure and Serum Reproductive Hormones or Leydig Cell Functionality in Adult Men

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Wang et al. 2016 Cross-sectional, 1,040 male partners of couples attending infertility clinic, China	**TT, FT, or E2**	**MEHP**	1st sample: IQR: 2.37–7.35 µg/g Cr 2nd sample: 2.53–8.80	↓
		MEHHP	1st sample: 6.80–15.07 2nd sample: 6.86–16.70	↔
		MEOHP	1st sample: 3.91–8.45 2nd sample: 3.94–9.27	↔
	FSH or LH	MEHP, MEHHP, or MEOHP	See above	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; E1 = estrone (pg/mL); 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; 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; PVC = polyvinyl chloride; SD = standard deviation; 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

Among the remaining seven studies that did not observe any association with serum testosterone (Table 2-8), three studies (Al-Saleh et al. 2019a; 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 estradiol levels in serum were also observed in males in several of these cross-sectional studies, although findings are inconsistent. Reduced serum estradiol was associated with increased urinary MEHP in four studies of male partners of sub-fertile couples (Meeker et al. 2009b; Mendiola et al. 2012; Pan et al. 2015; Wang et al. 2016), while another study observed increased serum estradiol with increasing urinary MEHP, MEHHP, MEOHP, and MECPP in sub-fertile men (Chang et al. 2017a, 2017b). In older men (≥60 years old), Woodward et al. (2020) reported decreased serum estradiol with increased ΣDEHP urinary metabolites in men. In contrast, Chang et al. (2019a) reported increased serum estradiol associated with increased urinary MEHP, MEHHP, MEOHP, and MECPP in older men (mean age 62.5 years) diagnosed with benign prostatic hyperplasia and prostatic enlargement. Increased serum estrone was also associated with increased urinary MEOHP in this study. No associations with urinary DEHP metabolites and serum estradiol were observed in the other cross-sectional studies of the general population (Axelsson et al. 2015; Joensen et al. 2012; Jönsson et al. 2005) or male partners of sub-fertile couples (Al-Saleh et al. 2019a; Chang et al. 2015; Jurewicz et al. 2013).

In cross-sectional studies of male partners of sub-fertile couples, four of five studies reported increased serum SHBG with increased urinary levels of MEHP (Mendiola et al. 2011), MEOHP (Chang et al. 2015, 2017a, 2017b; Mendiola et al. 2012), MEHHP (Chang et al. 2017a, 2017b; Mendiola et al. 2012), and/or MECPP (Chang et al. 2017a, 2017b); no association was observed with MEHP in the fifth study (no other metabolites were evaluated) (Pan et al. 2015). No association between DEHP exposure and serum SHBG was observed in the available general population studies (Chang et al. 2019a, 2019b; Joensen et al. 2012; Jönsson et al. 2005; Woodward et al. 2020).

Decreased serum FSH was associated with increased urinary metabolite levels in one study in male partners of sub-fertile couples (MEHHP, MEOHP, MECPP, or ΣDEHP) (Al-Saleh et al. 2019a) and one general population study (MEHP) (Joensen et al. 2012). This association was not observed in the remaining six studies in sub-fertile couples or three general population studies that examined serum FSH. None of the available studies observed a relationship between DEHP metabolites in urine and LH or inhibin B (Table 2-8).

Three 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) and Chang et al. (2017a, 2017b) observed an inverse association between INSL-3 and urinary MEHP, while Chang et al. (2015) saw no relationship with any DEHP metabolite.

Two cohort studies and 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 2-9. Eleven of fifteen general population and fertility clinic patient studies did not show an association between sperm count and/or concentration and DEHP metabolites. Of the four showing associations, all were studies in males from sub-fertile couples. Two of these showed a negative association between sperm count/concentration and urinary DEHP metabolites (Chang et al. 2017a; Minguez-Alarcon et al. 2018a), while the other two showed a positive association (Al-Saleh et al. 2019a; Bloom et al. 2015a). Minguez-Alarcon et al. (2018a) also reported decreased percent normal sperm morphology with increasing MEHP levels; no association was observed with other urinary DEHP metabolites in this study. The other 12 studies evaluating sperm morphology did not observed an association with urinary DEHP metabolites.

Available studies evaluated sperm motility either as a continuous variable (n=10) or as a dichotomous variable (based on World Health Organization [WHO] reference values; n=5). When percent motile sperm was evaluated as a continuous variable, negative relationships were reported in five studies (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Chang et al. 2017a; Jurewicz et al. 2013; Mínguez-Alarcón et al. 2018a, 2018b), with another study reporting a positive relationship (Tian et al. 2019), and four other studies reporting no association (Al-Saleh et al. 2019a; Joensen et al. 2012; Jönsson et al. 2005; Pan et al. 2015). Studies that dichotomized percent motile sperm reported no association between risk of low motility sperm and DEHP urinary metabolites (Han et al. 2014b; Hauser et al. 2006; Herr et al. 2009; Liu et al. 2012; Wirth et al. 2008).

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Sperm Parameters

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Occupationally exposed populations				
Huang et al. 2014a Occupational, 47 male PVC workers (36 with "high" exposure, mean age 36.3years; 11 with "low" exposure, mean age 35.5 years) and 15 unexposed men (mean age 25.3 years), Taiwan	**Sperm motility**	**MEHP**	High IQR: 11.5–31.9 µg/g Cr	↓
		MEHHP	47.1–111.5	↓
		MEOHP	41.0–99.4	↓
	Sperm concentration or morphology	MEHP, MEHHP, or MEOHP	See above	↔
General population studies				
Axelsson et al. 2015 Cross-sectional, 314 men (age 17–20 years), Sweden	**Sperm motility**	MEHP	Range: 0.01–19 nmol/mmol Cr	↔
		MEHHP	0.5–340	↓
		MEOHP	0.2–200	↓
		MECPP	0.3–110	↓
	Sperm count, concentration, or morphology	MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Han et al. 2014b Cross-sectional, 232 adult men (age 20–40 years), China	Sperm count, concentration, morphology, or motility[b]	MEHP	5^{th}–95^{th} percentile: <LOD–31.4 µg/g Cr	↔
Joensen et al. 2012 Cross-sectional, 881 men (age ~18–22 years), Denmark	Sperm count, concentration, morphology, or motility	MEHP	IQR: 0.4–18 ng/mL	↔
Jönsson et al. 2005 Cross-sectional, 234 men (age 18–21 years), Sweden	Sperm count, concentration, or motility	MEHP	IQR: <LOD–12 nmol/mmol Cr	↔

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Sperm Parameters

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Populations recruited from fertility clinics				
Al-Saleh et al. 2019a Cross-sectional, 599 male partners (mean age 37.86 years) of infertile couples, Saudi Arabia	**Sperm concentration**	**ΣDEHP**	IQR: 0.161–0.433 µmol/L	↑
		MEHP	IQR: 9.467–22.368 µg/L	↔
		MEHHP	5.889–20.496	↑
		MEOHP	9.875–28.432	↑
		MECPP	17.044–53.328	↑
	Sperm motility or morphology	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
	WHO-diagnosed infertility in 47.7% of men, based on sperm concentration, motility, and morphology (≤15 million/mL, 32%, and 4% respectively).			
Bloom et al. 2015a, 2015b Cohort, 473 male partners of infertile couples (mean age 31.8 years), United States (Michigan, Texas)	**Sperm motility**	MEHP	IQR: 0[c]–4.87 ng/mL	↔
		MEHHP	5.56–37.94	↔
		MEOHP	3.06–17.9	↓
		MECPP	8.60–46.4	↓
	Sperm count	MEHP, MEOHP, MECPP	See above	↔
		MEHHP	See above	↑
	Sperm morphology	MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Chang et al. 2017a, 2017b Cross-sectional, 253 male partners of sub-fertile couples from infertility clinics (124 men with normal semen quality, mean age 33.3 years; 129 men with abnormal semen quality, mean age 35.4 years) and 37 male partners of fertile couples (mean age 32.7 years), Taiwan	**Sperm concentration or motility**	**MEHP**	All men: IQR: 3.19–7.42 ng/mL	↓
		MEHHP	8.01–18.6	↔
		MEOHP	5.12–12.5	↔
		MECPP	10.1–23.4	↔
	Sperm morphology	MEHP, MEHHP, MEOHP, or MECPP	See above	↔

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Sperm Parameters

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Hauser et al. 2006 Cross-sectional, 463 male partners of sub-fertile couples (mean age 36.3 years), United States (Massachusetts)	Sperm concentration, morphology, or motility[b]	MEHP	IQR: 3.1–20.9 ng/mL (SG-adj)	↔
		MEHHP	23.4–113	↔
		MEOHP	15.8–73.0	↔
Herr et al. 2009 Cross-sectional, 349 male partners of sub-fertile couples (mean age 34.2 years), Germany	Sperm concentration, morphology, or motility[b]	ΣDEHP	IQR: 23.20–74.70 ng/mL	↔
Jurewicz et al. 2013 Cross-sectional, 269 men (mean age 32 years) attending infertility clinic, Poland	**Sperm motility**	**MEHP**	Range: 0.5–399.3 µg/g Cr	↓
		MEOHP	1.2–131.0	↓
	Sperm morphology or concentration	MEHP or MEOHP	See above	↔
Liu et al. 2012 Cross-sectional, 97 male partners of sub-fertile couples (mean age 31.5 years), China	Sperm motility or concentration[b]	MEHP	33rd–66th percentile: 0.35–1.93 µg/g Cr	↔
		MEOHP	1.89–3.05	↔
Mínguez-Alarcón et al. 2018a, 2018b Cohort, 936 male partners (median age 35.7 years) of couples seeking infertility treatment, United States (Massachusetts)	**Sperm concentration**	ΣDEHP	NR	↔
		MEHP	IQR: 1.12–7.00 ng/mL	↓
		MEHHP	6.44–32.9	↓
		MEOHP	3.82–20.1	↓
		MECPP	9.00–39.1	↔
	Sperm count	**ΣDEHP, MEHP, MEHHP, MEOHP, MECPP**	See above	↓
	Sperm motility or normal morphology	ΣDEHP, MEHHP, MEOHP, or MECPP	See above	↔
		MEHP	See above	↓

Table 2-9. Summary of Epidemiological Studies of DEHP Exposure and Sperm Parameters

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Pan et al. 2015 Cross-sectional,1,066 male partners of infertile couples (mean age 29.1 years), China	Sperm count, concentration, morphology or motility	MEHP	IQR: 2.4–8.7 ng/mL	↔
Tian et al. 2019 Cross-sectional, 86 men (mean age 31.6 years) undergoing fertility assessment, China	**Sperm motility**	**ΣDEHP**	IQR: 2.06–6.35 µg/g Cr	↑
		MEHP	0.25–2.77	↔
		MEOHP	1.48–3.76	↔
	Sperm count, concentration, or morphology	ΣDEHP, MEHP, or MEOHP	See above	↔
Wirth et al. 2008 Cross-sectional, 45 male partners of sub-fertile couples (mean age 34.8 years), United States (Michigan)	Sperm concentration, morphology or motility[b]	ΣDEHP	NR	↔
		MEHP	IQR: 4.6–22.1 ng/mL	NR
		MEHHP	32.7–137.1	NR
		MEOHP	20.1–79.3	NR

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.
[b]Analysis of sperm parameters was dichotomized based on WHO reference values for sperm concentrations (<20 million/mL), motility (<50% motile sperm), and/or morphology (<4% normal sperm)
[c]Value reported in study was less than zero, reflecting correction for analytical blank; adjusted to 0 for reporting in this table.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; IQR = interquartile range; 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; NR = not reported; PVC = polyvinyl chloride; SG-adj = specific gravity-adjusted; WHO = World Health Organization

The potential for paternal DEHP exposure to affect fertility or pregnancy outcome has not been well-studied. In prospective cohort studies, no associations were observed between paternal urinary DEHP metabolite levels and time-to-pregnancy (Buck Louis et al. 2014), *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) fertility rate (Al-Saleh et al. 2019b, 2019c), or preterm birth (Zhang et al. 2020a, 2020d). However, the probability of clinical pregnancy and live birth after IVF/ICSI was negatively associated with urinary paternal MEOHP and MECPP levels (Al-Saleh et al. 2019b, 2019c). A case-control study of 150 fertile and 139 infertile men showed that odds of infertility *decreased* with increasing urinary MEHP levels; no associations were observed for other DEHP metabolites (Liu et al. 2017). However, there is no information (qualitative or quantitative) on exposures prior to diagnosis; therefore, this study has limited usefulness for evaluating potential effects of DEHP exposure on male fertility.

One prospective cohort study of 68 sub-fertile men reported an association between increased preconception paternal urinary DEHP metabolite levels and decreased placental weight (Mustieles et al. 2019). While decreased placental weight may lead to intrauterine growth restriction (IUGR), low birth weight, or perinatal mortality, the findings are considered preliminary due to small sample size and inclusion of only sub-fertile men. No other studies of this endpoint were identified in the available literature.

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).

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. In a 1-generation study

in mice, male and female exposure to doses up to 0.34 mg/kg/day for 2 weeks prior to mating through lactation did not result in any changes in mating, fertility, pregnancy outcomes, testes or epididymis weights, or sperm counts (Cha et al. 2018).

One study reported altered mating behavior in male C57Bl/6J mice 2 weeks after a 4-week exposure to DEHP at very low doses of ≥0.005 mg/kg/day, including increased latency to first intromission and ejaculation and reduced sexual interest in an unexposed female partner (Dombret et al. 2017). However, available data do not provide clear support for effects on male reproduction at these low doses. Specifically, mating indices were not affected in CD-1 mice exposed to doses up to 0.34 mg/kg/day for 2 weeks before mating and during mating (Cha et al. 2018). In addition, no effect on fertility was seen at doses up to 13 mg/kg/day in a continuous mating trial in Crl:CD-1 mice (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984) or up to 180.77 mg/kg/day in a 2-generation study of CD-1 mice (Tanaka 2002). In rats, no effects on fertility were seen at doses up to 57 mg/kg/day in a 3-generation continuous mating study (Blystone et al. 2010; NTP 2005) or at doses up to 380 mg/kg/day in 2-generation studies (Schilling et al. 1999, 2001). Additionally, male mating behavior in rats was not affected by developmental exposure to DEHP at doses up to 100 mg/kg/day from GD 1 to PND 21 (Dalsenter et al. 2006) or 405 mg/kg/day from GD 6 to PND 21 (Andrade et al. 2006a); see Section 2.17 for more details. Based on the lack of effects on reproduction at doses much higher than those used by Dombret et al. (2017), the effects in this study are considered to be of uncertain toxicological significance; therefore, the study is not included in the LSE table.

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 a 9-week study, the percentage of sperm with bent tails was increased at ≥0.1 mg/kg/day and the percentage of normal sperm was decreased at 1 mg/kg/day (Hsu et al. 2016). No changes in sperm count or motility or reproductive organ weights were observed; reproductive organ histology was not assessed. At 1 mg/kg/day, there was a decreased normal sperm percentage, sperm DNA fragmentation, and increased hydrogen peroxide production from sperm. DNA fragmentation was associated with increased hydrogen peroxide production (Hsu et al. 2016). In other 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 in intermediate-duration studies, including testicular atrophy and degeneration, degeneration of the Leydig cells, decreased spermatogenesis/hypospermia, interstitial edema, and decreased testicular weights, were observed at ≥300 mg/kg/day in F344 rats (CMA 1986; Exxon Chemical Americas 1990; Myers 1992b; NTP 1982), Wistar rats (Shaffer et al. 1945), and Sprague-Dawley rats (Wang et al. 2020). However, three intermediate-duration studies reported no histopathological changes in the testes at doses up to 200 mg/kg/day for 28 days in Long-Evans rats (Akingbemi et al. 2001), 930 mg/kg/day for 3 weeks in F344 rats (Astill et al. 1986), or 3,000 mg/kg/day for 30 days in Wistar rats (Wang et al. 2020). 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, although the effective dose appears to differ among strains. The most sensitive strain is A/J mice, with Sertoli cell vacuolation and germ cell sloughing in seminiferous tubules 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). In ICR mice, decreased testes weights were observed following a 3-week exposure to 180 mg/kg/day (Feng et al. 2020); however, increased testes weights were observed following a 4-week exposure to 400 mg/kg/day (Feng et al. 2020; Xu et al. 2019).

No histopathological or spermatogenesis changes were observed at doses up to 400 mg/kg/day for 4 weeks (Xu et al. 2019). In BALB/c mice, slight localized degeneration of germ cells was observed after a 30-day exposure to ≥1,000 mg/kg/day (Wang et al. 2020). However, in B6C3F1 mice, testicular effects (testicular atrophy, decreases/absent spermatogenesis, and decreased testes/epididymides weights) were observed after intermediate-duration exposure to doses ≥2,579 mg/kg/day, but not ≤2,500 mg/kg/day (Myers 1992a; NTP 1982). Similarly, slight seminiferous tubule atrophy was observed in C57BL/6J mice after a 30-day exposure to 3,000 mg/kg/day, but not ≤1,000 mg/kg/day (Wang et al. 2020). 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 rodents 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). In 30-day drinking water studies, significant decreases in serum testosterone were observed in Sprague-Dawley rats at 3,000 mg/kg/day (60% decrease) and BALB/c mice at ≥1,000 mg/kg/day (33–39% decrease) (Wang et al. 2020). No exposure-related changes were observed in similarly exposed Wistar rats or C57BL/6J mice at doses up to 3,000 mg/kg/day. In ICR mice, no exposure-related changes were observed in serum testosterone following a 28-day exposure to doses up to 400 mg/kg/day (Xu et al. 2019).

It is not clear whether DEHP has antiandrogenic potential when using the Hershberger assay. In the Hershberger assay, male rats were castrated and subsequently supplemented with testosterone so control and exposed animals had equivalent testosterone levels. In Sprague-Dawley rats exposed to DEHP 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. There were no exposure-related changes in serum testosterone. Using the same rat strain, duration of exposure, and number of rats per group, Kim et al. (2018b) did not observe any dose-related changes in ventral prostate, seminal vesicle, coagulating glands, LABC muscle, paired Cowper's glands, or glans penis following exposure to doses up to 400 mg/kg/day with or without testosterone supplementation; reproductive hormones were not assessed. However, using Wistar rats, Stroheker et al. (2005) observed decreased prostate weights at ≥200 mg/kg/day, decreased seminal vesicle weights at ≥400 mg/kg/day, and significantly decreased LABC muscle weights at ≥100 mg/kg/day; but had no findings at ≤20 mg/kg/day. As expected, no exposure-related changes in serum testosterone were observed. Reproductive organ histology was not assessed in any of the Hershberger assays.

In intact (not castrated) rats, no changes in prostate weight were at doses up to 150 mg/kg/day for 13 weeks starting on PND 6 (Kim et al. 2018c). Reproductive hormones and organ histology were not assessed by Kim et al. (2018c). Another study with intact mice reported a significant 16% increase in

absolute prostate weight (without a change in body weight) after a 28-day exposure to 400 mg/kg/day (Xu et al. 2019). No histopathological changes were observed for the prostate in this study (Xu et al. 2019).

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 (Hoyer et al. 2018; Shen et al. 2018). In a study in PVC workers, increased urinary DEHP metabolite levels were associated with both decreased sperm motility and sperm ROS generation (Huang et al. 2014a).

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). *In vitro* studies using human sperm suggest that mechanisms of altered sperm function induced by DEHP and MEHP may include DNA fragmentation or altered calcium signaling (Sumner et al. 2019; Sun et al. 2020).

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 Louis et al. 2013; Grindler et al. 2015; Huang et al. 2010, 2014a; Itoh et al. 2009; Kim et al. 2015; Lee et al. 2020; Pollack et al. 2015; Sun et al. 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). Studies that met inclusion criteria are presented in Table 2-10 and discussed below.

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). One of these studies (Jukic et al. 2016) evaluated the menstrual cycle, observing that most DEHP metabolites were not associated with altered luteal or follicular phase length. Out of three prospective cohort studies of females seeking IVF or ICSI treatment (Al-Saleh et al. 2019b, 2019c, 2019d; Deng et al. 2020; Machtinger et al. 2018), one reported decreased fertilization rate with increased maternal DEHP urinary metabolites (Machtinger et al. 2018). Two cohort studies in IVF

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Women recruited when trying to get pregnant or from infertility clinics				
Al-Saleh et al. 2019b, 2019c, 2019d Cohort, 599 female partners (mean age 32.8 years) of couples seeking IVF/ICSI treatment, Saudi Arabia	Fertilization rate	ΣDEHP	IQR: 0.137–0.381 µmol/L	↔
		MEHP	IQR: 8.73–21.7 µg/L	↔
		MEHHP	4.68–16.4	↔
		MEOHP	9.37–31	↔
		MECPP	14.2–44.9	↔
Buck Louis et al. 2014 Cohort, 454 women (age 18–44 years), recruited when attempting to become pregnant, United States (Michigan, Texas)	Fecundability	MEHP	Pregnant: IQR: 4.56 (3.40–6.11) ng/mL Not pregnant: 5.60 (3.81–8.24)	↔
		MEHHP	Pregnant: 15.24 (13.01–17.86) Not pregnant: 14.46 (11.52–18.14)	↔
		MEOHP	Pregnant: 8.65 (7.40–10.10) Not pregnant: 7.55 (5.86–9.74)	↔
		MECPP	Pregnant: 21.18 (18.25–24.58) Not pregnant: 21.21 (16.94–26.55)	↔
Deng et al. 2020 Cohort, 663 women receiving IVF/ICSI treatment (mean age 31.3 years), China	Fertilization, number of retrieved and mature oocytes, good quality embryos (day 3), or total and good quality blastocyte formation	MEHP	IQR: 3.85–16.77 µg/g Cr	↔
		MEHHP	7.47–18.87	↔
		MEOHP	4.94–13.59	↔
Hauser et al. 2016 Cohort, 256 women (age 21–43 years) undergoing IVF, United States (Massachusetts)	**Number of total and mature oocytes**	**ΣDEHP**	IQR: 0.10–0.42 µmol/L (SG-adj)	↓
		MEHP	IQR: 1.37–6.87 µg/L (SG-adj)	↓
		MEHHP	7.75–35.0	↓
		MEOHP	5.48–25.4	↓
		MECPP	14.6–57.2	↓

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Jukic et al. 2016 Cohort, 221 women (median age 29 years), recruited when attempting to become pregnant, United States (North Carolina)	**Luteal phase length**	ΣDEHP	NR	↔
		MEHP	IQR: 3.8–11.2 ng/mL	↔
		MEHHP	31.8– 80.8	↔
		MEOHP	19.5–48.9	↔
		MECPP	42.2–100.0	↑
	Fecundability or Follicular phase length	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Machtinger et al. 2018 Cohort, 136 women (mean age 30.9 years) receiving IVF treatment, Israel	**Number of total and mature oocytes or top-quality embryos**	**ΣDEHP**	IQR: 0.11–0.27 µmol/L (SG-adj)	↓
		MEHP	IQR: 2.2–7.6 µg/L (SG-adj)	↔
		MEHHP	8.6–22.2	↓
		MEOHP	6.4–16.1	↓
		MECPP	13.3–33.6	↓
	Number of fertilized oocytes	**ΣDEHP, MEHHP, or MEOHP**	See above	↓
		MEHP, MECPP	See above	↔
	Probability of implantation	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Messerlian et al. 2016a Cohort, 215 women (age 20–45 years) seeking infertility investigation, United States (Massachusetts)	**Antral follicle count**	**ΣDEHP**	IQR: 0.10–0.46 µmol/L (SG-adj)	↓
		MEHP	IQR: 1.6–6.7 µg/L (SG-adj)	↓
		MEHHP	8.2–41.1	↔
		MEOHP	5.1–25.0	↓
		MECPP	13.5–59.1	↓

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Thomsen et al. 2017 Cohort, 229 women (age 20–35 years), recruited when attempting to become pregnant, Denmark	Fecundability	MEHP	Median (range): 14.5 (0–348) ng/mL	↔
Pregnant women				
Johns et al. 2015 Cross-sectional, 106 pregnant women (age 18–40 years), Puerto Rico	Estradiol, SHBG, or progesterone	ΣDEHP	NR	↔
		MEHP	GWs 16–20: IQR: 1.61–6.36 ng/mL (SG-adj) GWs 24–28: 1.69–6.73	NR
		MEHHP	GWs 16–20: 6.14–19.9 GWs 24–28: 7.28–16.9	NR
		MEOHP	GWs 16–20: 5.57–16.5 GWs 24–28: 6.22–14.8	NR
		MECPP	GWs 16–20: 12.7–31.4 GWs 24–28: 13.4–29.3	NR
Sathyanarayana et al. 2017 Cross-sectional, 591 pregnant women (age 20–40 years), United States (California, Minnesota, New York, Washington)	**Estrone or estradiol**	ΣDEHP	IQR: 15.73–39.70 ng/mL (SG-adj)	↔
		MEHP	1.38–4.35	↑
		MEHHP	4.35–12.66	↔
		MEOHP	3.22–8.46	↑
		MECPP	5.89–15.71	↔
	Total testosterone	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
	Free testosterone	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔
		MECPP	See above	↓

Table 2-10. Summary of Epidemiological Studies of DEHP Exposure and Female Reproductive Effects

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Sathyanarayana et al. 2014 Cross-sectional, 180 pregnant women (age 20–40 years; 94 with male fetuses, 86 with female fetuses), United States (California, Minnesota, Missouri)	**Total or free testosterone**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	IQR: 5.53–21.05 µmol/L	M fetus: ↔ **F fetus: ↓**
	Estradiol	ΣDEHP	See above	M, F fetus: ↔
Nonpregnant women (general population)				
Meeker and Ferguson 2014 Cross-sectional, 697 women (age 20–80 years), United States (NHANES)	Testosterone	ΣDEHP	NR	↔
		MEHP	20–<40 years: IQR:1.07–3.57 ng/mL (Cr-adj) 40–<60 years: 0.90–2.90 60–80 years: 0.70–1.94	↔
		MEHHP	20–<40 years: 5.44–14.6 40–<60 years: 5.44–14.6 60–80 years: 5.27–13.7	↔
		MEOHP	20–<40 years: 3.62–10.0 40–<60 years: 3.73–10.0 60–80 years: 3.41–8.38	↔
		MECPP	20–<40 years: 9.06–21.7 40–<60 years: 10.4–23.9 60–80 years: 9.98–23.9	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; Cr = creatinine; Cr-adj = creatinine-adjusted; DEHP = di(2-ethylhexyl)phthalate; GW = gestation week; ICSI = intracytoplasmic sperm injection; IQR = interquartile range; IVF = *in vitro* fertilization; 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; SHBG = sex hormone binding globulin; SG-adj = specific gravity-adjusted

patients also reported decreased number of total and mature oocyte and/or decreased top-quality embryos with increased maternal DEHP urinary metabolites (Hauser et al. 2016; Machtinger et al. 2018). Another cohort study of women 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 2-10). 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 SHBG 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 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. Several cohort and case-control studies have evaluated potential associations between pregnancy outcomes (e.g., gestational age, pre- or post-term birth, pregnancy loss; Table 2-11).

Preterm birth as a categorical measure (<37 weeks of gestation) was evaluated in 10 epidemiological studies. Six of these studies reported increased odds of preterm birth associated with increased urinary DEHP metabolites, including cohort studies (Bloom et al. 2019a; Ferguson et al. 2019a, 2019b; Gao et al. 2019; Zhang et al. 2020a, 2020d) and case-control studies (Ferguson et al. 2014b, 2014c; Meeker et al. 2009a). In some of these studies, increased odds were only observed in a subset of study subjects. For example, Bloom et al. (2019a) found an association between preterm birth and urinary MEHP only in

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Adibi et al. 2009 Cohort, 283 pregnant women (mean age 30.2 years), United States (California, Iowa, Minnesota, Mississippi)	**Preterm birth (<37 weeks)**	**MEHP**	IQR: 1.1–8.2 ng/mL	↓
		MEHHP	5.6–25.5	↓
		MEOHP	5.1–24.6	↓
	Post-term birth (>41 weeks) or Gestational age	**MEHP, MEHHP, MEOHP**	See above	↑
Al-Saleh et al. 2019d Cohort, 599 women seeking IVF/ICSI treatment (mean age 32.8 years), Saudi Arabia	**Failed biochemical pregnancy (early pregnancy loss), failed clinical pregnancy or failed live birth**	ΣDEHP	IQR: 0.137–0.381 µmol/L	↔
		MEHP	IQR: 8.73–21.7 µg/L	↑
		MEHHP	4.68–16.4	↔
		MEOHP	9.37–31	↔
		MECPP	14.2–44.9	↔
		Al-Saleh et al. (2019c, 2019d) did not report increased risk of biochemical pregnancy and failed live birth with increased urinary MEHP in this cohort; however, models were not adjusted for male partner urinary phthalate levels.		
Bloom et al. 2019a, 2019b Cohort, 310 mother-infant pairs (152 African American and 158 White mothers; mean age 27.6 years), urinary metabolites measured at 18–22 weeks (1st visit) and 24–32 weeks (2nd visit); United States (South Carolina)	**Preterm birth**	ΣDEHP	All women (1st visit): IQR: 33.5–92.0 nmol/L (SG-adj)	↔
			All women (2nd visit): 37.8–81.7	↔
			African American (1st visit): 21.5–69.4	↔
			White (1st visit): 22.1–52.1	↔
		MEHP	All women (1st visit): IQR: 1.5–5.3 ng/mL (SG-adj)	↔
			All women (2nd visit): 1.4–4.5	↔
			African American (1st visit): 1.0–4.1	↔
			White (1st visit): 0.8–2.6	↑
		MEHHP	All women (1st visit): 3.5–9.1	↔
			All women (2nd visit): 3.5–8.1	↔
			African American (1st visit): 2.5–7.9	↔
			White (1st visit): 2.8–6.1	↔

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
		MEOHP	All women (1st visit): 4.1–12.2	↔
			All women (2nd visit): 4.7–10.9	↔
			African American (1st visit): 2.1–5.8	↔
			White (1st visit): 2.1–5.0	↔
		IQRs were estimated from graphically presented data using GrabIt! software.		
Casas et al. 2016 Cohort, 657 pregnant women (age ≥16 years), Spain	Gestational age	ΣDEHP	Range: 26.5–1,670 µg/g Cr	↔
Deng et al. 2020 Cohort, 663 women receiving IVF/ICSI treatment (mean age 31.3 years), China	Rate of clinical pregnancy, live birth, or early miscarriage	MEHP	IQR: 3.85–16.77 µg/g Cr	↔
		MEHHP	7.47–18.87	↔
		MEOHP	4.94–13.59	↔
Ferguson et al. 2014b Case-control,130 preterm births (<37 weeks; median age 32.8 years) and 352 random controls (≥37 weeks; median age 32.7 years), United States (Massachusetts)	**Preterm birth**	**ΣDEHP**	IQR: 20.2–63.2 µmol/mL (SG-adj)	↑
		MEHP	5.51–18.1	↑
		MEHHP	17.2–55.3	↔
		MEOHP	9.33–29.7	↔
		MECPP	20.6–73.8	↑
	Spontaneous preterm birth	**ΣDEHP, MEHP, MEOHP, or MECPP**	See above	↑
		MEHHP	See above	↔
		Using the same study population, Ferguson et al. (2014c) evaluated associations of DEHP metabolites at four timepoints during pregnancy with preterm birth. Positive associations were observed between spontaneous preterm birth and MECPP and ΣDEHP at visit 3 (22.9–29.3 weeks of gestation).		

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Ferguson et al. 2019c Cohort, 1,090 pregnant women examined at median GWs 17.6 (visit 1), 23.4 (visit 2), and 27.6 (visit 3) (age ≥18–<40 years), Puerto Rico	Gestational age, Preterm birth, or Spontaneous preterm birth	ΣDEHP	NR	↔
		MEHP	GM (visits 1–3): 2.30 ng/mL (SG-adj)	NR
		MEHHP	7.31	NR
		MEOHP	6.38	NR
		MECPP	13.3	NR
Ferguson et al. 2019a, 2019b Cohort, 783 pregnant women (age ≥18 years), including 281 women with at least 1 stressful life event (SLE) during pregnancy and 429 with no SLE during pregnancy, United States (California, New York, Minnesota, Washington)	**Preterm birth or Spontaneous preterm birth (all women)**	**ΣDEHP**	Pregnancy average: NR	
			1st trimester: IQR: 0.05–0.14 nmol/L (SG-adj)	↔
			2nd trimester: 0.05–0.14	↔
			3rd trimester: 0.06–0.14	↑
	Preterm birth (women with SLE)	**ΣDEHP**	3rd trimester: 0.05–0.14	↑
	Preterm birth (women without SLE)	ΣDEHP	3rd trimester: 0.06–0.14	↔
	SLE included job loss, serious illness, family death, relationship difficulties with spouse/partner, and legal or financial problems.			
Gao et al. 2017 Cohort, 3,103 mother-infant pairs (mean age 26.4 years), China	Gestational age	ΣDEHP	NR	↔
		MEHP	25th–95th percentile: 1.34–13.86 µg/g Cr	NR
		MEHHP	3.01–20.19	NR
		MEOHP	4.32–23.05	NR

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Gao et al. 2019 Cohort, 3,266 pregnant women, 19 very preterm (<33 weeks), 115 late preterm (34–36 weeks), 791 early-term (37–38 weeks), 1,986 full-term (39–40 weeks), 344 late-term (41 weeks), and 11 post-term (>42 weeks) births (mean age 26.61 years), China	**Preterm birth (overall <37 weeks) or post-term birth**	ΣDEHP	NR	↔
		MEHP	IQR: 3.45–9.61 µg/g Cr	↑
		MEHHP	5.62–14.16	↔
		MEOHP	7.15–15.42	↔
	Gestational age, Very preterm birth, late preterm birth, early-term birth, or late-term birth	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔
Hu et al. 2020 Cohort, 1,857 pregnant women (age ≥19 years), Canada	Preterm birth (<37 weeks), spontaneous preterm birth, or gestational age	ΣDEHP	Maternal (1st trimester): IQR: 0.04–0.11 µmol/L (SG-adj)	↔
		MEHP	IQR: 1.5–4.1 µg/L (SG-adj)	↔
		MEHHP	6.4–16.3	↔
		MEOHP	4.6–11.1	↔
Jukic et al. 2016 Cohort, 221 healthy women (median age 26 years), United States (North Carolina)	**Early pregnancy loss**	**ΣDEHP**	NR	↓
		MEHP	IQR: 3.8–11.2 ng/mL	↔
		MEHHP	31.8–80.8	↔
		MEOHP	19.5–48.9	↓
		MECPP	42.2–100.0	↔
Machtinger et al. 2018 Cohort, 136 women (mean age 30.9 years) receiving IVF treatment, Israel	Clinical pregnancy or Live birth	ΣDEHP	IQR: 0.11–0.27 µmol/L (SG-adj)	↔
		MEHP	IQR: 2.2–7.6 µg/L (SG-adj)	↔
		MEHHP	8.6–22.2	↔
		MEOHP	6.4–16.1	↔
		MECPP	13.3–33.6	↔
	Preterm birth	**ΣDEHP**	Controls: IQR: 0.16–0.55 µg/g Cr Cases: 0.28–0.45	↑
		MEHP	Controls: 1.7–7.4 Cases: 3.3–7.4	↔

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Meeker et al. 2009a Case-control, 30 preterm births and 30 controls (median age 27 years), Mexico		MEHHP	Controls: 11.4–52.1 Cases: 24.1–41.5	↔
		MEOHP	Controls: 9.5–42.1 Cases: 20.6–29.2	↔
		MECPP	Controls: 27.3–98.6 Cases: 52.7–77.4	↔
Messerlian et al. 2016b Cohort, 256 women (with 303 conceived pregnancies) undergoing medically assisted reproduction (mean age 34.9 years), United States (Massachusetts)	**Early pregnancy loss**	ΣDEHP	IQR: 0.10–0.40 µmol/L	↔
		MEHP	IQR: 1.5–6.4 ng/mL	↔
		MEHHP	7.8–35.4	↔
		MEOHP	5.5–24.4	↑
		MECPP	14.3–57.2	↔
	Pregnancy loss (total)	ΣDEHP, MEHP, or MECPP	See above	↔
		MEHHP or MEOHP	See above	↑
Mu et al. 2015a Case-control, 132 cases of spontaneous abortion and 172 controls (age 20–45 years), China	Pregnancy loss (clinical)	MEHP	Cases: 5^{th}–95^{th} percentiles: 1.53–103 µg/g Cr Controls: 1.27–20.8	↔
Shoaff et al. 2016 Cohort, 368 mother-infant pairs (age ≥18 years), United States (Ohio)	Preterm birth or gestational age	ΣDEHP	16 weeks: IQR: 0.14–0.72 nmol/mL 26 weeks: 0.10–0.52 nmol/mL	↔
Su et al. 2014 Cohort,130 mother-infant pairs (maternal age NR), Taiwan	Gestational age	ΣDEHP	95% CI: 42.28–60.83 µg/g Cr	↔
		MEHP	14.56–20.19	↔
		MEHHP	5.49–10.53	↔
		MEOHP	10.05–17.58	↔

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Toft et al. 2012 Cohort, 128 pregnant women including 48 with pregnancy loss and 80 with a liveborn child (age 20–35 years), Denmark	**Early pregnancy loss**	**MEHP**	Pregnancy loss: range: <LOD–84 µg/L Liveborn child: <LOD–64	↑
		MEHHP	Pregnancy loss: 9.5–207.1 Liveborn child: 3.6–215.3	↔
		MEOHP	Pregnancy loss: 5.7–245.9 Liveborn child: 2.7–222.2	↔
	Pregnancy loss (clinical)	MEHP, MEHHP, or MEOHP	See above	↔
Whyatt et al. 2009 Cohort, 311 mother-infant pairs (mean age 25.5 years), United States (New York)	**Gestational age**	**ΣDEHP**	NR	↓
		MEHP	IQR: 1.8–12.8 ng/mL	↓
		MEHHP	10.3–44.4	↓
		MEOHP	8.9–35.1	↓
		MECPP	18.7–76.2	↓
Wolff et al. 2008 Cohort, 404 mother-infant pairs (mean age 24 years), United States (New York)	**Gestational age**	ΣDEHP	IQR: 0.13–0.5 µmol/L	↔
		MEHP	IQR: 2.9–14 ng/mL	↑
		MEHHP	9.5–39	↔
		MEOHP	8.3–36	↔
		MECPP	16–70	↔

Table 2-11. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Pregnancy Outcomes

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Zhang et al. 2020a, 2020d Cohort, 419 females seeking fertility treatment (mean age 34.7 years), metabolites determined in preconception urine samples, United States (Massachusetts)	**Preterm birth (<37 weeks)**	**ΣDEHP**	IQR: 22.1–79.2 µmol/L (SG-adj)	↑
		MEHP	IQR: 1.2–4.0 ng/mL (SG-adj)	↑
		MEHHP	5.5–21.8	↑
		MEOHP	3.6–14.2	↑
		MECPP	10.1–35.4	↑

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; GW = gestation week; ICSI = intracytoplasmic sperm injection; IQR = interquartile range; IVF = *in vitro* fertilization; 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; NR = not reported; SG-adj = specific gravity adjusted

white women, not African American women. Additionally, Ferguson et al. (2019a, 2019b) found an interaction between preterm birth and the sum of third trimester urinary DEHP metabolites only in women with a stressful life event (e.g., job loss, serious illness, family death, relationship issues, or legal or financial problems). Other cohort studies observed either no association between exposure and preterm birth (Ferguson et al. 2019c; Hu et al. 2020; Shoaff et al. 2016) or decreased odds of preterm birth with increased exposure (Adibi et al. 2009). Two cohort studies reported increased odds of post-term (>41 weeks) birth with increased maternal urinary DEHP metabolite levels (Adibi et al. 2009; Gao et al. 2019).

In studies of gestational age as a continuous variable, no clear relationship with urinary DEHP metabolite levels was seen. Of the 10 studies that evaluated gestational age, two reported increased gestational age associated with increased urinary DEHP metabolite levels (Adibi et al. 2009; Wolff et al. 2008), one reported an association between decreasing gestational age and increasing metabolite levels (Whyatt et al. 2009), and the remaining studies reported no association (Casas et al. 2016; Ferguson et al. 2019c; Gao et al. 2017, 2019; Hu et al. 2020; Shoaff et al. 2016; Su et al. 2014). 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).

Four studies 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. 2014b, 2019a, 2019b, 2019c; Hu et al. 2020). Two cohorts observed an association between spontaneous preterm birth and the sum of DEHP metabolites in urine (Ferguson et al. 2014b, 2019a, 2019b). For the Ferguson et al. (2019a, 2019b) cohort, this finding was restricted to third trimester urine levels only; however, in the study by Ferguson et al. (2014b), 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. (2014b) 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 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, and/or failed live birth was evaluated in four cohort studies of pregnant women (Jukic et al. 2016; Machtinger et al. 2018; Messerlian et al. 2016b; Toft et al. 2012), two cohort studies of women receiving IVF/ICSI (Al-Saleh et al. 2019d; Deng et al. 2020), and one case-control study that measured exposure using urinary metabolites of DEHP (Mu et al. 2015a). When evaluating early (or biochemical) pregnancy loss, three studies reported increased risk of early pregnancy loss with an increase in urinary levels of one or more DEHP metabolites (Al-Saleh et al. 2019d; Messerlian et al. 2016b; Toft et al. 2012), one study observed decreased odds of early pregnancy loss with increased urinary metabolite levels (Jukic et al. 2016), and one study observed no association (Deng et al. 2020). Regarding clinical pregnancy loss, only one study observed an association with exposure to DEHP (Al-Saleh et al. 2019d).

One prospective cohort study of 132 sub-fertile females did not observe an association between preconception and prenatal urinary DEHP metabolite levels and decreased placental weight (Mustieles et al. 2019). No other studies of this endpoint were identified in the available literature.

In a case-control study of 50 cases of preeclampsia and 431 pregnancies without preeclampsia, 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 post-implantation 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 1-generation studies, no changes in fertility or pregnancy outcomes were observed in CD-1 or C57BL/6J x FVB mice following exposure to doses up to 0.34 or 100 mg/kg/day, respectively, for 2 weeks prior to mating through lactation (Bastos Sales et al. 2018; Cha et al. 2018).

In CD-1 mice exposed to ≥0.2 mg/kg/day for 30 days prior to mating, decreased oocyte fertilization, zygote fragmentation and arrested development, and a decreased number of preimplantation embryos were observed 24–96-hours post mating to untreated males; no effect was noted at 0.02 mg/kg/day (Parra-Forero et al. 2019). In similarly exposed female CD-1 mice that were super-ovulated, but not mated, the number of oocytes recovered was decreased at 2 mg/kg/day (Parra-Forero et al. 2019). 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). In female B6C3F1 mice, a complete absence of corpora lutea was observed after exposure to dietary doses of approximately 7,899 mg/kg/day DEHP for 28 days; ovarian histology was not evaluated at lower doses in the study (Myers 1992a).

A 14-day study in ICR mice reported decreased oocyte maturation and decreased IVF rates at ≥0.01 and 0.04 mg/kg/day (Lu et al. 2019); however, data cannot be adequately evaluated because the statistical unit of comparison is the oocyte (not the treated animal). Due to this issue, it cannot be determined if one or two animals are driving the observed results. This study also qualitatively reported altered morphology of the primary follicle, but the dose(s) at which these effects were observed were not reported. Due inadequate data reporting and inappropriate statistical analysis, this study is not included in the LSE table.

In a series of experiments in mice, female reproductive endpoints were evaluated 0–24 months after a 10-day exposure to DEHP at doses ranging from 0.02 to 750 mg/kg/day (Chiang and Flaws 2019; Chiang et al. 2020a, 2020b; Hannon et al. 2014). The study authors conclude in all studies that there is evidence that DEHP causes reproductive effects in females; however, the conclusions are based on numerous non-dose-related changes in organ weight, folliculogenesis, estrous cyclicity, and reproductive hormone levels with little concordance between studies and evaluation timepoints. One study (Chiang and Flaws 2019) reported reduced fertility 3 months post-exposure to 0.02 mg/kg/day, but fertility effects were not observed at doses ≥0.2 mg/kg/day or earlier or immediately, 9 months, or 12 months postexposure at any dose. None of the studies provided potential rationales supporting evidence or proposed mechanisms of action for a non-monotonic response. Based on lack of clearly adverse, dose-related findings, these studies were not included in the LSE table.

In gestation-only studies, 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 post-implantation 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 ≥250 mg/kg/day, and complete litter losses at ≥500 mg/kg/day (Gu et al. 2016; Pocar et al. 2012; NTP 1988; Schmidt et al. 2012; Shiota and Nishimura 1982; Shiota et al. 1980; Tyl et al. 1988; Ungewitter et al. 2017). No changes in pregnancy outcomes were observed at ≤91 mg/kg/day. In numerous 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 700 mg/kg/day in mice (Table 2-2).

In pregnant mice, exposure to DEHP on GDs 0–14 resulted in a significant 3- or 9-fold increase in serum progesterone levels at 50 and 200 mg/kg/day, respectively; serum estradiol levels were unaltered (Zhang

et al. 2020b). A significant 25% decrease in serum estradiol levels was observed on GD 12.5 in mouse dams exposed to 0.04 mg/kg/day via gavage from GD 0.5 to 19.5, compared with controls (Zhang et al. 2015). In nonpregnant mice, no exposure-related changes in serum estradiol were observed following exposure to doses up to 10 mg/kg/day for 45 days (Xie et al. 2019).

Additional studies in rodents that did not evaluate reproductive performance show limited evidence of reproductive effects in nonpregnant female mice. One gavage study in rats reported a 16–17% decrease in absolute and relative weight of the left ovary following exposure to ≥30 mg/kg/day for 13 weeks starting on PND 6; however, no changes were observed in the right ovary (Kim et al. 2018c). 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. Observed effects include 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 (Absalan et al. 2017; Li et al. 2012b, 2016; Mu et al. 2015b; Tripathi et al. 2019; Zhang et al. 2013, 2014, 2015). Apoptosis in ovarian granulosa cells appears to result from generation of ROS leading to reduced expression of steroidogenesis genes (Cyp11a1, Cyp19A1, Star, ERβ1) (Tripathi et al. 2019). Folliculogenesis effects appear to be mediated, in part, by DEHP or MEHP binding to PPARs and/or 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. 2015b). Zhang et al. (2018c) demonstrated a role for the induction of autophagy in the disruption of primordial folliculogenesis by DEHP. DEHP increased the expression of autophagy-related genes and resulted in an increase in recognizable autophagosome in ovarian cell culture. Impaired oocyte maturation post-fertilization may be due to impaired DNA replication during mitosis, as the numbers of 1-cell zygotes with DNA replication were significantly decreased in DEHP exposed animals (Parra-Forero et al. 2019).

In a review by Cheon (2020), it is proposed that DEHP affects uterine histology (e.g., thickness of the endometrium, change in the number of endometrial glands) through alteration of the expression and regulation of steroid hormone receptors. 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. Decreased PR has also been observed in placental cells of DEHP-exposed pregnant mice; this finding was associated with elevated serum progesterone levels and a decreased number of proliferating cells in the placenta (Zhang et al. 2020b). 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).

Several mechanisms have been proposed to contribute to DEHP-induced pregnancy loss and preterm birth, including alteration of ovarian steroidogenesis, placental alterations, intrauterine inflammation, and vitamin D deficiency (Basak et al. 2020; Johns et al. 2017; Marie et al. 2015).

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 and chest circumference (Table 2-12). Findings were inconsistent among the 15 studies that met inclusion criteria (Appendix B). 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. (2016b) reported increased birth weight in female infants, but not male infants, with increasing DEHP metabolite levels in

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Bloom et al. 2019a, 2019b Cohort, 310 mother-infant pairs (152 African American and 158 White mothers; mean age 27.6 years), urinary metabolites measured at 18–22 weeks (1st visit) and 24–32 weeks (2nd visit); United States (South Carolina)	**Small for gestational age**	**ΣDEHP**	All women (1st visit): IQR: 33.5–92.0 nmol/L (SG-adj)	↔
			All women (2nd visit): 37.8–81.7	↔
			African American (1st visit): 21.5–69.4	↔
			African American (2nd visit): NR	↔
			White (1st visit): 22.1–52.1	↓
			White (2nd visit): NR	↔
		MEHP	All women (1st visit): IQR: 1.5–5.3 ng/mL (SG-adj)	↔
			All women (2nd visit): 1.4–4.5	↔
			African American (1st visit): 1.0–4.1	↔
			African American (2nd visit): NR	↔
			White (1st visit): 0.8–2.6	↓
			White (2nd visit): NR	↔
		MEHHP	All women (1st visit): 3.5–9.1	↔
			All women (2nd visit): 3.5–8.1	↔
			African American (1st visit): 2.5–7.9	↔
			African American (2nd visit): NR	↔
			White (1st visit): 2.8–6.1	↔
			White (2nd visit): NR	↔
		MEOHP	All women (1st visit): 4.1–12.2	↔
			All women (2nd visit): 4.7–10.9	↑
			African American (1st visit): 2.1–5.8	↔
			African American (2nd visit): NR	↔
			White (1st visit): 2.1–5.0	↔
			White (2nd visit): NR	↔

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
	Birth weight for gestational age Z-score or low birth weight	ΣDEHP, MEHP or MEOHP	All women, African American women, White women (both time points): see above	↔
		IQRs were estimated from graphically presented data using GrabIt! software.		
Casas et al. 2016 Cohort, 657 pregnant women (age ≥16 years), Spain	Birth length; birth weight; or head circumference	ΣDEHP	Range: 26.5–1,670 µg/g Cr	↔
Chiu et al. 2018a, 2018b Cohort, 300 mother-infant pairs (mean age 34.6 years), United States (Massachusetts)	Birth weight	MEHP	IQR: 1.3–4.7 µg/L (SG-adj)	↔
		MEHHP	6.5–21.9	↔
		MEOHP	4.8–16.2	↔
		MECPP	10.7–32.7	↔
Gao et al. 2017 Cohort, 3,103 mother-infant pairs (mean age 26.4 years), China	Birth weight, Birth length, or Head or chest circumference	ΣDEHP	NR	↔
		MEHP	25^{th}–95^{th} percentile: 1.34–13.86 µg/g Cr	NR
		MEHHP	3.01–20.19	NR
		MEOHP	4.32–23.05	NR
Goodrich et al. 2019 Cohort, 56 mother-infant pairs (mean age 31.5 years), United States (Michigan)	Birth weight or Fenton Z-score (standardized birth weight for gestational age and sex)	ΣDEHP	IQR: 6.88–34.52 µg/L	↔
		MEHP	<LOD–4.24	↔
		MEHHP	2.45–11.63	↔
		MEOHP	1.21–6.08	↔
		MECPP	2.26–12.83	↔
Kim et al. 2016a Cohort, 128 mother-infant pairs including 65 boy infants (mean age 33 years) and 63 girl infants (mean l age 34 years), Korea	**Birth length**	**ΣDEHP**	NR	All: ↔ **Boys: ↑** Girls: ↔
		MEHHP	Infant (first urine) IQR: 3.21–11.87 ng/mL (SG-adj)	All: ↔ **Boys: ↑** Girls: ↔

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
		MEOHP	1.51–6.50	All: ↔ **Boys:** ↑ Girls: ↔
	Ponderal index at birth	**ΣDEHP, MEHHP, MEOHP**	See above	All: ↔ **Boys:** ↓ Girls: ↔
	Birth weight or head circumference	ΣDEHP, MEHHP, or MEOHP	See above	↔
Messerlian et al. 2017a Cohort, 364 mother-infant pairs including 208 conceived via IVF (mean age 35.0 years) and 156 non-IVF (mean age 34.3 year) and 195 male partners of sub-fertile couples including 119 conceived via IVF (mean age 36.0 years) and 76 non-IVF (mean age 35.6 years), United States (Massachusetts)	**Birth weight (IVF conceived)**	**ΣDEHP**	**Paternal, preconception**: IQR: 32.4–136.6 ng/mL (SG-adj)	↓
			Maternal, prenatal: 25.3–75.5	↓
		MEHP	Paternal, preconception: 1.4–7.2	↔
			Maternal, prenatal: 1.4–4.7	↓
		MEHHP	**Paternal, preconception:** 8.5–40.8	↓
			Maternal, prenatal: 6.6–21.9	↓
		MEOHP	**Paternal, preconception:** 5.4–22.7	↓
			Maternal, prenatal: 4.8–15.9	↓
		MECPP	**Paternal, preconception:** 14.8–66.1	↓
			Maternal, prenatal: 10.7–33.3	↓
	Birth weight (non-IVF conceived)	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	Paternal, preconception: see above	↔
			Maternal, prenatal: see above	↔
		Birth weight was not associated with maternal preconception metabolite levels in either IVF or non-IVF infants.		
Sathyanarayana et al. 2016b Cohort, 753 mother-infant pairs including 369 boys and 384 girls (age ≥18 years), United States (California, Minnesota, New York, Washington)	**Birth weight**	**ΣDEHP**	NR	Boys: ↔ **Girls**: ↑
		MEHP	IQR: 1.37–4.35 ng/mL	Boys: ↔ **Girls**: ↑
		MEHHP	4.35–12.77	Boys: ↔ **Girls**: ↑

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
		MEOHP	3.13–8.70	Boys: ↔ **Girls**: ↑
		MECPP	5.90–15.95	Boys: ↔ **Girls**: ↑
Shoaff et al. 2016 Cohort, 368 mother-infant pairs (age ≥18 years), United States (Ohio)	Birth weight	ΣDEHP	16 weeks: IQR: 0.14–0.72 nmol/mL 26 weeks: 0.10–0.52	↔
Su et al. 2014 Cohort, 130 mother-infant pairs (maternal age NR), Taiwan	Birth length, birth weight, or head circumference	ΣDEHP	IQR: 42.28–60.83 µg/g Cr	↔
		MEHP	14.56–20.19	↔
		MEHHP	5.49–10.53	↔
		MEOHP	10.05–17.58	↔
Tsai et al. 2018a, 2018b Cohort, 112 mother-infant pairs from Cathy General Hospital (CGH) group (potentially exposed to tainted food; mean age 31.93 years)) and 245 mother-infant pairs from Taiwan Maternal and Infant Cohort (TMIC) (became pregnant after the tainted food products were removed from the market; mean age 31.99 years), Taiwan	Birth weight or height or head or chest circumference	ΣDEHP	1st trimester: CGH, IQR: 178.16–463.36 µg/g Cr TMIC: 103.19–208.10	↔
			2nd trimester: CGH: 210.76–471.14 TMIC: 48.18–151.75	↔
			3rd trimester: CGH: 202.14–513.31 TMIC: 94.01–220.78	↔
		MEHP	1st trimester: CGH: 14.85–46.78 TMIC: 2.98–8.82	↔
			2nd trimester: CGH: 21.56–43.89 TMIC: 0.24–5.57	↔
			3rd trimester: CGH: 18.13–51.35 TMIC: 1.58–6.93	↔

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
		MEOHP	1st trimester: CGH: 6.73–21.70 TMIC: 5.47–12.83	↔
			2nd trimester: CGH: 7.44–23.66 TMIC: 2.13–8.83	↔
			3rd trimester: CGH: 8.44–23.98 TMIC: 5.95–15.34	↔
		MEHHP	1st trimester: CGH: 9.80–29.04 TMIC: 7.87–16.58	↔
			2nd trimester: CGH: 8.91–28.51 TMIC: 2.60–10.22	↔
			3rd trimester: CGH: 9.25–30.13 TMIC: 7.07–18.95	↔
		MECPP	1st trimester: CGH: 13.57–37.76 TMIC: 10.68–22.76	↔
			2nd trimester: CGH: 14.58–36.06 TMIC: 6.75–18.43	↔
			3rd trimester: CGH: 14.48–41.90 TMIC: 11.22–24.67	↔
Wolff et al. 2008 Cohort, 404 mother-infant pairs (mean age 24 years), United States (New York)	Birth length, birth weight, or head circumference	ΣDEHP	IQR: 0.13–0.5 µmol/L	↔
		MEHP	IQR: 2.9–14 ng/mL	↔
		MEHHP	9.5–39	↔
		MEOHP	8.3–36	↔
		MECPP	16–70	↔

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Zhang et al. 2018d Cohort, 3,103 mother-infant pairs including 74 mother-infant pairs with low birth weight infants (<2,500 g; 35 boys, 39 girls; mean age 26.07 years), 2,783 mother-infant pairs with normal birth weight infants (2,500–4,000 g; 1,391 boys, 1,383 girls; mean age 26.39 years), and 246 mother-infant pairs with high birth weight infants (>4,000 g; 138 boys, 107 girls; mean age 26.46 years), China	**Birth weight (low birth weight infants)**	**ΣDEHP**	1st trimester: IQR: 2.40–3.28 ng/mL 2nd trimester: 2.43–3.42 3rd trimester: 1.99–2.92	**All:** ↓ **Boys:** ↓ **Girls:** ↓
		MEHP	1st trimester: 0.45–1.57 2nd trimester: 0.86–1.97 3rd trimester: 0.36–1.57	**All:** ↓ **Boys:** ↓ Girls**:** ↔
		MEHHP	1st trimester: 1.22–2.19 2nd trimester: 1.31–2.42 3rd trimester:0.84–1.87	**All:** ↓ **Boys:** ↓ Girls**:** ↔
		MEOHP	1st trimester: 1.55–2.46 2nd trimester: 1.49–2.47 3rd trimester: 1.07–2.04	**All:** ↓ **Boys:** ↓ Girls**:** ↔
	Birth weight (normal birth weight infants)	ΣDEHP, MEHHP, or MEOHP	See above	↔
		MEHP	See above	All: ↔ **Boys:** ↑ Girls**:** ↔
	Birth weight (high birth weight infants)	**ΣDEHP**	See above	All: ↔ Boys: ↔ **Girls:** ↓
		MEHP	See above	**All:** ↓ Boys: ↔ Girls**:** ↔
		MEHHP	See above	**All:** ↓ Boys: ↔ **Girls:** ↓
		MEOHP	See above	↔
	Birth weight (all infants)	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Zhao et al. 2014 Case-control, 42 IUGR infants and 84 controls (maternal age NR), China	**Birth weight**	ΣDEHP	All: IQR: 13.6–46.3 ng/mL Cases: 16.4–54.5 Controls: 9.3–41.5	↔
		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	↓
		MEOHP	All: 1.7–9.7 Cases: 2.4–15.0 Controls: 1.4–6.4	↓
	Birth length	ΣDEHP, MEHP, MEHHP, MEOHP	See above	↔
	IUGR	ΣDEHP, MEHP, or MEOHP	See above	↔
		MEHHP	See above	↑
Zhu et al. 2018 Cohort, 1,002 mother-infant pairs (525 boys, 477 girls; mean age 28.7 years), China	**Birth weight or birth weight Z-score**	**ΣDEHP**	IQR: 104–255 nmol/g Cr	↑ **(boys)** ↔ (girls)
		MEHHP	IQR: 10.0–25.4 µg/g Cr	↔
		MEOHP	8.90–23.2	↑ **(boys)** ↔ (girls)
		MECPP	11.4–27.6	↑ **(boys)** ↔ (girls)
	Birth length	ΣDEHP, MEHHP, MEOHP, or MECPP	See above	↔

Table 2-12. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Birth Size

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
	Ponderal index (birth weight/birth length)	ΣDEHP, MEHHP, or MEOHP	See above	↔
		MECPP	See above	↑ **(boys)** ↔ (girls)

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; IQR = interquartile range; IUGR = intrauterine growth retardation; IVF = *in vitro* fertilization; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NR = not reported; SG-adj = specific gravity adjusted

maternal urine, while Zhu et al. (2018) reported increased birth weight and ponderal index (birth weight/birth length) in male infants, but not female infants, with increasing DEHP metabolite levels in maternal urine. Kim et al. (2016a) reported an increase in birth length with a corresponding decrease in ponderal index in boys, but not girls, with increasing DEHP metabolite levels in infant first urine.

In a cohort study that stratified analysis by birth weight status (low, normal, or high birth weight), maternal urine DEHP metabolite levels were associated with decreasing birth weight in low-birth weight male and female infants, increased birth weight in normal weight male infants, and decreased birth weight in high weight female infants (Zhang et al. 2018d). Among sub-fertile couples, birth weight in babies conceived via IVF was negatively associated with paternal preconception and maternal prenatal urinary DEHP metabolite levels (Messerlian et al. 2017a). Bloom et al. (2019a, 2019b) reported decreased risk of small for gestational age in white, but not African American, women with increasing sum DEHP or MEHP metabolites; when both races were combined, an increased risk of small for gestation age was observed with increasing urinary MEOHP levels. Other studies did not observe an association between DEHP exposure and measures of birth size (Casas et al. 2016; Chiu et al. 2018a, 2018b; Gao et al. 2017; Goodrich et al. 2019; Shoaff et al. 2016; Su et al. 2014; Tsai et al. 2018a, 2018b; Wolff et al. 2008).

Epidemiological studies evaluating the effects of prenatal exposure to DEHP and growth or obesity parameters in children have also not shown consistent results, as shown in Table 2-13. In general, no association was observed between maternal metabolite levels and BMI measured at ages ranging from 2 to 14 years of age (Agay-Shay et al. 2015; Buckley et al. 2016a; Harley et al. 2017; Heggeseth et al. 2019a, 2019b; Shoaff et al. 2017a, 2017b; Vafeiadi et al. 2018a, 2018b). Two studies reported decreased BMI with an increased prenatal DEHP exposure (Lee et al. 2020; Valvi et al. 2015). Lee et al. (2020) observed decreased BMI in 6-year-old girls, but not boys, with increased MEHHP in maternal urine. In contrast, Valvi et al. (2015) observed decreased BMI in 4- and 7-year-old boys, but not girls, with increased ΣDEHP in maternal urine; this association was not observed at 1 year of age. Kim et al. (2016a) 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.

Fewer data are available for other measures of growth or obesity (Table 2-13). One study reported increased odds of being overweight or obese at 12 years of age when DEHP metabolite levels were

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Measures of Adiposity

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Agay-Shay et al. 2015 Cohort, 470 children assessed at age 7 years, Spain	BMI	MEHP	Maternal range: 1.8–266.9 µg/g Cr	↔
		MEHHP	5.3–503.4	↔
		MEOHP	4.1–378.3	↔
		MECPP	7.7–718.9	↔
Buckley et al. 2016a Cohort, 707 children assessed at age 4–7 years, United States (New York and Ohio)	BMI	ΣDEHP	Maternal IQR: 0.128–0.562 µmol/L	↔ Maresca et al. (2016) evaluated the same outcome in a subset of this cohort; no significant association was observed.
Buckley et al. 2016b Cohort, 180 children assessed at age 4–9 years, United States (New York)	Percent fat mass	ΣDEHP	Maternal IQR: 125–530 nmol/L	↔
Harley et al. 2017 Cohort, 345 children assessed at age 5–12 years, United States (California)	**Overweight or obese**	**ΣDEHP**	Maternal IQR: 0.1–0.3 µmol/L	5–10.5 years: ↔ **12 years**: ↑
	Waist circumference	**ΣDEHP**	See above	**5 years**: ↑ 7–12 years: ↔
	BMI or percent body fat	ΣDEHP	See above	5–12 years: ↔
Heggeseth et al. 2019a, 2019b Cohort, 335 children assessed four or more times between age 2 and 14 years, United States (California)	BMI	MEHP	Maternal IQR: 2.1–6.9 ng/mL	↔
		MEHHP	8.2–26.3	↔
		MECPP	15.6–41.4	↔
		MEOHP	6.4–19.375	↔
Kim et al. 2016a Cohort, 128 infants assessed at 3 months, Korea	**BMI Z-score (change from birth 3 months)**	**ΣDEHP**	NR	↑
		MEHHP	Infant (first urine) IQR: 3.21–11.87 ng/mL	↑
		MEOHP	1.51–6.50	↑

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Measures of Adiposity

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Lee et al. 2020 Cohort/Cross-sectional, 481 children (255 boys, 226 girls) assessed at age 6 years, South Korea	**BMI Z-score**	ΣDEHP	Maternal): IQR: 0.06–0.17 nmol/g Cr	↔
			Child (6 years): 0.23–0.47	↔
		MEHHP	Maternal: IQR: 9.4–26.5 µg/g Cr	All: ↔ Boys: ↔ **Girls:** ↓
			Child: 39.8–80.3	↔
		MEOHP	Maternal: 10.4–24.7	↔
			Child: 26.3–55.7	↔
	Percent body fat, Fat mass index (kg/m^2)	ΣDEHP, MEHHP, or MEOHP	Maternal: see above	↔
			Child: see above	↔
Maresca et al. 2016 Cohort, 424 children assessed at age 7 years, United States (New York)	Waist circumference	ΣDEHP	Maternal GM (GSD): 292.89 (3.24) nmol/L	↔
	Percent body fat	ΣDEHP	See above	↔
Shoaff et al. 2017a, 2017b Cohort/Cross-sectional, 219 children assessed at age 8 years, United States (Ohio)	**Percent body fat**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	Maternal: mean (range): 144.76 (6.09–2,408.59) ng/mL	↔
			Child (1 year): 161.17 (4.23–4,319.71)	↓
			Child (2 years): 176.20 (5.52–3,099.46)	↔
			Child (3 years): 191.22 (5.08–191.22)	↔
			Child (4 years): 176.17 (2.66–1,919.49)	↔
			Child (5 years): 106.20 (5.20–1,395.99)	↑

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Measures of Adiposity

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
			Child (8 years): 87.46 (4.47–1,274.77)	↔
	Waist circumference	**ΣDEHP**	Maternal, child (1, 2, 4, or 8 years): see above	↔
			Child (5 years): see above	↑
	BMI Z-score	ΣDEHP	Maternal, child (any age)	↔
Vafeiadi et al. 2018a, 2018b Cohort/Cross-sectional, 500 children (279 boys, 221 girls) assessed at age 4–6 years, Greece	**Waist Circumference**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	Maternal: IQR: 0.1–0.2 µmol/g	↔
			Child (4 years): 0.2–0.5	All: ↔ **Boys:** ↓ Girls: ↔
	Waist-to-height ratio or skinfold thickness (sum of subscapular, triceps, suprailiac, quadriceps)	**ΣDEHP**	Maternal: see above	↔
			Child: see above	All: ↔ Boys: ↔ **Girls:** ↑
	BMI Z-score	ΣDEHP	Maternal or child: see above	↔

Table 2-13. Summary of Epidemiological Studies of Prenatal DEHP Exposure and BMI, Waist Circumference, and Measures of Adiposity

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Valvi et al. 2015 Cohort, 391 children (205 boys, 186 girls) assessed at age 1, 4, and 7 years, Spain	**BMI (4 or 7 years)**	**ΣDEHP**	Maternal range: 64.9–139 µg/g Cr (as MEHP)	All: ↔ **Boys**: ↓ Girls: ↔
	BMI (1 year or all years)	ΣDEHP	See above	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; BMI = body mass index; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; GSD = geometric standard deviation; IQR = interquartile range; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NR = not reported

doubled in maternal urine; however, sensitivity analysis indicated that maternal BMI influenced these results (Harley et al. 2017). 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 percent body fat at 9–12 years and maternal urinary DEHP levels. Maternal urinary DEHP levels were not associated with percent body fat/mass, fat mass index, or waist circumference in other studies (Lee et al. 2020; Maresca et al. 2016; Shoaff et al. 2017a, 2017b; Vafeiadi et al. 2018a, 2018b). When urinary metabolites were measured in children's urine, Shoaff et al. (2017a, 2017b) observed a negative association between percent body fat at 8 years of age and DEHP metabolite in urine collected at 1 year, while a positive association was observed for percent body fat and waist circumference at 8 years of age with DEHP metabolites in urine collected 5 years. In another cohort, urinary metabolite levels at 4 years were negatively associated with waist circumference in boys at 4–6 years, but not girls, and positively associated with waist-to-height ratio and skinfold thickness in girls at 4–6 years, but not boys (Vafeiadi et al. 2018a, 2018b).

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). 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; NTP 1988; Schilling et al. 1999, 2001; Tanaka 2002; Tomita et al. 1982a; Ungewitter et al. 2017; Yagi et al. 1980). However, one study did not report an increase in fetal deaths in mice following maternal exposure to doses up to 200 mg/kg/day from GD 0 to 17 (Shen et al. 2017).

Several studies 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.

Early postnatal exposure on PNDs 3–23 in Sprague-Dawley rats resulted in an increased incidence of developmental malformations in the lung parenchyma at 600 mg/kg/day (Camacho et al. 2020). 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). In C57Bl/6 × B6129S4 mouse offspring, the total number of malformations was increased following maternal exposure to 250 mg/kg/day from GD 7 to 16; the most common defects were limb malformations and exencephaly (Ungewitter et al. 2017).

No changes in neonatal survival, external malformations, or acquisition of early postnatal developmental landmarks (e.g., eye opening, incisor eruption, pinna detachment) were observed in Sprague-Dawley rats following maternal exposure to doses up to 300 mg/kg/day from GD 8 to PND 21 (Nardelli et al. 2017). 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 (NTP 1988).

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). Consistent with this, body weight decreases in Sprague-Dawley neonates following direct exposure on PNDs 3–7 or 3–23 were only observed at 600 mg/kg/day (Camacho et al. 2020). 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/or lactational exposure to maternal doses up to 700 mg/kg/day (Carbone et al. 2010, 2012; Dalsenter et al. 2006; Schilling et al. 1999, 2001; Venturelli et al. 2015). However, a few studies reported decreased offspring weights following maternal exposure. One study reported decreased birth weights at maternal doses ≥300 mg/kg/day (Christiansen et al. 2010). Other studies reported decreased postnatal body weights at maternal doses ≥1 mg/kg/day (measured on PNDs 9–22; Parsanathan et al. 2019) or ≥10 mg/kg/day (measured on PND 80; Rajagopal et al. 2019a). 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 in most studies at ≥191 mg/kg/day, but generally not at doses ≤100 mg/kg/day (Maranghi et al. 2010; NTP 1988; Shiota et al. 1980; Shiota and Nishimura 1982; Tyl et al. 1988; Ungewitter et al. 2017). Similarly, 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). One gestational study also reported decreased fetal body weight and crown-rump length at maternal doses ≥50 mg/kg/day during gestation (Shen et al. 2017).

In contrast, *increased* F1 offspring body weight and visceral adipose tissue were reported in 1-generation studies at doses ≥0.05 mg/kg/day (Fan et al. 2020; Schmidt et al. 2012). However, other 1-generation studies report a lack of body weight effects in offspring at maternal doses up to 180.77 mg/kg/day (Bastos Sales et al. 2018; Tanaka 2002). Similarly, 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). Venturelli et al. (2015) also did not observe body weight effects in Wistar rats exposed to doses up to 75 mg/kg/day for 30 days post-weaning. 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 doses up to 500 mg/kg/day for 14–15 days post-weaning (Vo et al. 2009b; Zhang et al. 2018a).

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 low birth weight and IUGR, including alteration of ovarian steroidogenesis, thyroid dysfunction, placental alterations, and intrauterine inflammation (Basak et al. 2020; Marie et al. 2015; Shen et al. 2017; Yu et al. 2018).

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).

There is some evidence that hepatic cellular alterations are occurring in the developing animal following DEHP exposure. However, at low DEHP doses and/or short exposure durations, these alterations appear to be reversible. Exposure for longer durations and/or to higher DEHP dose levels results in elevated liver weights accompanied by histological changes. Reversible 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). Reversible 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. No changes in liver histology were observed in male PND 7 Sprague-Dawley rats following direct exposure to doses up to 600 mg/kg/day from PND 3 to 7, though relative liver weights were increased at ≥300 mg/kg/day (Camacho et al. 2020). With continued exposure from PND 3 to 23, relative liver weights were only increased at 600 mg/kg/day; this was accompanied by hepatocellular hypertrophy.

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 in Sprague-Dawley rat offspring at PND 21 or 63 following maternal exposure to doses up to 400 mg/kg/day from GD 6 to PND 20 (Kobayashi et al. 2006) or at PND 3, 8, or 21 following maternal exposure to doses up to 300 mg/kg/day from GD 8 to PND 21 (Nardelli et al. 2017). 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).

Significant increases in serum ALP, AST, and ALT were observed in male PND 80 Wistar rat offspring following maternal exposure to DEHP at doses ≥10 mg/kg/day from GD 9 to PND 21 (Rajagopal et al. 2019a). Liver weight and histology were not assessed. In another study, male PND 92 Wistar rat offspring showed decreased serum triglycerides and cholesterol following lactational exposure to ≥7.5 and 75 mg/kg/day, respectively (Venturelli et al. 2015). In contrast, increased serum cholesterol was observed in male PND 90 offspring following exposure to 700 mg/kg/day from GD 13 to PND 21 (Venturelli et al. 2019). Serum triglycerides and cholesterol levels were not observed when young Wistar rats were similarly exposed for 30 days post-weaning (Venturelli et al. 2015). No change in liver weight was observed following gestational plus lactational, lactational, or post-weaning exposure paradigms; histology was not assessed.

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.

The Wei et al. (2012) study that reported impaired kidney development and function also 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.

Wei et al. (2012) also observed significant changes in offspring kidney weights, some of which may be attributable to observed decreases in offspring body weight. High-dose females at PNW 15 had significantly decreased absolute kidney weight and body weight. Females in the low-dose group at PNW 15 had slightly decreased absolute kidney weight and slightly increased body weight, resulting in a significantly decreased relative kidney weight. High-dose males at PNWs 15 and 21 had increased absolute kidney weight and decreased body weight. At birth and weaning (PNW 3), pups had significant decreases in body weight with minimal decreases in kidney weight, resulting in statistically significant relative kidney weights on these days.

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 neonatal, 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; Nardelli et al. 2017).

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), or in adult offspring following maternal exposure to doses up to 700 mg/kg/day from GD 13 to PND 21 or 75 mg/kg/day from PND 1 to 21 (Venturelli et al. 2015, 2019). Similarly, no changes in kidney weight were observed in young Wistar rats exposed to doses up to 75 mg/kg/day for 30 days post-weaning (Venturelli et al. 2015). Measures of renal function and kidney histology were not assessed in these studies. No changes in kidney weight or histology were observed in male PND 7 Sprague-Dawley rats following direct exposure

on PNDs 3–7 to doses up to 600 mg/kg/day (Camacho et al. 2020). However, with longer exposure (PNDs 3–23), decreased kidney weight and renal tubule degeneration were observed at ≥300 mg/kg/day.

Significant increases in serum urea and creatinine were observed in male PND 80 Wistar rat offspring following maternal exposure to DEHP at doses ≥10 mg/kg/day from GD 9 to PND 21 (Rajagopal et al. 2019a). Kidney weight and histology were not assessed.

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 (Table 2-14) are birth cohort studies that evaluated exposure using maternal urine samples; some studies additionally evaluated child 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 26 studies of 13 birth cohorts (Table 2-14). Many cohorts were longitudinal in design, evaluating cognitive/mental and psychomotor development across several ages. 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. 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. Of the selected studies, three suggested associations between poorer performance on the mental development index at 6 months (Kim et al. 2011), 23–26 months of age (Qian et al. 2019a, 2019b), and 2–3 years of age

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Columbia Center for Children's Environmental Health (CCCEH) cohort studies				
Ipapo et al. 2017 168 children, FTII administered at 27 weeks of age, United States (New York)	Visual recognition memory	ΣDEHP	NR	↔
		MEHP	Maternal (3rd trimester) IQR: 1.90–9.85 ng/mL	↔
		MEHHP	10.25–40.80	↔
		MEOHP	8.35–37.10	↔
		MECPP	17.95–74.55	↔
Whyatt et al. 2012 319 children (151 boys, 168 girls), BSID-II (MDI and PDI) administered to infants between 27 and 42 months of age (mean 36.4 months), CBCL when children were between 33 and 48 months of age (mean 36.6 months), United States (New York)	BSID or CBCL	ΣDEHP	NR	↔
		MEHP	Maternal (3rd trimester) range: <LOD–613 ng/mL	NR
		MEHHP	1.1–1,750	NR
		MEOHP	0.7–1,320	NR
		MECPP	3.0–1,840	NR
Factor-Litvak et al. 2014 328 children (155 boys, 173 girls), WISC administered to children at 7 years of age, United States (New York)	WISC	MEHP	Maternal (3rd trimester) IQR: 1.9–12.4 ng/mL	↔
		MEHHP	10.6–47.2	↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Balalian et al. 2019; Daniel et al. 2020 209 children (93 boys, 116 girls, BOT-2 administered at 11 years of age, United States (New York)	**Total motor skills**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	Maternal (3rd trimester) IQR: 137.1–577.7 (molar sum)	↔
			Child (age 3): 186.80–919.3	↔
			Child (age 5): 203.53–852.9	↔
			Child (age 7): 245.7–865.4	↓ **(Boys)** ↔ (Girls)
	Fine motor skills	**ΣDEHP**	Maternal, child (age 5): see above	↔
			Child (age 3 or 7): see above	↓ **(Boys)** ↔ (Girls)
	Gross motor skills	ΣDEHP	Maternal or child (any age)	↔
Health Outcomes and Measures of the Environment (HOME) cohort studies				
Yolton et al. 2011 350 infants (163 boys, 187 girls), NNNS measured at 5 weeks of age, United States (Ohio)	**Nonoptimal reflexes**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	Maternal (16 weeks) GM (95% CI): 311 (269–360) nmol/L	Boys: ↔ Girls: ↔
			Maternal (26 weeks): 245 (213–281)	**Boys**: ↑ Girls: ↔
		No significant association for other subscales of the NNNS in males or females.		
Braun et al. 2014 175 children, SRS administered at 4–6 years of age, United States (Ohio)	SRS	MEHP	Maternal IQR (average of 16 and 26 weeks): 2.9–7.5 µg/g Cr	↔
		MEHHP	15–49	↔
		MECPP	21–70	↔
Braun et al. 2017a, 2017b 198 children (91 boys, 107 girls), VMWM administered at 8 years of age, United States (Ohio)	Visual-spatial abilities	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Maternal (average of 16 and 26 weeks) IQR: 44–148 µg/g Cr	All: ↔ Boys: ↔ Girls: ↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Percy et al. 2016 227 children (101 boys, 126 girls), mothers completed GIQ and children completed PPPSI at 8 years of age, United States (Ohio)	GIQ or PPPSI	ΣDEHP	Maternal (16 weeks) GM (95% CI): 87.9 (73.4, 105.2) nmol/L Maternal (26 weeks): 65.9 (55.2, 78.5)	↔
		MEHP	Maternal (16 weeks) GM (95% CI): 4.9 (4.1, 6) ng/mL Maternal (26 weeks): 4.3 (3.6, 5)	↔
		MEHHP	Maternal (16 weeks): 27 (22.4, 32.7) Maternal (26 weeks): 19.4 (16.1, 23.4)	↔
		MEOHP	Maternal (16 weeks): 20.1 (16.7, 24.2) Maternal (26 weeks): 15.9 (13.2, 19.2)	↔
		MECPP	Maternal (16 weeks): 39.3 (33, 46.9) Maternal (26 weeks): 29.1 (24.5, 34.6)	↔
Mount Sinai Children's Environmental Health Study cohort				
Doherty et al. 2017 250 children (134 boys, 116 girls), BSID (MDI and PDI) administered at approximately 24 months of age, United States (New York)	MDI and PDI	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Maternal (31 weeks) GM (SE): 0.28 (3.7) µmol/L	↔
Miodovnik et al. 2011 137 children, SRS administered at 7–9 years of age, United States (New York)	SRS	ΣDEHP ((MEHP, MEHHP, MEOHP, MECPP)	NR	↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Study for Future Families (SFF) cohort studies				
Swan et al. 2010 145 children (74 boys, 71 girls), mothers completed PSAI when children were approximately 5 years old, United States (California, Minnesota, Missouri, Iowa)	**PSAI scores for masculine play**	**ΣDEHP**	Maternal (mid-pregnancy) IQR: 11.7, 40.3 ng/mL	**Boys: ↓** Girls: ↔
		MEHP	1.4, 6.2	Boys: ↔ Girls: ↔
		MEHHP	5.2, 17.3	**Boys: ↓** Girls: ↔
		MEOHP	4.7, 17.9	**Boys: ↓** Girls: ↔
	PSAI scores for composite or feminine play	ΣDEHP, MEHP, MEHHP, MEOHP	See above	↔
Kobrosly et al. 2014 153 children (77 boys, 76 girls), mothers completed CBCL when children were 72–126 months of age (mean 102 months or 8.5 years), United States (California, Minnesota, Missouri, Iowa)	**Anxiety/depression**	**ΣDEHP**	NR	All: ↔ Boys: ↔ **Girls**: ↓
		MEHP	Maternal (26 weeks) IQR: 1.1, 9.9 ng/mL	NR
		MEHHP	6.1, 24.2	NR
		MEOHP	5.1, 22.0	NR
		DEHP metabolites were not associated with other CBCL behavioral scores.		
Taiwan maternal and infant cohort studies				
Huang et al. 2015 110 children (58 boys, 52 girls), BSID-II administered at age 2 years; WPPSI-R at age 5 years; WISC-III at age 8 years, and WISC-IV at age 11 years, Taiwan	IQ	MEHP	Maternal (3rd trimester) GM (95% CI): 19.79 (16.38, 23.92) µg/g Cr	↔
		MEHHP	8.49 (5.97, 12.09)	↔
		MEOHP	12.97(9.23, 18.21)	↔
		Decreased IQ was associated with increased MEOHP and ∑DEHP metabolites in child's urine; however, samples were taken at the same time as tests administered.		

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Ku et al. 2020 208 children, CTTS administered at age 2 years, BSQ-C at age 5 years, and MCTQ-C at age 11 years, Taiwan	**Withdrawal**	**ΣDEHP**	NR	**2 years:** ↑ 5/11 years: ↔
		MEHP	Maternal (3rd trimester) GM (95% CI): 19.20 (16.69, 22.09) µg/g Cr	**2 years:** ↑ 5/11 years: ↔
		MEHHP	8.24 (6.39,10.62)	**2 years:** ↑ **5 years:** ↓ 11 years: ↔
		MEOHP	12.41 (9.79,15.73)	**2 years:** ↑ **5 years:** ↓ 11 years: ↔
	Threshold of responsiveness	**ΣDEHP, MEHP, MEOHP**	See above	**2/5 years:** ↓ 11 year: ↔
		MEHHP	See above	↔
	Distractibility	**ΣDEHP, MEHP**	See above	**2 years:** ↑ 5/11 year: ↔
		MEHHP, MEOHP	See above	↔
	Intensity of reaction	**ΣDEHP, MEHP**	See above	**2 years:** ↓ 5/11 years: ↔
		MEHHP, MEHOP	See above	↔
	Activity level	ΣDEHP, MEHHP, MEHOP	See above	↔
		MEHP	See above	2/5 years: ↔ **11 years:** ↑
		DEHP metabolites in maternal urine were not associated with other temperament scores. DEHP metabolites in child's urine were associated with increased adaptability and decreased persistence at 2 years of age, decreased positive mood and withdrawal at 5 years of age, and decreased intensity of reaction and increased odds of ADHD symptoms at 11 years of age; however, samples were taken at the same time as tests administered.		

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Lien et al. 2015 122 children, mothers completed CBCL when children were 8 years of age, Taiwan	**Delinquent behavior (clinical range)**	MEHP	Maternal (3rd trimester) GM (95% CI): 16.93 (14.32, 20.02) µg/g Cr	↔
		MEHHP	7.91 (5.69, 11.02)	↔
		MEOHP	13.59 (10.27, 18.00)	↑
	Aggressive behavior, externalizing problems (clinical range), or borderline or borderline/clinical scores for all behaviors	**MEHP, MEHHP, MEOHP**	See above	↑
Chen et al. 2019 122 children, mothers completed CBCL when children were 8, 11, and 14 years of age (results combined in analysis), Taiwan	**Delinquent behavior, externalizing problems**	**ΣDEHP**	NR	**All:** ↑ **Boys:** ↑ **Girls:** ↑
		MEHP	Maternal (3rd trimester) GM (range): 16.93 (1.79, 706.10) µg/g Cr	NR
		MEHPP	7.91 (0.05, 489.28)	NR
		MEOHP	13.59 (0.16, 1010.72)	NR
	Withdrawn, social problems, internalizing problems	**ΣDEHP**	NR	**All:** ↑ **Boys:** ↑ Girls: ↔
	Aggressive behavior	**ΣDEHP**	NR	**All:** ↑ Boys: ↔ **Girls:** ↑
	Anxious/depressed, thought problems, attention problems	**ΣDEHP**	NR	**All:** ↑ Boys: ↔ Girls: ↔
	Somatic complaints	ΣDEHP	NR	↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Huang et al. 2019 153 children, mothers completed CBCL when children were 8, 11, and 14 years of age (results combined in analysis), Taiwan	**Anxious/depressed, social problems, thought problems, attention problems, aggressive behavior, internalizing problems**	ΣDEHP (MEHP, MEHHP, MEOHP)	Maternal (3rd trimester) GM (95% CI): 0.17 (0.15, 0.20) µmol/g Cr	↔
		MEHP	16.73 (14.46, 19.36) µg/g Cr	↑
	Delinquent behavior, externalizing problems; borderline or clinical internalizing or externalizing problems	**ΣDEHP, MEHP**	See above	↑
		DEHP metabolites in maternal urine were not associated with other CBCL behavioral scores. DEHP metabolites in child's urine at 2–3, 5–6, or 8–9 years of age were not associated with any CBCL behavioral scores at 8–14 years of age.		
Other cohort studies				
Engel et al. 2018 MoBa cohort (nested case-control), 850 children including 297 with ADHD and 553 without ADHD evaluated at ≥3 years (cases and controls combined for analysis), Norway,	**ADHD**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	Maternal (17 weeks) IQR: Case: 0.21–0.41 µmol/L Control: 0.18–0.34	**All:** ↑ **Boys:** ↑ Girls: ↔
Gascon et al. 2015b INMA cohort, 367 children (187 boys, 178 girls), BSID-II (MDI and PDI) administered at 1 year of age, MSCA, CPSCS and ADHD evaluated at age 4 years, SDQ and short form of CSRS (includes ADHD index) evaluated at age 7 years, Spain	BSID-II or MSCA	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	Maternal (average 1st and 3rd trimester) IQR: 68–146 µg/g Cr	↔
	Social competence (4 years)	**ΣDEHP**	See above	↑
	Risk of inattention symptoms, ADHD (4 and 7 years)	**ΣDEHP**	See above	↓

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Kim et al. 2018f CHECK cohort, 86 children, BSID-II (MDI and PDI), SMS (social quotient), and CBCL were administered at 13–24 months of age, Republic of Korea	BSID-II, SMS, or CBCL	MEHP	Maternal (delivery) IQR: 7.8–19.1 µg/g Cr	↔
		MEHHP	14.9–35.4	↔
		MEOHP	13.5–31.1	↔
Kim et al. 2011 MOCEH cohort, 460 children (235 boys and 225 girls), BSID-II (MDI and PDI) administered to infants at 6 months of age, Republic of Korea	**MDI and PDI**	**MEHHP**	Maternal (3rd trimester) IQR: 4.3–21.4 ng/mL	**Boys: ↓** Girls: ↔
		MEOHP	3.8–17.1	**Boys: ↓** Girls: ↔
Olesen et al. 2018a, 2018b OCC cohort, 518 children (271 boys, 247 girls), MB-CDI administered every third month from 16 to 36 months of age, Demark	**MB-CDI (vocabulary or complexity score)**	**ΣDEHP**	Maternal (week 28) IQR: 10.0–34.4 ng/mL	**Boys: ↓** Girls: ↔
		MEHP	0.5–2.2	Boys: ↔ Girls: ↔
		MEHHP	2.2–8.6	**Boys: ↓** Girls: ↔
		MEOHP	2.0–6.9	**Boys: ↓** Girls: ↔
		MECPP	2.5–8.5	**Boys: ↓** Girls: ↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
Polanska et al. 2014 REPRO_PL Cohort, 165 children (72 boys, 93 girls), BSID-III administered to infants at 24 months of age, Poland	**Motor scores**	**ΣDEHP**	Maternal (3rd trimester) range: 0.0004–1.5 µmol/g Cr	↓
		MEHP	0.02–4.3 µg/g Cr	↔
		MEHHP	0.02–431	↓
		MEOHP	0.04–140	↓
	MDI: cognitive scores; language scores	ΣDEHP, MEHP, MEHHP, MEOHP	See above	↓
Qian et al. 2019a, 2019b Wuhan prenatal cohort, 476 children, BSID-CR (MDI and PDI) administered at 23–26 months of age, China	**MDI**	**ΣDEHP**	Maternal (average across three trimesters) median: 91.71 nmol/L	↔
			1st trimester: 81.14	↔
			2nd trimester: 70.35	↔
			3rd trimester: 88.22	**All:** ↓ Boys: ↔ Girls: ↔
		MEHP	Maternal (average) median: 3.23 µg/L	↔
			1st trimester: 2.80	↔
			2nd trimester: 2.26	↔
			3rd trimester: 2.41	↔
		MEHHP	Maternal (average): 6.91	↔
			1st trimester: 6.31	↔
			2nd trimester: 4.89	↔
			3rd trimester: 6.48	**All:** ↓ **Boys:** ↓ Girls: ↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEOHP	Maternal (average): 5.62	↔
			1st trimester: 4.81	↔
			2nd trimester: 4.18	↔
			3rd trimester: 5.38	↔
		MECPP	Maternal (average): 10.62	↔
			1st trimester: 9.31	↔
			2nd trimester: 8.14	↔
			3rd trimester: 10.54	**All:** ↓ **Boys:** ↓ Girls: ↔
	PDI	**ΣDEHP**	Maternal (average or 3rd trimester): see above	All: ↔ **Boys:** ↑ Girls: ↔
			1st or 2nd trimester: see above	↔
		MEHP	Maternal (average or 1st trimester): see above	**All:** ↔ **Boys:** ↑ Girls: ↔
			2nd trimester: see above	All: ↔ **Boys:** ↑ Girls: ↔
			3rd trimester: see above	↔

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MEHHP	Maternal (average, 1st, 2nd, or 3rd trimester): see above	↔
		MEOHP	Maternal (average or 3rd trimester): see above	All: ↔ **Boys**: ↑ Girls: ↔
			1st or 2nd trimester: see above	↔
		MECPP	Maternal (average): 10.62	**All:** ↑ **Boys:** ↑ Girls: ↔
			1st or 2nd trimester: see above	↔
			Maternal (3rd trimester): 10.54	All: ↔ **Boys:** ↑ Girls: ↔
Téllez-Rojo et al. 2013 ELEMENT cohort, 135 children (64 boys, 71 girls), BSID-II (MDI and PDI) administered to children at 24, 30, and 36 months of age (results combined in analysis), Mexico	**MDI**	**ΣDEHP**	Maternal (3rd trimester) GM (95% CI): 0.35 (0.30, 0.40) nmol/mL (SG-adj)	All: ↔ Boys: ↔ **Girls:** ↓
		MEHP	6.56 (5.72, 7.53) ng/mL (SG-adj)	All: ↔ Boys: ↔ **Girls:** ↓
		MEHHP	22.08 (18.77, 25.96)	All: ↔ Boys: ↔ **Girls:** ↓
		MEOHP	14.23 (12.05, 16.80)	All: ↔ Boys: ↔ **Girls:** ↓

Table 2-14. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Selected Neurodevelopmental Outcomes

Reference, population	Outcome evaluated	Metabolite	Urine concentration[a]	Result
		MECPP	39.65 (34.32, 45.81)	All: ↔ Boys: ↔ **Girls: ↓**
		DEHP metabolites were not associated with PDI scores in either sex.		

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; ADHD = attention-deficit/hyperactivity disorder; BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency-2; BSID = Bayley Scales of Infant Development; BSID-CR = Bayley Scales of Infant Development Chinese Revision; BSQ-C = Behavior Style Questionnaire-Chinese version; CBLC = child behavior checklist; CHECK = Children's Health and Environmental Chemicals in Korea cohort; CI = confidence interval; CPSCS = California Preschool Social Competence Scale; Cr = creatinine; CSRS = Connors' Parent Rating Scales; CTTS = Chinese Toddler Temperament Scale; DEHP = di(2-ethylhexyl)phthalate; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; FTII = Fagan Test of Infant Intelligence; GIQ = Gender Identity Questionnaire; GM = geometric mean; INMA = Infancia y Medio Ambiente (Environment and Childhood) birth cohort; IQ = intelligence quotient; IQR = interquartile range; LOD = limit of detection; MCTQ-C = Middle Childhood Temperament Questionnaire-Chinese version; 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; MoBa = Norwegian Mother and Child Cohort; MOCEH = Prospective Mothers and Children's Environmental Health Cohort; MSCA = McCarthy Scales of Children's Abilities; NNNS = NICU Network Neurobehavioral Scale; OCC = Odense Child Cohort; PDI = Psychomotor Development Index; PPPSI = Playmate and Play Style Preferences Structured Interview; PSAI = preschool Activities Inventory; REPRO_PL = Polish Mother and Child Cohort; SDQ = Strengths and Difficulties Questionnaire; SG-adj = specific gravity adjusted; SMS = social maturity scale; SRS = Social Responsiveness Scale; VMWM = Virtual Morris Water Maze; WISC = Wechsler Intelligence Scale for Children; WWPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised

(Téllez-Rojo et al. 2013) and prenatal DEHP exposure. The affected sex differed between the studies with Kim et al. (2011) and Qian et al. (2019a, 2019b) reporting an association for male infants and Téllez-Rojo et al. (2013) observing an association only in female infants. A fourth study reported impaired language development in boys, but not girls, between 16 and 36 months of age with increased prenatal DEHP exposure (Olesen et al. 2018a, 2018b). Three studies (Kim et al. 2011; Polanska et al. 2014; Qian et al. 2019a, 2019b) reported associations between prenatal DEHP exposure and psychomotor development index in young children (6–26 months); two of the studies (Kim et al. 2011; Qian et al. 2019a, 2019b) observed the association in males only. Using a different assessment (BOT-2; Bruininks-Oseretsky Test of Motor Proficiency-2), no association between prenatal DEHP exposure and motor skills at age 11 was observed (Balalian et al. 2019; Daniel et al. 2020). However, motor skills at 11 years of age, particularly fine motor skills, were impaired in boys only with increased DEHP metabolites in children's urine collected at 3 or 7 years (Balalian et al. 2019; Daniel et al. 2020). Other birth cohort studies did not observe an association between maternal urinary DEHP metabolite levels and cognitive/mental or psychomotor abilities children assessed at ages ranging from 6 months to 11 years of age (Braun et al. 2017a, 2017b; Doherty et al. 2017; Factor-Litvak et al. 2014; Gascon et al. 2015b; Huang et al. 2015; Ipapo et al. 2017; Kim et al. 2018f; Whyatt et al. 2012).

The database for epidemiological studies of behavior and attention includes 13 studies of 9 birth cohorts (Table 2-14). Evaluations included various validated measures of overall behavioral development, social behavior (including screening for social impairments related to Autism Spectrum Disorder [ASD]), gender-related play, and measures of attentiveness (including screening for Attention Deficit Hyperactivity Disorder [ADHD]). In these cohorts, increases and decreases in a variety of behaviors have been associated with increased prenatal DEHP exposure; however, comparison across studies is complicated 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. Social Responsiveness Scale (SRS), which is a validated scale for measuring ASD-related behaviors, no association between social impairment and prenatal DEHP exposure was observed in children at ages 4–6 years (Braun et al. 2014) or 7–9 years (Miodovnik et al. 2011). Another study reported improved social competence in 4-year-olds with increasing prenatal DEHP exposure (Gascon et al. 2015a). Other studies examining potential relationships between DEHP exposure and ASD 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 included in Table 2-14 or considered useful for hazard identification.

Two cohort studies evaluated potential associations between gender-related play in children and maternal urinary DEHP metabolite levels (Percy et al. 2016; Swan et al. 2010). In a multicenter U.S. birth cohort (74 boys, 71 girls), prenatal maternal urinary metabolite levels were associated with reduced scores on the Pre-School Activities Inventory (PSAI), indicative of decreased masculine play activities, among 5-year-old boys (Swan et al. 2010). In contrast, another the U.S. birth cohort (101 boys, 126 girls) 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 at 8 years of age (Percy et al. 2016). Results from these studies are difficult to compare, primarily due to use of different metrics and different ages at analysis.

In 3–12-year-old children recruited in Taiwan after the phthalate-tainted food scandal in 2011, current urinary MEOHP levels were inversely associated with verbal comprehension in school-aged children; no association between current DEHP urinary levels and cognitive/mental and psychomotor development were observed in preschoolers (Huang et al. 2017). When past DEHP exposure was estimated (prior to 2011), no association with past exposure was observed.

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.

Increased anxiety in an open field was shown in CD-1 mouse offspring at 18 months of age following maternal exposure to ≥0.2 mg/kg/day from GD 11 until parturition (Barakat et al. 2018). However, the anxiety effects observed at the low dose are difficult to interpret because another measure of anxiety (elevated plus maze) did not show significant increases in anxiety in 18-month-old offspring until maternal doses of 750 mg/kg/day. At 16 months of age, mouse offspring also showed impaired recognition memory at maternal doses ≥500 mg/kg/day and impaired spatial memory at the maternal dose of 0.2 mg/kg/day (but not ≥500 mg/kg/day). No evidence of overall changes in activity levels were observed during these behavioral assessments (Barakat et al. 2018). Consistent with this study, no changes in object recognition and/or spontaneous locomotion were observed in mouse offspring exposed to a maternal dose of 33 mg/kg/day during gestation and lactation (Bastos Sales et al. 2018) or up to 95 mg/kg/day during gestation only (NTP 1988).

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). No changes in brain weight were observed in CD-1 mouse offspring at 22 months of age following maternal exposure to doses up to 750 mg/kg/day from GD 11 until parturition (Barakat et al. 2018). However, a significant decrease in the number of pyramidal neurons in the hippocampus was observed at maternal doses ≥0.2 mg/kg/day, and neurons were shrunken and loosely aligned with enlarged inter-neural space between neurons.

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. (2014a) 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. Tau hyperphosporylation of microtubule proteins was associated with reduced neurite outgrowth in mouse neuroblastoma cells *in vitro* (Wang et al. 2017b). 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 and adult rats following pre- or postnatal exposure to DEHP, including decreased axonal innervation, decreased cell density, decreased dendritic spine density, decreased dendritic length and branching, and reduced neurogenesis (Barakat et al. 2018; Smith and Holahan 2014; Smith et al. 2011; You et al. 2018). Structural changes in hippocampal pyramidal neurons following developmental exposure to DEHP were associated with decreases in microtubule-associated protein 2 (MAPc2) and stathmin, which are both key molecules for neural cytoskeleton synthesis (You et

al. 2018). Neuronal excitability and synaptic plasticity were also reduced in rat hippocampal slices incubated with DEHP via inhibition of the voltage-gated potassium channel (Ran et al. 2019).

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).

Neurodevelopmental effects of DEHP may be related to decreased thyroid hormone transfer across the placenta. DEHP was shown to disrupt thyroid hormone uptake in placental trophoblastic cells through mechanisms involving reduced expression and internalization of transthyretin (Du et al. 2020).

Observed DEHP-moderated alterations in oxidative stress and inflammatory pathways (Barakat et al. 2018; Ferguson et al. 2012, 2015, 2017; Wu et al. 2017) could potentially contribute to neurodevelopmental toxicity of DEHP. DEHP induced oxidative stress in cultured mouse neural stem cells, which was associated with cytotoxicity and apoptosis (Wu et al. 2019).

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, AGD, and penile size in infants and children and onset of puberty in adolescents (Table 2-15).

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

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Reproductive Development in Males

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Reproductive tract development				
Adibi et al. 2015; Barrett et al. 2016; Martino-Andrade et al. 2016; Swan et al. 2015 Cohort, 366 male newborns, AGD measured shortly after birth, United States (Minnesota, California, New York, Washington)	**Anopenile or anoscrotal distance**	**ΣDEHP**	GM (95% CI): 71.7 (65.6, 78.3) nmol/L	↓
		MEHP	GM (95% CI): 1.93 (1.76, 2.11) ng/mL	↓
		MEHHP	6.04 (5.49, 6.64)	↓
		MEOHP	4.22 (3.84, 4.63)	↓
		MECPP	8.12 (7.42, 8.89)	↔
		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, and between penile width and maternal urinary metabolites in the second trimester, but not first or third trimester.		
Arbuckle et al. 2019 Cohort, 147 male newborns, AGD measured at mean age 3.5 days, Canada	Anopenile or anoscrotal distance	ΣDEHP	Low stress: GM (95% CI): 56.3 (46.5, 68.1) nmol/L	↔
			High stress: 50.3 (41.6, 60.7)	↔
		MEHP	Low stress: 2.0 (1.6, 2.4) ng/mL	↔
			High stress: 1.9 (1.6, 2.3)	↔
		MEHHP	Low stress: 8.4 (6.9, 10.2)	↔
			High stress: 7.0 (5.7, 8.6)	↔
		MEOHP	Low stress: 5.7 (4.8, 6.9)	↔
			High stress: 5.1 (4.2, 6.2)	↔
	The low stress group consisted of women reporting no stressful life events (SLE) or reporting 1 SLE but classified it as not at all stressful during pregnancy. The high stress group consisted of women reporting ≥1 SLE as somewhat, moderately, or very much stressful.			

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Reproductive Development in Males

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Bornehag et al. 2015 Cohort, 196 male infants, AGD measured at mean age 20.8 months, Sweden	Anopenile or anoscrotal distance	ΣDEHP	IQR: 84.56–220.71 nmol/L	↔
		MEHP	IQR: 1.91–5.86 ng/mL	↔
		MEHHP	8.69–22.85	↔
		MEOHP	5.67–15.60	↔
		MECPP	8.00–22.50	↔
Bustamante-Montes et al. 2013 Cohort, 73 male infants, reproductive measurements 24–48 hours after birth, Mexico	Anoscrotal distance or distance from anus to anterior or posterior base of penis; penile width	MEHP	IQR: 0.4–19.5 ng/mL	↔
	Penile length	MEHP	See above	↓
Chevrier et al. 2012 Nested case-control, 21 cases of hypospadias, 50 cases of cryptorchidism, and (for each) 3:1 matched controls, France	Hypospadias or cryptorchidism	ΣDEHP	NR	↔
		MEHP	5^{th}–95^{th} percentile: 0.8–40.7 ng/mL	NR
		MEHHP	4.6–147.0	NR
		MEOHP	3.6–112.0	NR
		MECPP	11.6–183.0	NR
Jensen et al. 2016 Cohort, 273 male infants, reproductive measurements at age 3 months, Denmark	Anopenile or anoscrotal distance, penile width	ΣDEHP	Molar sum: 11.4–36.1 ng/mL	↔

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Reproductive Development in Males

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Sathyanarayana et al. 2016a Cohort, 371 males, genital anatomical anomalies evaluated during physical exam at birth, United States (Minnesota, California, New York, Washington)	**Genital anomaly or hydrocele**	**ΣDEHP**	IQR: 14.86–38.80 nmol/L (SG-adj)	↑
		MEHP	IQR: 1.28–3.63 ng/mL (SG-adj)	↑
		MEHHP	3.76–11.24	↑
		MEOHP	2.54–7.25	↑
		MECPP	6.42–16.21	↔
	Hypospadias or cryptorchidism	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Swan 2008 Cohort, 106 male infants, reproductive measurements at age 12.8 months, United States (Minnesota, Missouri, California) **Swan et al. 2005** reported previous analysis of this cohort (smaller n)	**Distance from anus to cephalad base of penis**	**MEHP**	Short AGD: Median 6.2 ng/mL Intermediate AGD: 2.9 Long AGD: 2.3	↓
		MEHHP	Short AGD: 19.8 Intermediate AGD: 10.0 Long AGD: 8.2	↓
		MEOHP	Short AGD: 21.3 Intermediate AGD: 11.7 Long AGD: 7.3	↓
	Probability of normal testicular descent	ΣDEHP, MEHHP, or MEOHP	NR	↔
		MEHP	See above	↓
	Penile width	ΣDEHP, MEHHP, or MEOHP	NR	↔
		MEHP	See above	↓
	Penile length	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Reproductive Development in Males

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Suzuki et al. 2012 Cohort, 111 male infants, AGD measured at birth, Japan	**Distance from anus to anterior genitalia**	**ΣDEHP**	IQR: 23.20–74.70 ng/mL	↓
Wenzel et al. 2018 Cohort, 171 male newborns, AGD measured within 48 hours of birth, United States (South Carolina)	**Anopenile distance**	ΣDEHP	IQR: 36.3–92.8 nmol/L (SG-adj)	↔
		MEHP	IQR: 1.7–5.3 ng/mL (SG-adj)	↓
		MEHHP	4.5–12.2	↔
		MEOHP	3.8–9.0	↔
	Anoscrotal distance	ΣDEHP, MEHP, MEHHP, or MEOHP	See above	↔
Timing of puberty				
Berger et al. 2018 Cohort, 159 adolescent boys (including 55 normal weight boys and 89 overweight/obese boys), reproductive development assessed every 9 months from age 9–13 years, United States (California)	**Age at genital or pubic hair development (overweight/obese boys)**	**ΣDEHP**	NR	↓
		MEHP	IQR: 2.6–7.6 ng/mL (SG-adj)	NR
		MEHHP	10.9–32.1	NR
		MEOHP	7.7–21.4	NR
		MECPP	20.7–47.0	NR
	Age at genital or pubic hair development (all boys or normal weight boys)	ΣDEHP	See above	↔
Cathey et al. 2020a, 2020b Cohort, 91 adolescent boys, reproductive development evaluated at age 8–14 years (visit 1) and age 9–18 years (visit 2), Mexico	Genital or pubic hair development or Testicular volume	ΣDEHP	NR	↔
		MEHP	GM: 6.18 (SG-adj)	↔
		MEHHP	21.2	↔
		MEOHP	12.2	↔
		MECPP	37.0	↔
	Units were not reported for the GM urinary concentrations.			

Table 2-15. Summary of Epidemiological Studies of Prenatal DEHP Exposure and Reproductive Development in Males

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Ferguson et al. 2014a, 2014d Cohort, 110 adolescent boys, reproductive development evaluated at age 8–14 years, Mexico	**Pubic hair development**	MEHP	IQR: 2.97–9.91 ng/mL	↔
		MEHHP	12.1–37.5	↓
		MEOHP	7.55–21.5	↔
		MECPP	23.4–54.4	↔
	Genital development or Testicular volume	MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Su et al. 2015 Cohort, 59 adolescent boys, testicular volume evaluated at age 8 and 11 years, Taiwan	Testicular volume	ΣDEHP	Mean (SD): 0.94 (2.12) µg/g Cr	↔
		MEHP	0.30 (0.68)	↔
		MEHHP	0.38 (1.03)	↔
		MEOHP	0.25 (0.53)	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; AGD = anogenital distance; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; IQR = interquartile range; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NR = not reported; SD = standard deviation; SG-adj = specific gravity adjusted

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. (2016a) 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.

Twelve epidemiological studies have investigated the association between reduced AGD in male infants and prenatal DEHP exposure in eight different birth cohorts at various ages between birth and 2 years of age. Associations between 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 three of the four remaining cohorts (Bornehag et al. 2015; Bustamante-Montes et al. 2013; Jensen et al. 2016) were suggestive of 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. No association between AGD at 3.5 days of age and prenatal DEHP exposure was observed in a Canadian birth cohort (Arbuckle et al. 2019).

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. American cohorts reported negative associations between penile width in newborns and 2nd trimester (but not 1st or 3rd trimester) maternal DEHP urinary metabolites (Martino-Andrade et al. 2016) and 1-year-old boys and maternal urinary MEHP levels (Swan 2008). However, no association between penile width

and maternal DEHP metabolites was observed in Mexican newborns (Bustamante-Montes et al. 2013) or Danish infants 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; however, this association was not observed the cohort evaluated by Swan (2008).

Four studies examined the relationship between timing of puberty in boys and maternal DEHP exposure. One cohort of 8–14-year-old boys observed a decreased odds of pubic hair development with increased maternal MEHHP urinary levels (but not other metabolites); no associations were observed for genital development or testicular volume (Ferguson et al. 2014a). No associations between pubic hair development, genital development, and/or testicular volume in boys ages 8–18 years of age were observed in the other cohorts (Berger et al. 2018; Cathey et al. 2020a; Su et al. 2015). However, Berger et al. (2018) observed a decrease in the mean age at pubic hair development with increased prenatal DEHP exposure specifically in overweight or obese boys.

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. In another cross-sectional study, urinary DEHP metabolite levels in Taiwanese boys <12 years of age were not associated with serum testosterone (total or free), FSH, LH, or estradiol and urinary DEHP metabolite levels, but a negative association was observed between SHBG and urinary MEHP levels (but not other metabolites) (Wen et al. 2017). Cross-sectional studies were not included in Table 2-15; no other data on serum reproductive hormone levels 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 2–4-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). Another gestation plus lactation exposure study in Wistar rats did not observe hypospadias until 700 mg/kg/day (Venturelli et al. 2019).

In Long-Evans rats, testicular lesions were also observed at maternal doses ≥3 mg/kg/day in offspring exposed to DEHP during gestation and lactation (Arcadi et al. 1998). In Sprague-Dawley rat offspring exposed via maternal doses of 300 mg/kg/day from GD 8 to PND 21, abnormal findings included increased multinucleated gonocytes at PND 3 and increased incidences of hemorrhagic testes at PND 8 (Nardelli et al. 2017). These findings were not observed at ≤30 mg/kg/day, and nipple retention (another demasculinization endpoint) was not observed at doses up to 300 mg/kg/day. In another study 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). No change in testes histology was observed in male rat offspring at PND 3, 90, or 120 following maternal exposure to doses up to 10 mg/kg/day from GD 14 through parturition (Walker et al. 2020). Abdel-Maksoud et al. (2019) qualitatively reported histopathological changes in Long-Evans rat offspring at PND 35 after maternal exposure to 0.05 mg/kg/day on GDs 12–21, including focal germ cell loss, sloughing of germ cells, and diffuse interstitial cell hyperplasia. However, due to lack of quantitative data, these findings cannot be independently reviewed for NOAEL/LOAEL determination. Therefore, it is not included in the LSE table.

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. Similarly, in CD-1 mice exposed from GD 11 until PND 0, no external malformations at birth or histopathological changes in the testes of epididymides at PND 21 or 60 were observed at maternal doses up to 750 mg/kg/day (Barakat et al. 2017). When male offspring were evaluated at 22 months of age, histopathological changes, including hypospermatogenesis, germ cell degeneration, fewer developing spermatids, abnormal residual bodies in the lumen, and presence of epididymal vacuoles and germ cells in lumen of epididymis, were observed in surviving mice at ≥0.2 mg/kg/day. These effects were not evaluated at the low dose (0.02 mg/kg/day), because all low-dose mice died prior to 22 months of age (the cause of death was undetermined, but was unlikely to be related to treatment due to survival in higher dose groups). Due to premature death of all low-dose animals, a reliable NOAEL/LOAEL could not be established for this study. Therefore, Barakat et al. (2017) is not included in the LSE table.

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). However, in GD 18.5 C57Bl/6 × B6129S4 mouse offspring, no changes in the number of germ cells were observed following maternal exposure to doses up to 250 mg/kg/day from GD 7 to 16 (Ungewitter et al. 2017).

Alterations in male reproductive organ histology have also been reported in neonatal 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). Altered morphology of germ cells (mitotic alterations in gonocytes and/or enlarged and multinucleated gonocytes) were observed in male Sprague-Dawley rats following exposure to ≥100 mg/kg/day on PND 3 or ≥60 mg/kg/day from PND 3 to 7; reduced Sertoli cell proliferation and apoptosis observed at ≥100 mg/kg/day (Camacho et al. 2020; Li et al. 2000). With exposure on PNDs 3–23, decreased seminiferous tubule diameter was observed at ≥60 mg/kg/day with decreased testicular area and increased severity of germinal cell depletion and Sertoli cell vacuolization at ≥300 mg/kg/day (Camacho et al. 2020).

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. Similarly, decreased thickness and vacuolization of the seminiferous epithelium were observed in weanling Sprague-Dawley rats exposed to ≥150 mg/kg/day from PND 22 to 35; this progressed to severe vacuolization and lack of spermatids in tubules at 450 mg/kg/day (Zhang et al. 2018a). Noriega et al. (2009) also reported hypospermia and testicular and epididymal degeneration in weanling Sprague-Dawley rats at exposure levels ≥300 mg/kg/day, but 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).

One study reported a variety of histopathological changes in the testes and epididymides in Wistar rats exposed to very low doses of ≥0.0005 mg/kg/day starting at weaning (PND 21) through PND 120 (Oudir et al. 2018). Observed histopathological effects at PND 120 included decreased spermatozoa in testes and increased oligospermia and scattered cellular dispersion in epididymides at ≥0.0005 mg/kg/day. These effects did not show clear dose-response relationships at the lower doses; for example, spermatozoa were found in 80, <50, 60, and <25% of seminiferous tubules in control through high dose animals, and severe oligospermia was found in 2/10 animals in each of the 0.0005 and 5 mg/kg/day groups but not in any animals at 0.05 mg/kg/day. Similarly, sperm counts were significantly decreased by approximately 41 and 46% (compared to control) at 0.0005 and 5 mg/kg/day, respectively, but not at 0.05 mg/kg/day. Leydig cell number was significantly increased at 0.05 mg/kg/day, but not changed in other groups. Sertoli cell counts were decreased by 22 and 42% at 0.05 and 5 mg/kg/day, respectively. None of the developmental studies discussed above evaluated doses as low as the ones evaluated by Oudir et al. (2018), and several reported similar effects only at higher doses. For example, Parmar et al. (1995) did not observe any testicular germ cell changes in Wistar rats exposed on PNDs 25–54 to doses as high as of 100 mg/kg/day. Additionally, Hsu et al. (2016) did not observe sperm effects in Sprague-Dawley rats at a dose of 0.03 mg/kg/day following exposure from PND 42 to 105 (see Section 2.16 for more details). Based on the poor evidence for a dose-response relationship at low doses and lack of corroborating findings of male reproductive effects following exposure to very low DEHP exposures, this study (Oudir et al. 2018) is not included in the LSE table.

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/or 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; Nardelli et al. 2017; Walker et al. 2020), 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). With 5- or 21-day postnatal

exposure beginning on PND 3, decreased testes weights were observed in Sprague-Dawley rats at ≥60 mg/kg/day (Camacho et al. 2020).

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 500–700 mg/kg/day in others (Dalsenter et al. 200; Venturelli et al. 2019). 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) or in PND 92 Wistar rats following lactation exposure to doses up to 75 mg/kg/day (Venturelli et al. 2015).

Three 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 in one study 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 in some studies. There was a decrease in ventral prostate weight observed in the offspring of rats and mice exposed to DEHP during gestation and lactation at ≥10 mg/kg/day (Christiansen et al. 2010). Dalsenter et al. (2006) and Gray et al. (2009) also observed decreased ventral prostate as well as seminal vesicle weights in rats at 500 and 300 mg/kg/day, respectively. An additional study reported decreased seminal vesicle weights at low exposure levels ≥0.05 mg/kg/day (Pocar et al. 2012). Decreased LABC muscles weights were observed in two studies following maternal exposure to ≥10 mg/kg/day (Christiansen et al. 2010) and 300 mg/kg/day (Gray et al. 2009). Gray et al. (2009) also reported decreased weights of the glans penis, Cowper's glands, and epididymides at 300 mg/kg/day. Epididymal weights were also reportedly decreased at ≥0.1 mg/kg/day in a study by Wang et al. (2017a).

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, Nardelli et al. 2017). Similarly, there were no male reproductive organ changes 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). In other studies in Wistar rats, no changes in male reproductive organs were

observed at PNDs 90–92 following lactation exposure to doses up to 75 mg/kg/day or gestation plus lactation exposure up to 700 mg/kg/day (Venturelli et al. 2015, 2019).

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; Zhang et al. 2018a). 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). Yet 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). In young Wistar rats, changes in the weights of the seminal vesicles, ventral prostate, epididymis, or testes were not observed following exposure to doses up to 75 mg/kg/day for 30 days post-weaning (Venturelli et al. 2015).

Decreased AGD, suggesting demasculinization, has been reported in male rat offspring following gestational and/or lactational 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 (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 (Lin et al. 2009). In Sprague-Dawley rats, AGD and or and the anogenital index (AGI; corrected for body weight) were significantly decreased at PNDs 2–3 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; Nardelli et al. 2017). Decreased AGD was also observed in PND 63 male offspring of Sprague-Dawley rat dams exposed to DEHP from GD 11 to 21 at ≥100 mg/kg/day. No changes in AGD were observed in PND 3 or 120 male offspring of Sprague-Dawley rat dams exposed to doses up to 10 mg/kg/day from GD 10 until parturition (Walker et al. 2020). Gestation/lactation exposure studies in Wistar rats reported decreased AGD at PND 1 at doses ≥10 mg/kg/day (Christiansen et al. 2010) and decreased AGI at PND 4 at 700 mg/kg/day (Venturelli et al. 2019).

Multigeneration studies have equivocal results for AGD and AGI. In a 2-generation study in Wistar rats, both AGD and AGI were significantly decreased on PND 1 or 2 in both F1 and F2 males at doses

≥340 mg/kg/day (Schilling et al. 2001). These findings were not observed until doses of 1,040 mg/kg/day in an earlier study by the same group (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).

Studies in mice generally do not show changes in AGD or AGI. One study reported decreased AGD 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 mouse offspring following gestational exposure up to 500 mg/kg/day (Do et al. 2012), or gestation plus lactation exposure to doses up to 5 mg/kg/day (Pocar et al. 2012). In C57BL/6J × FVB offspring, no exposure-related changes in AGD were observed following maternal exposure to doses up to 100 mg/kg/day from 2 weeks premating through lactation (Bastos Sales et al. 2018). In C57BL/6J × B6129S4 offspring, there was a significant increase, as opposed to a decrease, in AGI at GD 18.5 following gestational exposure to 250 mg/kg/day (Ungewitter et al. 2017).

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). PPS was also significantly delayed in male offspring of Wistar rats exposed to 700 mg/kg/day from GD 13 to PND 21, despite transient increases in body weight during lactation and early postweaning periods (Venturelli et al. 2019). 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 rat offspring following maternal exposure to doses up to 500 mg/kg/day during gestation and/or lactation (Dalsenter et al. 2006; Gray et al. 2009; Nardelli et al. 2017; Venturelli et al. 2015), direct exposure to doses up to 150 mg/kg/day on PNDs 6–96 (Kim et al. 2018c), or direct exposure to doses up to 75 mg/kg/day on PNDs 22–52 (Venturelli et al. 2015). A subset of the offspring also received direct DEHP exposure on PNDs 18–64; 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). No changes in male fertility were observed in offspring of female Sprague-Dawley rats exposed to doses up to 10 mg/kg/day from GD 14 though parturition (Walker et al. 2020). 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 (NTP 1988).

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.

Another study with gestation-only exposure reported an increase in the percentage of abnormal sperm in 22-month-old CD-1 mouse offspring at ≥0.2 mg/kg/day, including sperm head, neck, and midpiece, and tail abnormalities (Barakat et al. 2017). At the highest dose (750 mg/kg/day), sperm concentration and motility were reduced by approximately 45 and 35%, respectively. Fertility was also significantly reduced by 61% at 750 mg/kg/day when evaluated at 19 months of age, but not 4, 5, or 7 months of age, suggesting early senescence at this dose. However, since all low-dose (0.02 mg/kg/day) mice died prior to study termination, a reliable NOAEL/LOAEL cannot be established. Therefore, this study is not included in the LSE table.

In a study with a non-traditional design, male reproductive effects in third-generation (F3) CD-1 offspring were evaluated following exposure 0.02 or 0.2 mg/kg/day in F0 dams only from GD 11 until parturition (no direct exposure to F1, F2, or F3 mice) (Barakat et al. 2020). Fertility percentage was significantly decreased by 33% in paternal lineage F3 males in the 0.02 mg/kg/day group; however, fertility was comparable to control at 0.2 mg/kg/day in the paternal lineage and at both doses in the maternal lineage. Decreased fertility only at the low dose in the paternal lineage is difficult to interpret, as is decreased severity of other observed reproductive effects in paternal lineage males at the high dose, compared to the low dose, including decreased serum testosterone, sperm effects, and testicular lesions. Maternal lineage F3 offspring showed normal fertility, but decreased serum testosterone and sperm concentration were observed at 0.02 mg/kg/day and germ cell degeneration was observed at 0.2 mg/kg/day. Based on low animal number (n=4/dose), lack of clear dose-response, and evaluation only in F3 animals (following exposure in F0 generation only), this study is not included in the LSE table.

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). Using the same exposure parameters, Walker et al. (2020) did not observe changes in serum testosterone at PND 3, 90, or 120 at doses up to 10 mg/kg/day. 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 mg/kg/day, respectively (Dalsenter et al. 2006; Lin et al. 2009; Rajagopal et al. 2019a).

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) or at PND 3, 90, or 120 male offspring at maternal doses up to 10 mg/kg/day (Walker et al. 2020). However, a significant >30% decrease in serum estradiol in adult male Wistar rat offspring rats at maternal doses ≥10 mg/kg/day was reported by Rajagopal et al. (2019a).

In other studies, no exposure-related changes in serum testosterone, estradiol, FSH, or LH were observed in weanling and/or adult male offspring following maternal exposure to doses up to 300 mg/kg/day during gestation and lactation in Sprague-Dawley rats (Gray et al. 2009; Nardelli et al. 2017). 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).

In a gestation-only exposure study in CD-1 mice, serum testosterone levels at PND 21 were similar between the groups; however, at 16 months, testosterone levels significantly decreased by approximately 97, 85, 66, and 63% in mice at 0.02, 0.2, 500, and 750 mg/kg/day DEHP, respectively, compared to control (Barakat et al. 2017). The significance of this non-dose-related response is unclear without further study of the pituitary-testes axis; therefore, this study is not included in the LSE table. When evaluated in similarly exposed CD-1 mouse offspring at 22 months, testosterone levels were significantly decreased by 82 and 72% at 500 and 750 mg/kg/day, respectively; findings were not significant at 0.2 mg/kg/day (Barakat et al. 2018). Other reproductive hormones were also altered in aged offspring, included increased serum estradiol at 16 months at 750 mg/kg/day and increased serum LH concentrations at 22 months at ≥500 mg/kg/day (Barakat et al. 2017). Low-dose mice (0.02 mg/kg/day) were not examined at 22 months due to premature death of all animals.

Alterations in male reproductive hormones following post-weaning exposure to DEHP 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). 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 (Akingbemi et al. 2001). No changes in serum hormone levels were observed at doses up to 200 mg/kg/day using the same exposure paradigms (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) or GD 18.5 fetuses of C57Bl/6 × B6129S4 mouse offspring following maternal exposure to doses up to 250 mg/kg/day from GD 7 to 16 (Ungewitter et al. 2017).

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. Several studies suggest that oxidative stress and inflammatory processes (i.e., macrophage infiltration and cytokine production) play a role in testicular toxicity induced by DEHP or MEHP in neonatal or prepubertal rats (Stermer et al. 2017; Tang et al. 2019; Voss et al. 2018; Zhang et al. 2017, 2020e).

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 Jégou 2014; Arzuaga et al. 2019; Dorman et al. 2018; NAS 2017). Prenatal exposure to DEHP also altered the expression of genes related to sexual differentiation in the epididymis (AR, ER, Wnt4, β-catenin, MAPK, HOXD4) (Abdel-Maksoud et al. 2018). 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 Jégou 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 three pregnancy cohorts (Adibi et al. 2015; Arbuckle et al. 2019; 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 any cohort (Table 2-16).

Table 2-16. Summary of Epidemiological Studies of DEHP Exposure and Reproductive Development in Females

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Reproductive tract development				
Adibi et al. 2015; Barrett et al. 2016; Swan et al. 2015 Cohort, 373 female newborns, AGD measured shortly after birth, United States (Minnesota, California, New York, Washington)	Anoclitoral or anofourchette distance	ΣDEHP	Maternal GM (95% CI): 71.7 (65.6, 78.3) nmol/L	↔
		MEHP	GM (95% CI): 1.93 (1.76, 2.11) ng/mL	↔
		MEHHP	6.04 (5.49, 6.64)	↔
		MEOHP	4.22 (3.84, 4.63)	↔
		MECPP	8.12 (7.42, 8.89)	↔
Arbuckle et al. 2019 Cohort, 153 female newborns, AGD measured at mean age 3.5 days, Canada	Anoclitoris or anofourchette distance	ΣDEHP	Maternal: Low stress: GM (95% CI): 56.3 (46.5, 68.1) nmol/L	↔
			High stress: 50.3 (41.6, 60.7)	↔
		MEHP	Low stress: 2.0 (1.6, 2.4) ng/mL	↔
			High stress: 1.9 (1.6, 2.3)	↔
		MEHHP	Low stress: 8.4 (6.9, 10.2)	↔
			High stress: 7.0 (5.7, 8.6)	↔
		MEOHP	Low stress: 5.7 (4.8, 6.9)	↔
			High stress: 5.1 (4.2, 6.2)	↔
	The low stress group consisted of women reporting no stressful life events (SLE) or reporting 1 SLE but classified it as not at all stressful during pregnancy. The high stress group consisted of women reporting ≥1 SLE as somewhat, moderately, or very much stressful.			
Wenzel et al. 2018 Cohort, 128 female newborns, AGD measured within 48 hours of birth, United States (South Carolina)	Anoclitoral or anofourchette distance	ΣDEHP	Maternal IQR: 36.3–92.8 nmol/L (SG-adj)	↔
		MEHP	IQR: 1.7–5.3 ng/mL (SG-adj)	↔
		MEHHP	4.5–12.2	↔
		MEOHP	3.8–9.0	↔

Table 2-16. Summary of Epidemiological Studies of DEHP Exposure and Reproductive Development in Females

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Timing of puberty				
Berger et al. 2018 Cohort, 165 adolescent girls (including 84 normal weight and 81 overweight/obese girls), reproductive development assessed every 9 months from age 9 to 13 years, United States (California)	**Age at breast development or menarche (all, normal weight, or overweight/obese)**	**ΣDEHP**	NR	↑
		MEHP	Maternal IQR: 2.6–7.6 ng/mL (SG-adj)	NR
		MEHHP	10.9–32.1	NR
		MEOHP	7.7–21.4	NR
		MECPP	20.7–47.0	NR
	Age at pubic hair development (all, normal weight, or overweight/obese)	ΣDEHP	See above	↔
Binder et al. 2018a, 2018b Cohort, 200 adolescent girls, urine collected at Tanner Stage B1 (median age 7.9 years) and Tanner Stage B4 (median age 11.2 years), assessed for menarche every 6 months prior to reaching Tanner stage B4 and every 3 months after reaching Tanner stage B4, Chile	**Late menarche**	**ΣDEHP**	**Child (Tanner Stage B1):** NR	↑
			Child (Tanner Stage B4): NR	↔
		MEHP	**B1**: GM (95% CI): 2.38 (2.13, 2.65) ng/mL (SG-adj)	↑
			B4: 2.23 (1.98, 2.52)	↔
		MEHHP	**B1:** 24.71 (22.22, 27.48)	↑
			B4: 17.33 (15.43, 19.47)	↔
		MEOHP	**B1:** 15.05 (13.56, 16.70)	↑
			B4: 11.21 (10.00, 12.56)	↔
		MECPP	B1: 50.60 (45.91, 55.78)	↔
			B4: 36.00 (32.39, 40.01)	↔

Table 2-16. Summary of Epidemiological Studies of DEHP Exposure and Reproductive Development in Females

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Cathey et al. 2020a, 2020b Cohort, 103 adolescent girls, assessed for reproductive development at age 8–14 years (visit 1) and age 9–18 years (visit 2), Mexico	**Initial breast development (visit 1)**	**ΣDEHP**	NR	↑
		MEHP	Maternal GM: 6.38 (SG-adj)	↔
		MEHHP	23.3	↑
		MEOHP	13.7	↑
		MECPP	41.0	↑
	Progression of breast development (from visit 1 to 2)	ΣDEHP MEHP, MECPP, or MEHHP	See above	↔
		MEOHP	See above	↓
	Pubic hair development or menarche	ΣDEHP, MEHP, MEHHP, MEOHP, or MECPP	See above	↔
	Units were not reported for the GM urinary concentrations.			
Watkins et al. 2014 Cohort, 116 adolescent girls, assessed for reproductive development at age 8–13 years, Mexico	**Pubic hair development**	**MEHP**	Maternal IQR 2.52–9.50 ng/mL	↑
		MEHHP	9.13–37.5	↔
		MEOHP	5.80–24.7	↔
		MECPP	15.1–58.1	↔
	Breast development or menarche	MEHP, MEHHP, MEOHP, MECPP	See above	↔
Wolff et al. 2014 Cohort, 1239 adolescent girls (including 834 normal weight and 405 overweight girls), assessed for reproductive development for 7 years after initial urine collection at age 6–8 years, United States (New York, Ohio, California)	**Pubic hair development (all girls)**	**ΣDEHP**	Child: Interquintile range: 59–510 µg/g Cr	↓
		MEHP	NR	↓
		MEHHP	NR	↓
		MEOHP	NR	↓
		MECPP	NR	↔
	Pubic hair development (normal weight girls)	**ΣDEHP**	See above	↓

Table 2-16. Summary of Epidemiological Studies of DEHP Exposure and Reproductive Development in Females

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
	Pubic hair development (overweight girls)	ΣDEHP	See above	↔
	Breast development or menarche	ΣDEHP, MEHP, MEHHP, MEOHP, MECPP	See above	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; AGD = anogenital distance; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; IQR = interquartile range; MECPP = mono-2-ethyl-5-carboxypentylphthalate; MEHHP = mono-2-ethyl-5-hydroxyhexylphthalate; MEHP = mono(2-ethylhexyl)phthalate; MEOHP = mono-(2-ethyl-5-oxohexyl)phthalate; NR = not reported; SG-adj = specific gravity adjusted

The timing of puberty has been examined in four studies using urinary biomarkers of DEHP exposure measured prior to outcome evaluation (e.g., maternal or prepubertal child); results were mixed (Table 2-16). One cohort study reports a delay in breast development in adolescent girls associated with increased prenatal DEHP exposure (Berger et al. 2018), while another reports increased initial breast development but delayed progression of breast development in association with increased prenatal DEHP exposure (Cathey et al. 2020a). In other cohorts, no association was observed between breast development and maternal (Watkins et al. 2014) or prepubertal (Wolff et al. 2014) urinary DEHP metabolite levels. Similarly, increased prenatal DEHP exposure was associated with early pubic hair development in one cohort (Watkins et al. 2014), but not others (Cathey et al. 2020a; Berger et al. 2018). Delayed pubic hair development was associated with increased prepubertal DEHP exposure, particularly in normal weight girls (Wolff et al. 2014). Two studies report an association between prenatal DEHP exposure and increased age at first menarche (Berger et al. 2018); two others did not observe this association (Cathey et al. 2020a; Watkins et al. 2014). Onset of menarche was not associated with prepubertal DEHP exposure (Wolff et al. 2014).

In a cross-sectional study in Taiwanese girls <12 years of age, a positive association between serum FSH and maternal MEEHP and MEOHP levels was observed (Wen et al. 2017). No association was observed for serum testosterone (total or free), LH, estradiol, or SHBG. Cross-sectional studies were not included in Table 2-16; no other data on serum reproductive hormone levels in prepubertal girls were located.

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, changes in female AGD or AGI at PNDs 21–22 were not observed following gestational and lactational exposure to doses up to 405 mg/kg/day (Grande et al. 2006; Nardelli et al. 2017). 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). Similarly, no exposure-related changes in female AGI were observed in offspring of Wistar rats exposed to doses up to 700 mg/kg/day from GD 13 to PND 21 (Venturelli et al. 2019). 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, the percent of littermates with complete vaginal opening on PND 38 was significantly decreased in female offspring of Sprague-Dawley rats exposed to 300 mg/kg/day from GD 8 to PND 21 in the absence of decreased body weight (Nardelli et al. 2017). Similarly, 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 Wistar rats, vaginal opening was significantly delayed by 3 to 7 days in female offspring (n=31–32/group) following maternal exposure to ≥70 mg/kg/day from GD 13 to PND 21 despite transient elevations in post-weaning offspring body weights (Venturelli et al. 2019). No change in the timing of vaginal opening was observed in Sprague-Dawley rats (n=9–10/group) following direct exposure to doses up to 150 mg/kg/day on PNDs 6–96 (Kim et al. 2018c). The observed differences in vaginal opening may be due to rat strain differences, timing of DEHP exposure, and/or number of animals per dose group.

In contrast, accelerated vaginal opening was observed in Wistar rats following direct exposure to 5 mg/kg/day on PNDs 15–43 (Shao et al. 2019) or 1,000 mg/kg/day on PNDs 22–49 (Liu et al. 2018a). Rats exposed from PND 22 to 49 also showed prolonged estrous and various changes in serum hormone levels (increased progesterone and decreased FSH, LH, and testosterone) at ≥500 mg/kg/day (Liu et al. 2018a). The study authors proposed that precocious puberty was due to early activation of the hypothalamus-pituitary-ovarian axis, as evidenced by elevated serum and/or hypothalamic hormone levels (e.g., growth hormone, gonadotropin-releasing hormone, insulin-like growth factor 1) following exposure to ≥1 mg/kg/day on PNDs 15–43 (Shao et al. 2019) or ≥250 mg/kg/day on PNDs 22–49 (Liu et

al. 2018a). Additional support for early activation of the hypothalamus-pituitary-ovarian axis includes decreased apoptosis and increased neuronal activation in the hypothalamus following exposure to ≥0.2 and 5 mg/kg/day, respectively, on PNDs 15–43 (Shao et al. 2019). Yu et al. (2020) propose that low and high doses of DEHP have a differential effect on the hypothalamus-pituitary-ovarian axis. In support, accelerated vaginal opening and prolonged estrous were observed following exposure to 5 mg/kg/day on PNDs 22–70, but delayed vaginal opening was observed at 500 mg/kg/day. These findings were associated with opposing changes in the hypothalamic kisspeptin system at the low versus high dose. Due to non-monotonic findings, the study by Yu et al. (2020) is not included in the LSE table.

In adult female offspring exposed to DEHP from GD 6 to PND 21, 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). Similarly, no exposure-related changes in serum hormone levels or reproductive organ weight were observed in rat offspring following maternal exposure to doses up to 700 mg/kg/day during gestation and lactation (Nardelli et al. 2017; Venturelli et al. 2019). 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 series of studies with a non-traditional design, female reproductive effects in F1, F2, and/or F3 generation CD-1 offspring were evaluated following exposure to dose ranging from 0.02 to 750 mg/kg/day in F0 dams only from GD 11 until parturition from GD 0.05 to PND 21 (no direct exposure to F1, F2, or F3 mice) (Brehm et al. 2018; Rattan et al. 2017, 2018). Study authors conclude in all studies that there is evidence that DEHP causes generational reproductive effects in females; however, the conclusions are based on numerous non-dose related changes in organ weight, folliculogenesis, estrous cyclicity, and reproductive hormone levels with little concordance between generations and studies. One study (Rattan et al. 2018) reported reduced fertility in F1 offspring at 0.2 mg/kg/day, but not higher doses up to 750 mg/kg/day. A study with a similar design by Pocar et al. (2017) exposed F0 CD-1 mouse dams to DEHP from GD 0.05 to PND 21 and evaluated female reproductive endpoints in F1, F2, and F3 offspring (no direct exposure in F2 or F3 offspring, and F1 exposure only via dam). Fertility was not impacted in any generation, and observed ovarian effects lacked clear dose dependence (e.g., reduced oocyte quality and embryonic developmental competence in all 3 generations at 0.05 mg/kg/day but not 5 mg/kg/day). These findings are consistent with those seen in other studies with similar design. None of the studies provide potential rationales, supporting evidence, or proposed mechanisms of action to explain a non-monotonic dose response. Based on lack of clearly adverse, dose-related findings, these studies were not included in the LSE table.

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. 2015b; Zhang et al. 2013, 2015, 2018c). In addition to interaction with ERs (Cavanagh et al. 2018; Mu et al. 2015b; 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. 2015b). 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 impaired meiotic progression and repair of DNA damage in fetal mouse oocytes and altered the expression of genes related to apoptosis, gonad development, cell-cell communication, signal transduction, and plasma membrane, extracellular matrix, and ion channel functional classes (Liu et al. 2017).

DEHP may cause heritable epigenetic alterations in germ cells, which may contribute to altered ovarian development (Li et al. 2014; Rattan et al. 2019; Zhang et al. 2013, 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). Rattan et al. (2019) demonstrated a transgenerational (through the F3 generation) reduction in the expression of ovarian pathways required for folliculogenesis and steroidogenesis following prenatal exposure in mice (exposed from GD 10.5 through birth; gene expression measured on PND 21).

Animal Studies—Other Noncancer (Metabolic Syndrome and Glucose/Insulin Homeostasis). Metabolic syndrome and/or altered glucose homeostasis has been observed in rats and mice following developmental exposure to DEHP during gestation, gestation plus lactation, or lactation.

Adult offspring of Wistar rats exposed to DEHP at doses ≥1 mg/kg/day (lowest dose tested) during gestation 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 Balasubramanian 2014). Similarly, adult male offspring of Wistar rats exposed to DEHP at doses ≥10 mg/kg/day (lowest dose tested; female offspring not assessed) during gestation and lactation also showed alterations in glucose homeostasis, including a 36–71% increase in fasting blood glucose, a 100–152% increase in fasting serum insulin, elevated serum glucose levels in both the glucose and insulin tolerance tests, and increased insulin resistance (Rajagopal et al. 2019a). Lactation-only exposure to

DEHP also resulted in altered glucose homeostasis in adult Wistar rat offspring at maternal doses ≥1 mg/kg/day (Mangala Priya et al. 2014; Venturelli et al. 2015). Observed effects included elevated fasting blood glucose, decreased insulin sensitivity, and decreased *ex vivo* insulin secretion by isolated pancreatic islet cells. In contrast, evidence of altered glucose homeostasis in adult Wistar rat offspring following gestation plus lactation exposure was not observed until much higher maternal doses of DEHP (Venturelli et al. 2019). Observed effects included decreased *ex vivo* insulin secretion by isolated pancreatic islet cells at ≥70 mg/kg/day and elevated fasting blood glucose levels at 700 mg/kg/day. Elevated fasting blood glucose was also observed in male PND 22 Wistar rat offspring (female offspring were not assessed) following lactation-only exposure to DEHP at a maternal dose of 100 mg/kg/day, but not ≤10 mg/kg/day (Parsanathan et al. 2019). With early postweaning exposure on PNDs 22–52, elevated fasting blood glucose was observed in PND 53 male Wistar rats at 75 mg/kg/day, but not 7.5 mg/kg/day (Venturelli et al. 2015).

Altered glucose homeostasis, along with pancreatic dysfunction, was also observed in weanling and adult offspring of Wistar rats following maternal exposure to doses ≥1.25 mg/kg/day during gestation and lactation (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. 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.

Evidence of metabolic syndrome has been reported in mice following gestational exposure to DEHP. In ICR mouse offspring exposed to a maternal dose of 0.2 mg/kg/day, observed effects at PNW 12 included altered glucose homeostasis (glucose and insulin tolerance tests), increase in serum lipid levels, reduced energy expenditure, and white adipocyte hypertrophy and increased lipid deposits in the liver cells (Fan et al. 2020). In C57Bl/6J mouse offspring exposed to a maternal dose of 0.05 mg/kg/day, observed effect at PNW 9 included increased visceral (gonadal) fat pad weight and increased serum leptin, insulin, triglycerides, total cholesterol, and fasting glucose levels (Gu et al. 2016). However, in a study with gestation plus lactation exposure in C57BL/6J x FVB mice, no exposure-related changes in glucose or insulin tolerance were observed in PNWs 30–31 mice following maternal exposure to 33 mg/kg/day from 2 weeks premating through lactation (Bastos Sales et al. 2018). No changes were observed in the sucrose preference test at PNW 40. Following exposure to a high-fat diet for 9 weeks, no DEHP-related changes in serum insulin, glucagon, or fasting glucose levels were observed at PNWs 55–57.

Insulin sensitivity was observed in PNW 16 FVB 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.

Mechanisms of Developmental Metabolic Syndrome and Altered Glucose/Insulin Homeostasis). Several tissues have shown decreased glucose uptake and oxidation, decreased insulin binding, and/or decreased glycogen content following developmental exposure to DEHP, including skeletal muscle, liver, and cardiac tissue (Mangala Priya et al. 2014; Parsanathan et al. 2019; Rajagopal et al. 2019a; Rajesh and Balasubramanian 2014).

Several genes or gene products involved in insulin signaling were dysregulated in adult rat offspring following developmental exposure to DEHP. These include downregulation, posttranslational modification, and/or epigenetic silencing of glucose transporters (*GLU2*, *GLU4*) and insulin receptors (IRβ) (Rajagopal et al. 2019a, 2019b; Rajesh and Balasubramanian 2014). Additionally, alterations in transcription factors involved in glycogenesis and gluconeogenesis were observed in the liver of developmentally exposed rats (Rajagopal et al. 2019a, 2019b).

Alterations in mRNA expression of genes essential for pancreatic β-cell function were also observed following developmental exposure to DEHP, including downregulation of *Pdx-1* and upregulation of *Atf4*, *Atf6*, *Bip*, and *Ucp2* (Lin et al. 2011; Venturelli et al. 2019). DEHP also produced cytotoxicity in cultured pancreatic β cells (INS-1) and the apoptotic process was shown to be mediated by oxidative stress and autophagy (Li et al. 2019a; She et al. 2017).

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; Dong et al. 2019; 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 and metabolic syndrome have 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 in adults that used urinary metabolite levels to assess DEHP exposure (Table 2-17) have reported associations with increased fasting blood glucose, increased serum insulin, and/or insulin resistance (as assessed by homeostatic model assessment-insulin resistance [HOMA-IR]) (Attina and Trasande 2015; Chen et al. 2017; Dales et al. 2018; Huang et al. 2014b; James-Todd et al. 2012; Li et al. 2019a; Lin et al. 2016, 2020; Trasande et al. 2013b). Dales et al. (2018) also reported an association between DEHP exposure and increases levels of HbA1c. 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. In contrast, a small number of studies did not observe associations between DEHP exposure and measures of glucose homeostasis (Ko et al. 2019; Stahlhut et al. 2007) 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.

Findings pertaining to glucose homeostasis in children and adolescents are inconsistent (Table 2-17). Han et al. (2019) reported an association between insulin resistance and urinary DEHP metabolite levels at 7–9 years of age, but not 3–5 years; conversely, fasting blood glucose levels were associated with increased urinary DEHP metabolite levels at 3–5 years of age, but not 7–9 years. Kim et al. (2018a) observed a positive association between urinary MEHHP levels in prepubertal girls and insulin resistance; this was not observed with other metabolites or in pubertal girls. In other cross-sectional studies, no association between insulin resistance and/or fasting blood glucose and DEHP metabolite levels in urine were observed in children aged 8–14 years (Watkins et al. 2016) or adolescents aged 12–19 years (Chen et al. 2017).

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 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

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

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Attina and Trasande 2015 Cross-sectional, 356 adolescents (age 12–19 years), United States (NHANES)	**Insulin resistance (HOMA-IR >4.39)**	**ΣDEHP**	IQR: 0.07–0.32 µM	↑
		MEHP	NR	↑
		MEHHP	NR	↑
		MEOHP	NR	↑
		MECPP	NR	↑
	HOMA-IR	ΣDEHP	See above	↔
Chen et al. 2017 Cross-sectional, 786 adolescents and young adults (234 adolescents age 12–19 years, 552 young adults age 20–30 years), Taiwan	**Serum insulin or HOMA-IR (young adults)**	**MEHP**	All subjects: mean (SD): 5.05 (12.86) µg/g Cr	↑
		MEHHP	26.70 (2.53)	↔
		MEOHP	16.65 (2.51)	↔
	Fasting glucose (young adults)	MEHP, MEHHP, or MEOHP	See above	↔
	Serum insulin, HOMA-IR, or fasting glucose (adolescents)	MEHP, MEHHP, or MEOHP	See above	↔
Dales et al. 2018 Cross-sectional, 2,119 non-diabetic adolescents and adults (age 12–79 years, mean age 37.28 years), Canada	**HbA1c (%)**	**ΣDEHP**	Mean (SE): 47.28 (1.45) µg/L	↑
		MEHP	2.09 (0.05)	↑
		MEHHP	12.72 (0.32)	↑
		MEOHP	7.53 (0.19)	↔
	HOMA-IR	**ΣDEHP, MEHHP, or MEOHP**	See above	↑
		MEHP	See above	↔
	HOMA-β (%)	**ΣDEHP, MEHP, MEHHP, or MEOHP**	See above	↑
	Fasting glucose	**ΣDEHP or MEHHP**	See above	↑
		MEHP or MEOHP	See above	↔

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

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
	Fasting insulin	**ΣDEHP**	See above	↑
		MEHP, MEHHP, or MEOHP	See above	↔
Dirinck et al. 2015 Cross-sectional, 123 adult obese subjects without a history of type 2 diabetes, Belgium	**Insulin resistance**	MEHP	Range: 0.49–181.9 µg/g Cr	↔
		MEHHP	2.6–135.8	↓
		MEOHP	0.82–42.3	↑
		MECPP	0.1–268.8	↔
	AUC insulin	MEHP, MEHHP, or MECPP	See above	↔
		MEOHP	See above	↑
	Insulin sensitivity	MEHP, MEHHP, or MECPP	See above	↔
		MEOHP	See above	↓
	HbA1c levels, AUC glucose, HOMA-IR, or insulinogenic index	MEHP, MEHHP, MEOHP, or MECPP	See above	↔
Han et al. 2019 Cross-sectional, 164 children assessed at age 3–5 and 7–9 years, South Korea	**HOMA-IR**	**ΣDEHP**	3–5 years: IQR: 258.18–595.69 µg/g Cr	↔
			7–9 years: 159.43–370.86	↑
		MEHP	3–5 years**:** 14.14–37.55	↔
			7–9 years: 10.35–31.76	↑
		MEHHP	3–5 years: 89.79–212.80	↔
			7–9 years: 58.19–127.45	↑
		MEOHP	3–5 years: 54.92–134.51	↔
			7–9 years: 33.33–74.17	↑
		MECPP	3–5 years: 75.08–190.57	↔
			7–9 years: 49.22–120.65	↑

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

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
	Fasting glucose	ΣDEHP, MEHP, MEOHP, or MECPP	3–5 years: see above	↔
			7–9 years: see above	↔
		MEHHP	**3–5 years:** see above	↑
			7–9 years: see above	↔
Huang et al. 2014b Cross-sectional, 3,083 non-diabetic, nonpregnant subjects (age 12–80 years), United States (NHANES)	**Fasting blood glucose or HOMA-IR**	**ΣDEHP** (MEHP, MEHHP, MEOHP)	Men: IQR: 5.3–19.7 µmol/100 g Cr Women: 6.5–23.1	↑
James-Todd et al. 2018 Cohort, 245 pregnant women without history of diabetes (mean age 35.3 years), United States (Massachusetts)	Non-fasting blood glucose (GW 27)	ΣDEHP (MEHP, MEHHP, MEOHP, MECPP)	1st trimester (median GW 7): IQR: 0.09–0.36 nmol/mL (SG-adj)	↔
			2nd trimester (median GW 21): 0.07–0.23	↔
James-Todd et al. 2016b Cohort, 298 pregnant women with full term births (47 with impaired glucose tolerance), mean age 31.9 years, United States (Massachusetts)	**Impaired glucose tolerance**	**ΣDEHP** (MEHP, MEHHP, MEOHP, MECPP)	Controls: GM: 0.2–0.8 µmol/L (SG-adj) IGT cases: 0.2–1.4	↑
	Blood glucose	ΣDEHP	See above	↔
James-Todd et al. 2012 Cross-sectional, 215 female cases of self-reported diabetes, 2,135 women without diabetes (age 20–79 years), United States (NHANES)	Fasting blood glucose or A1c%	ΣDEHP (MEHP, MEHHP, MEOHP)	GM (95% CI): 1,110 (1,030, 1,200) (units not reported)	↔
	HOMA-IR	**ΣDEHP**	See above	↑

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

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Kim et al. 2018a Cross-sectional, 137 girls including 68 prepubertal and 69 pubertal (age 6–13 years), Korea	**HOMA-IR (all prepubertal girls)**	MEHP	All girls: IQR: 9.7–19.6 µg/g Cr	↔
		MEHHP	26.8–56.7	↑
		MEOHP	21.1–45.1	↔
		MECPP	55.5–140	↔
	HOMA-IR (all pubertal girls)	MEHP, MEHHP, MEOHP, or MECPP	See above	NR
	Pubertal girls were classified as girls who had reached Tanner stage 2 of breast development at the time of examination.			
Kim and Hong 2014; Kim et al. 2013 Panel study, 560 subjects (146 men, 414 women; age 60–87 years), Korea	**HOMA-IR (both sexes; women); fasting serum glucose (both sexes)**	**ΣDEHP**	NR	↑
		MEHHP	Range: 1.71–317.26 ng/mL	NR
		MEOHP	0.212–231.44	NR
	Fasting serum glucose (women)	ΣDEHP	See above	↔
Ko et al. 2019 Cross-sectional, 435 adults (mean age 32.16 years), Taiwan	High HOMA-IR (>75th percentile) or high fasting blood glucose (≥100 mg/dL)	ΣDEHP	NR	↔
		MEHP	25th–95th percentile: 0.269–2.789 µg/g Cr	NR
		MEHHP	0.908–6.045	NR
		MEOHP	0.486–2.603	NR
Li et al. 2019a, 2019b Cross-sectional, 1,605 adults (mean age 37.4 years), United States (NHANES)	**HOMA-IR**	**ΣDEHP**	IQR: 0.12–0.58 µmol/L	↑
		MEHP	0.9–5.7 ng/mL	NR
		MEHHP	10.5–52.8	NR
		MEOHP	7.0–35.9	NR
		MECPP	17.0–78.8	NR
Lin et al. 2020 Cross-sectional, 792 adolescents and adults (age 12–30 years; mean age 21.3 years), Taiwan	**HOMA-IR**	**MEHP**	GM (95% CI): 6.1 (5.1, 7.3) µg/g Cr	↑
		MEHHP	27.9 (26.1, 30.0)	↔
		MEOHP	17.5 (16.4, 18.5)	↔

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

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Lin et al. 2016 Cross-sectional, 793 students, 303 with and 486 without elevated blood pressure in childhood (mean age 21.28 years), Taiwan	**HOMA-IR**	**MEHP**	GM (95% CI): 6.1 (5.1, 7.32) µg/g Cr	↑
		MEHHP	27.90 (26.05, 29.96)	↔
		MEOHP	17.48 (16.44, 18.54)	↔
Robledo et al. 2015 Cohort, 72 pregnant women (age 18–38 years) without diabetes, United States (Oklahoma)	Blood glucose	ΣDEHP	IQR: 36.82–126.00 ng/mL	↔
		MEHP	1.40–7.75	↔
		MEHHP	10.35–40.85	↔
		MEOHP	7.70–24.20	↔
		MECPP	16.90–54.20	↔
Shapiro et al. 2015 Cohort, 1,274 pregnant women (age >18 years), 47 cases of impaired glucose tolerance (IGT) and 43 cases of gestational diabetes mellitus (GDM)	GDM or IGT	ΣDEHP	NR	↔
		MEHP	Controls: GM (GSD): 2.6 (2.5) ng/mL (SG-adj) IGT cases: 2.3 (2.4) GDM cases: 2.7 (2.9)	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
Stahlhut et al. 2007 Cross-sectional, 1,451 adult males (age >18 years), United States (NHANES)	HOMA-IR	MEHP	Mean (SE): 11 (1.3) µg/g Cr	↔
		MEHHP	65.8 (7.9)	↔
		MEOHP	38.7 (4.5)	↔

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

Reference, study type, and population	Outcome evaluated	Metabolite	Urine concentration	Result
Sun et al. 2014b Cohort, 394 females with type-2 diabetes and 393 controls (NHS cohort; age 23–79 years) and 577 females with type-2 diabetes and 577 controls (NHSII cohort; age 32–52 years), United States	**Type 2 diabetes**	**ΣDEHP**	NHS cases: IQR: 154.4–545.8 nmol/L NHS controls: 142.8–463.7 NHSII cases: 201.4–586.3 NHSII controls: 170.8–522.3	NR
		MEHP	NR	↔
		MEHHP	NR	↔
		MEOHP	NR	↔
		MECPP	NR	↑
Trasande et al. 2013b Cross-sectional, 766 adolescents (age 12–19 years), United States (NHANES)	**HOMA-IR (>2 SD above mean)**	**ΣDEHP**	IQR: 0.17–0.71 µM	↑
		MEHP	NR	↔
		MEHHP	NR	↑
		MEOHP	NR	↑
		MECPP	NR	↑
Watkins et al. 2016 Cross-sectional, 250 children (age 8–14 years), Mexico	Fasting serum glucose	ΣDEHP	IQR: 3.09–10.3 µmol/L	↔

[a]Metabolite units and reporting (range, IQR, etc.) defined for the first metabolite per study are applicable to all subsequent metabolites for that study unless otherwise noted.

Bold font indicates association with DEHP or DEHP metabolites: ↑ = association with increase; ↓ = association with decrease; ↔ = no association

ΣDEHP = sum DEHP metabolites; AUC = area under the curve; CI = confidence interval; Cr = creatinine; DEHP = di(2-ethylhexyl)phthalate; GM = geometric mean; GSD = geometric standard deviation; GW = gestation week; HbA1c = glycosylated hemoglobin; HOMA-β = homeostatic model assessment-beta cell function; HOMA-IR = homeostatic model assessment-insulin resistance; IQR = interquartile range; 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; NHS = Nurses' Health Study; NR = not reported; SD = standard deviation; SE = standard error; SG-adj = specific gravity-adjusted

within the Nurses' Health Study and Nurses' Health Study II (Sun et al. 2014b) 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 MECPP in urine. 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. 2016b). However, blood glucose levels were not associated with prenatal DEHP exposure (James-Todd et al. 2016b, 2018).

Animal Studies. Glucose homeostasis may be impaired in animals following exposure to DEHP. In rats, evidence of altered glucose metabolism and homeostasis was observed following intermediate-duration exposure to doses ≥5 mg/kg/day (Aydemir et al. 2018; Rajesh et al. 2013; Xu et al. 2018; Zhang et al. 2017). Altered endpoints included elevated serum glucose levels, decreased glycogen levels and glucose uptake in visceral adipose tissue, and/or elevated serum glucose and insulin levels during glucose and insulin tolerance tests. However, other studies in rats reported no changes in serum glucose following exposure 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 a 13-week study, increased serum glucose was observed in male rats exposed to doses ≥850.1 mg/kg/day; 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). In mice, evidence for impaired glucose homeostasis (e.g., elevated fasting blood glucose, elevated glucose levels after glucose challenge) was observed after acute exposure to 2,000 mg/kg/day or intermediate-duration exposure to ≥180 mg/kg/day (Ding et al. 2019; Lee et al. 2019a; Li et al. 2018). However, serum glucose changes were not observed in B6C3F1 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 (e.g., Lin et al. 2011; Mangala Priya et al. 2014; Rajesh and Balasubramanian 2014). 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. Increased volume and number of adipose cells in unspecified adipose tissue were observed in rats following gavage exposure to ≥5 or 500 mg/kg/day, respectively, for 8 weeks (Zhang et al. 2019, 2020c). In another rat study with the same exposure paradigm, irregular adipocytes and macrophage infiltration in adipose tissue was observed at ≥50 mg/kg/day with increased number and volume of adipocytes at 500 mg/kg/day (Zhou et al. 2019). Zhou et al. (2019) reported increased serum leptin (an appetite-controlling hormone) and decreased serum adiponectin (regulates lipid and glucose metabolism) at ≥50 mg/kg/day; these parameters were unchanged in the study by Zhang et al. (2019, 2020c). Serum leptin was also elevated in rats exposed to ≥50 mg/kg/day for 28 days (Xu et al. 2018). In mice, increases in visceral adipose tissue and adipocyte hypertrophy were observed 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 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). No changes in retroperitoneal or ovarian adipose tissue weights were observed in Wistar rat dams exposed to DEHP at doses up to 700 mg/kg/day from GD 13 to PND 21 (Venturelli et al. 2019). Rajesh and Balasubramanian (2014) 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 2014). 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.

Mechanisms of Impaired Glucose Homeostasis and Metabolic Syndrome. Several tissues have shown decreased glucose uptake and oxidation, decreased glycogen content, an/or alterations in metabolic pathways involved in glucose metabolism following exposure to DEHP, including cardiac, liver, and adipose tissue (Ding et al. 2019; Li et al. 2018; Rajesh et al. 2013). Additionally, several genes or gene

products involved in glucose transport, insulin signaling, and lipid metabolism were dysregulated in rodents following exposure to DEHP (Ding et al. 2019; Rajesh et al. 2013; Xu et al. 2018; Zhang et al. 2017, 2019, 2020c). Wang et al. (2020) propose that significant alterations in the gut microbiome following oral DEHP exposure may contribute to increased risk of diabetes. Following a 30-day oral exposure, Sprague-Dawley rats, showed an increase in bacterial species *Fimicutes* and *Proteobacteria*, which are associated with obesity and diabetes. Sprague-Dawley rats also showed DEHP-associated weight gain. In contrast, Wistar rats and BALB/c and C57BL/6J mice did not have increased *Fimicutes* and *Proteobacteria* and showed normal weight gain.

Proposed mechanisms for impaired glucose homeostasis in developing animals are discussed in Section 2.17 (Developmental).

Summary. Several epidemiological studies, primarily cross-sectional, found potential associations between DEHP exposure and diabetes-related outcomes (e.g., impaired glucose homeostasis) in humans. A limited number of animal studies report altered glucose homeostasis and metabolic syndrome.

2.19 CANCER

Epidemiological Studies—Cancer. One population-based study did not find an association between DEHP exposure and breast cancer using NHANES data for urinary MEHP, MEHHP, or MEOHP collected during the 2003–2010 annual survey cycles (Morgan et al. 2017). Additional epidemiological studies of the association between cancer and DEHP exposure in humans are limited to case-control studies in which exposure (as urinary metabolite levels) was measured after the outcome (cancer) was observed. Cancers evaluated in these studies include breast cancer (Holmes et al. 2014; Lopez-Carrillo et al. 2010; Martinez-Nava et al. 2013; Merida-Ortega et al. 2016; Reeves et al. 2019), prostate cancer (Chuang et al. 2020), and thyroid cancer (Liu et al. 2020; Marotta et al. 2019; Miao et al. 2020). 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, 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). NTP (1982) reported metastasis of hepatic carcinoma to the lungs in 37% of tumor cases in DEHP-exposed mice; metastasis was not observed in control mice or exposed or control rats.

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, 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.

Hepatocellular adenomas were also observed in 1/15, 2/15, and 4/15 male rasH2 transgenic mice following exposure to DEHP at a dietary dose of 1, 100, or 1,100 mg/kg/day, respectively, for 26 weeks, compared to 0/15 controls (Toyosawa et al. 2001). RasH2 transgenic mice carry a human prototype c-Ha-ras gene. Due to increased susceptibility to developing cancer, it is proposed that carcinogenic potential can be assessed using shorter-durations and fewer animals than a standard 2-year bioassays. Hepatocellular tumors were not induced in similarly treated female rasH2 transgenic mice or male or female wild-type mice (Toyosawa et al. 2001).

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; Ito et al. 2019; 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).

Other molecular targets possibly related to DEHP-induced liver cancer include activation of nuclear factor kappa B (NFκB) leading to chronic inflammation or CAR activation resulting in cell proliferation and foci formation (Ito et al. 2019; Wei et al. 2017).

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 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. 1953; 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).

In a developmental study, the incidences of prostate cancer or precursor lesions were not increased in adult Sprague-Dawley rat offspring following exposure to doses up to 1 mg/kg/day from GD 7 to PND 21 (Wang et al. 2017a). However, the cancer analysis is limited due to small animal number (11/group),

which may have been inadequate to detect a significant effect for a lesion with high background incidence.

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, TA1537)	Gene mutation	–	NS	Kanode et al. 2017
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Lee et al. 2019b
S. typhimurium (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1985
Escherichia coli PQ37	Gene mutation	–	–	Sato et al. 1994

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
E. coli WP2UVRA$^+$	Gene mutation	–	–	Yoshikawa et al. 1983
E. coli WP2UVRA	Gene mutation	–	–	Yoshikawa et al. 1983
E. coli WP2UVRA	Gene mutation	-	-	Lee et al. 2019b
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
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	+	Erkekoglu et al. 2010a
Human HepaRG cells	DNA damage	–	NA	Le Hegarat et al. 2014
Human thyroid carcinoma	DNA damage	NS	+	Kim et al. 2019a
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

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
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
Chinese hamster lung (CHL/OU)	Chromosomal aberrations	–	–	Lee et al. 2019b
SHE cells	Chromosomal aberrations	–	–	Tsutsui et al. 1993
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

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
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
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

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

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
CHO cells (AS52)	Mutagenicity	NS	+	Chang et al. 2017c
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
CHO cells (AS52)	DNA damage	NS	+	Chang et al. 2017c
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
SHE cells	Chromosomal aberrations	+	−	Tsutsui et al. 1993
CHO transformed cells	Gene mutation	NS	+	Chang et al. 2017c
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
Mouse (Oral)	Micronuclei in bone marrow	–	Lee et al. 2019b
Human (unknown)	DNA damage in sperm and granulosa cells	+	Al-Saleh et al. 2019b
Human (unknown)	DNA damage in peripheral blood cells	–	Franken et al. 2017
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 (gavage)	DNA damage in sperm	+	Hsu et al. 2016
Rat (gavage)	DNA damage in blood lymphocytes and sperm	+	Karabulut and Barlas 2018
Rat (gavage)	DNA damage in thyroid	+	Kim et al. 2019a
Mouse (pipette)	Oxidative DNA damage in brain	+	Barakat et al. 2018
Mouse (gavage)	Oxidative DNA damage in oocytes	+	Lu et al. 2019
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
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

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

Species (exposure route)	Endpoint	Results	Reference
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, 30 *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 (Chang et al. 2017c; Kim et al. 2019a; 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). MEHP produced a mutagenic response in Chinese hamster ovary (CHO) cells carrying a single functional copy of the bacterial *gpt* gene (AS52 cells). This effect was reversed by addition of N-acetyl cysteine, suggesting that the mutagenic effect resulted from oxidative stress (Chang et al. 2017c).

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). Exposing Wistar or Sprague-Dawley rats orally to DEHP resulted in DNA damage to blood lymphocytes, sperm cells, and thyroid tissue (Hsu et al. 2016; Karabulut and Barlas 2018; Kim et al. 2019a). DNA damage in granulosa and sperm cells and markers of oxidative DNA damage in seminal plasma and follicular fluid were associated with DEHP urinary metabolites in a prospective birth cohort seminal plasma (Al-Saleh et al. 2019b). In adolescents, a positive association was observed between markers of oxidative DNA damage and DEHP urinary metabolites; however, DNA damage in peripheral blood cells were not associated with DEHP exposure (Franken et al. 2017). Oxidative DNA damage was also observed in mouse oocytes following oral exposure to DEHP (Lu et al. 2019) and in the brain of adult mouse offspring following maternal oral exposure to DEHP during gestation (Barakat et al. 2018). 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; Chang et al. 2017c; Choi et al. 2010; Erkekoglu 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. DNA damage was reversed by the addition of N-acetyl cysteine, suggesting a role for oxidative stress in this process (Chang et al. 2017c). 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

The uptake of particle-phase DEHP was studied in 16 volunteers exposed to 123±21 µg/m^3 full ring-deuterated DEHP (DEHP-D_4) for 3 hours (Andersen et al. 2018; Krais et al. 2018). DEHP uptake values of 0.51±0.34 µg/kg or 0.0014±0.00088 (µg/kg)/(µg/m^3)/hour were calculated from the urinary

concentrations of five DEHP metabolites. These values were adjusted for deposition, assuming that the deposited particles mass was 26% of the inhaled mass (determined by a multi-path particle dosimetry model). Absorption was also 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 absorption was demonstrated in four male volunteers (21–61 years old) who ingested a single dose (645±20 μg/kg) of 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; Plichta et al. 2019; Rhodes et al. 1986; Short et al. 1987; Sjöberg et al. 1985a; Williams and Blanchfield 1974). In studies of dogs and rabbits, absorption was confirmed by the presence of phthalate in urine during 3 days postexposure (Shaffer et al. 1945). 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. 2012a). 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. 2012a; 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. 2012a). 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. 2012a).

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.

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 $1.05±0.21x10^{-7}$ cm/hour for isolated human epidermal membranes and $4.31±1.34x10^{-7}$ cm/hour for isolated rat skin (whole skin). Scott et al. (1987) estimated coefficients to be $0.57±0.12x10^{-5}$ cm/hour for human epidermal membranes and $2.28±0.23x10^{-5}$ 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.

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. 2012a; 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).

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 ^{14}C Following an Intravenous Dose of 50 mg/kg [^{14}C]-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
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 ^{14}C 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. (2012a) 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).

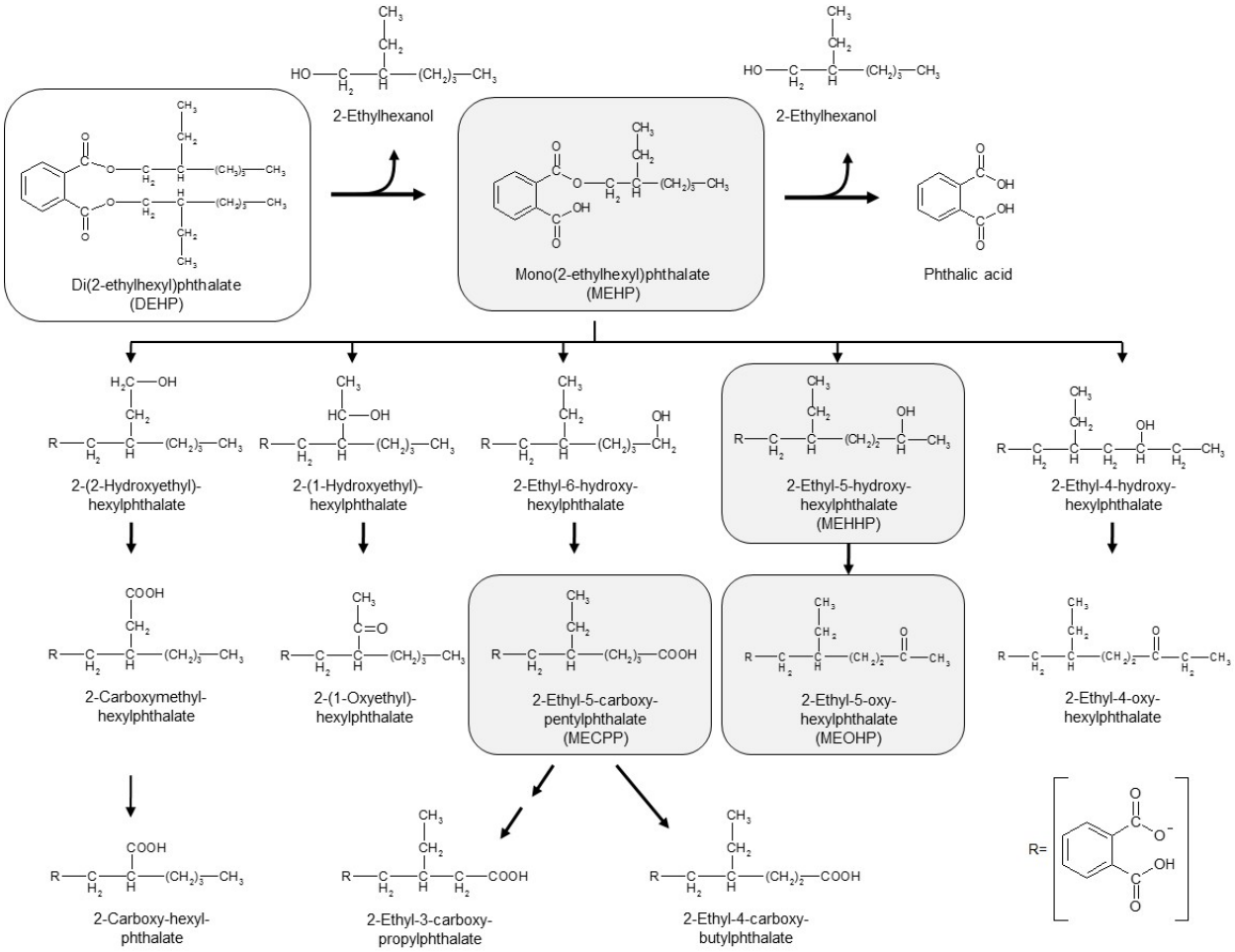
3.1.3 Metabolism

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. 2014; Ozaki et al. 2017). 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. (1985a) 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). Hanioka et al. (2019) examined the kinetics of DEHP hydrolysis by liver and intestinal microsomes from humans, monkeys, dogs, rats, and mice. For liver microsomes, K_m values were similar among species, while V_{max} values varied up to 9-fold. Intrinsic clearance values (V_{max}/K_m) followed the order of mice > dogs > monkeys $\geq$ rats > humans. V_{max} and intrinsic clearance values were 5–25% lower for intestinal microsomes (compared with liver microsomes) from mice, rats, and monkeys, and DEHP hydrolysis activity was not detected in dog or human intestinal microsomes.

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. 2012a; Schmid and Schlatter 1985; Zhao et al. 2018). 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). Zhao et al. (2018) demonstrated that the relative proportion of the primary urinary metabolites of DEHP in pregnant women varies with the stage of pregnancy and maternal age.

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; Shaffer et al. 1945). 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. Urinary excretion by humans was reported to be greatest 5-7 hours after exposure, totaling 4.5% in 24 hours (Shaffer et al. 1945). Excretion was similar in dogs, being greatest on day 2 post-exposure and totaling 2.0 or 4.5% in 3 days. Significantly greater excretion ranging from 26 to 65% in 3 days was reported for rabbits (Shaffer et al. 1945). 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. [2012a]; 0.005–0.65 mg/kg from Koch et al. [2004, 2005a]). 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. 1985a; 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. 2012a).

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) (Kessler et al. 2004, 2012; Koch et al. 2004, 2005a; Koo and Lee 2007; Ljungvall et al. 2004; Oishi 1989, 1990; Pollack et al. 1985a; 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; Kessler et al. 2004; Koo and Lee 2007; Oishi 1989, 1990; Pollack et al. 1985a; Sjöberg et al. 1985b).

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. 1985a
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. 1985a
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	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	1,000	MEHP	Plasma	7.4	NA	Koo and Lee 2007
Rat	Oral	2,800	MEHP	Plasma	5.2	NA	Teirlynck and Belpaire 1985
Rat	Arterial	100	DEHP	Blood	15	1,290	Pollack et al. 1985a

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	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. 1985a
Rat	Venous	50	MEHP	Blood	3.2	690	Pollack et al. 1985a

[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

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. 1985a; Teirlynck and Belpaire 1985).

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; Krais et al. 2018; 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 or concentration (mg/kg or µg/m^3)	Measured chemical	Elimination $t_{1/2}$ (hours)	Reference
Human	Inhalation	123	Sum of MEHP, MECPP, MEHHP, MEOHP, MEOPP	4.6	Krais et al. 2018
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.

Table 3-6. Urinary Elimination Half-Lives ($t_{1/2}$) for DEHP, MEHP, and Metabolites

Species	Route of administration[a]	DEHP dose or concentration (mg/kg or µg/m^3)	Measured chemical	Elimination $t_{1/2}$ (hours)	Reference

[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 orally (Kessler et al. 2004; Koo and Lee 2007; Pollack et al. 1985a; 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 (Keys 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), a simplified humanized mouse model (Adachi et al. 2015), a human PBPK model that simulates the kinetics of orally administered DEHP (Sharma et al. 2018), and a human PBPK model that simulates the transfer of MEHP from the maternal system to the fetus (Martinez et al. 2018).

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. 1985a; 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. 1985a; 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 sub-models, 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. 2012a).

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.

Sharma et al. (2018)

Sharma et al. (2018) developed a human PBPK model that simulates the kinetics of orally administered DEHP. Tissue compartments represented in the model include blood, fat, liver, gut (absorptive regions), gonads, and a lumped compartment representing the rest of the body. The model simulates absorption of DEHP from the gut, distribution to tissues and elimination by metabolism, and urinary excretion of metabolites. Metabolic pathways simulated include formation of MEHP from DEHP and conversion of MEHP to MEHHP, MEHOP, MECPP, and phthalic acid. All metabolism pathways are assigned to the gut and liver. The model simulates the tissue distribution and urinary excretion of DEHP and MEHP, and the distribution to blood and urinary excretion of the metabolites MEHHP, MEOHP, and MECPP. The conversion of MEHP to phthalic acid is simulated as an elimination pathway; the distribution and excretion of phthalic acid is not simulated.

Absorption of DEHP from the gut is flow-limited and governed by a gut/plasma partition coefficient and blood (plasma) flow rate (L/hour). Rates of absorption of metabolites formed in the gut are governed by first-order rate coefficients (hour-1). Tissue distribution of DEHP and MEHP are assumed to be flow-limited, with rates governed by tissue/plasma partition coefficients and tissue blood flow rates (L/hour). Transfers of MEHHP and MEOHP to blood are assumed to be first-order (hour-1). All metabolic pathways are represented as saturable reactions acting on the unbound fraction in tissue, with rates governed by a K_m (µ/L) and V_{max} (µg/minute/mg microsomal protein). *In vivo* rates of metabolism are scaled to the mass of microsomal protein in each tissue. Urinary excretion of metabolites is assumed to be first-order (hour-1). Other viable elimination mechanisms for DEHP, including 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 plasma DEHP elimination kinetics.

Chemical parameters were assigned log-normal distributions representing uncertainty (see Table 1 of Sharma et al. 2018). The distributions were used in a Monte Carlo analysis to propagate parameter uncertainty into model outputs (e.g., plasma concentrations and amounts excreted in urine of parent compound and metabolites).

The model was optimized against observations of plasma and urine levels of DEHP and metabolites following a single oral dose of 48.5 mg DEHP (Koch et al. 2004, 2005a). Sharma et al. (2018) reported that central estimates for the first-order transfer coefficients of MEHHP and MEOHP to blood were optimized to observations. However, values of all other parameters estimated from other studies appear to have been optimized by adjusting their standard deviations to achieve 2.5 –97.5th percentile ranges of predictions that encompassed observations. The predicted 2.5th–97.5th percentile ranges encompassed the observed time course for plasma concentrations of MEHP, MEHHP, MECPP, and MEOHP. This indicates that the optimization of the uncertainty distributions was successful.

The model was evaluated against observation of urinary metabolite profiles following a single oral dose of 0.31 or 2.8 mg DEHP (Anderson et al. 2001). The predicted 2.5th–97.5th percentile ranges for the fraction of dose excreted in urine encompassed the observations for urinary MEHP, MEHHP, MECPP, MEOHP, and the sum of metabolites (Sharma et al. 2018).

Martinez et al. (2020) applied the Sharma et al. (2018) model to predicting cumulative urinary in a cohort of pregnant women. DEHP intakes from dermal application and ingestion of DEHP-containing products, inhalation, and diet were estimated from surveys of the cohort (Martinez et al. 2017, 2018). The

estimated total DEHP intakes were used as inputs to the Sharma et al. (2018) model to predict cumulative urinary excretion of MEHP, which were comparted to observations from biomonitoring (spot urine samples). The PBPK model underpredicted the median observed excretion of MEHP and predicted a narrower distribution of individual excretion (see Estimated exposure and Biomonitoring data in Figure 3 of Martinez et al. 2020). Closer agreement with biomonitoring data was achieved when dose inputs to the PBPK model were reconstructed for each subject from urinary excretion fractions (FUE, fraction of dose excreted in urine) previously estimated for each MEHP metabolite (Anderson et al. 2011). Predicted mean urinary excretion rates from the reconstructed doses were not different from observed (see Reconstructed exposure and Biomonitoring data in Figure 3 of Martinez et al. 2020). However, this comparison is not surprising given that the model was previously shown to predict the urinary excretion fractions observed in the Anderson et al. (2011) study (Sharma et al. 2018).

Martinez et al. (2018)

Martinez et al. (2018) extended the Sharma et al. (2018) model to simulate transfers from the maternal system to the fetus. The model includes compartments for placenta and fetus, and several additional maternal compartments not in the Sharma et al. (2018) model, including brain, fat, skin, and stomach; and placenta, fetus, and amniotic fluid. The model structure and parameter values are described in Annex-I of Martinez et al. (2017). However, the Annex provides only a partial description of the model; it does not provide a complete description of how the fate of metabolites, other than MEHP, are represented in the model. Transfers between plasma and tissues are assumed to be flow-limited and governed by tissue plasma flow rates and tissue/plasma partition coefficients (only those for DEHP and MEHP are reported in the Annex).

The fetus is simulated with compartments representing brain, liver, and rest of body. Transfer of MEHP to the fetus occurs from the placenta compartment, with the transfer assumed to be flow-limited and governed by placental blood flow and bidirectional transfer fractions of the unbound concentration in fetal and maternal plasma. Within the fetus, distribution of MEHP to tissue compartments is flow-limited. Elimination pathways for MEHP in the fetus include metabolism (V_{max}, K_m) and transfers between fetal liver and amniotic fluid, governed by bidirectional plasma-amniotic fluid transfer fractions. Metabolites of MEHP are not simulated in fetal compartments. Fetal growth is represented as exponential (fetal volume) or polynomial (amniotic fluid) of gestational age. Volumes of fetal tissues are proportions of fetal volume.

The maternal fetal model was used to simulate maternal and fetal plasma MEHP following a single dose of DEHP at levels representing the 4th and 95th percentile for dietary, non-dietary, and total DEHP intake estimated in a population of pregnant women (Martinez et al. 2018). Predicted peak concentrations in fetal and maternal plasma were similar; however, peak concentration occurred sooner (approximately 1 hour after dosing) in fetal plasma compared to maternal plasma (approximately 5 hours). Observations were not reported to allow evaluation of these predictions from the maternal-fetal model.

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. 2012b). 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 (CAT, MPO, and SOD2) (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). The within-woman ICC values for individual metabolites measured during the three trimesters of pregnancy ranged from 0.21 to 0.44, suggesting low to moderate variability (Li et al. 2019a). 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. Howdeshell 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. 2017; Laurenzana et al. 2016; Sarath Josh et al. 2016; Sheikh et al. 2016; Singh and Li 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 they 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.

Jarfelt et al. (2005) 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. 2013, 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. (2013) 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. (2005) 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 and Kavlock 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 it 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, 1988). 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.

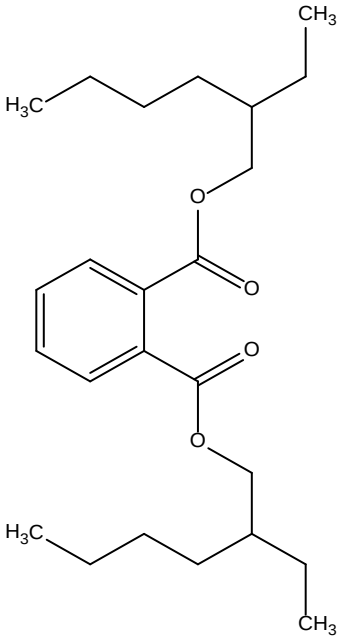
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

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

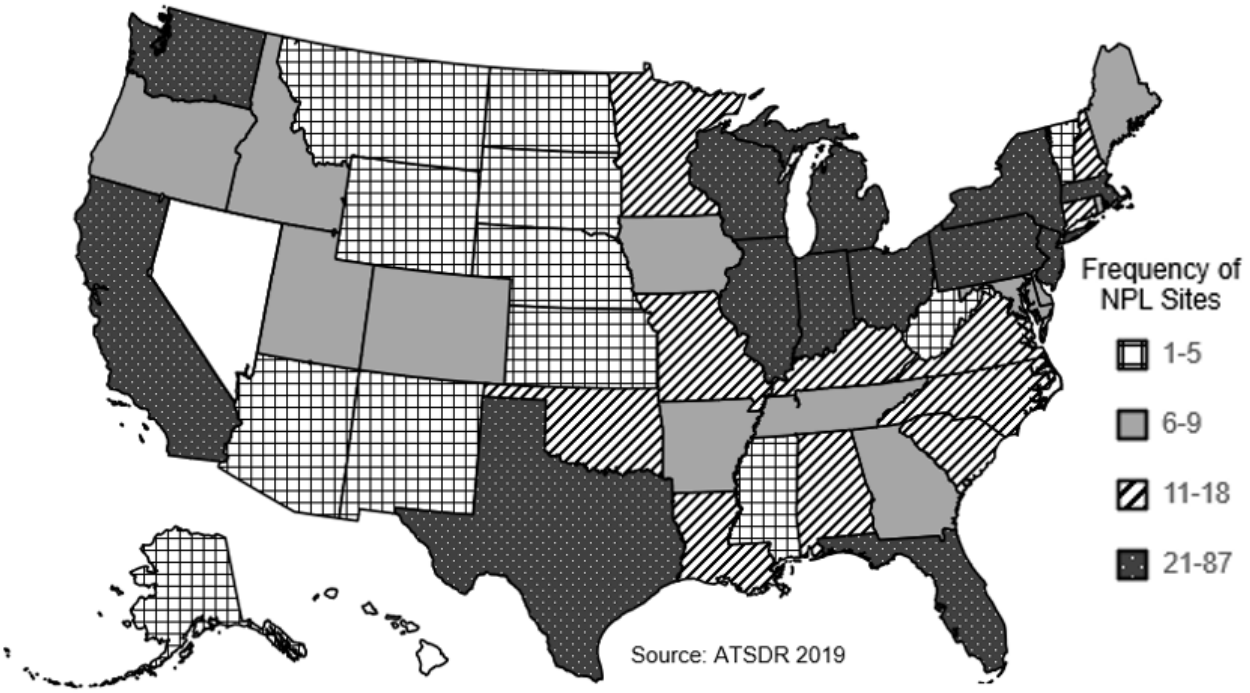
[a]The solubilities of DEHP in distilled water that have been determined both experimentally and theoretically vary between 1.1 and 1,200 µg/L (Staples et al. 1997). The highest values are likely to be overestimated as measurements that used the traditional shake flask method often led to these higher 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 757 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). 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, 750 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



- 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. DEHP was a ubiquitous laboratory contaminant, which made it difficult to determine low levels accurately due to the potential for false identification of elevated phthalate concentrations from sample contamination. In recent years, DEHP-free laboratory equipment has been made available, reducing the potential for contaminating a sample.

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 2010a). DEHP is produced by the esterification of phthalic anhydride with 2-ethylhexyl alcohol in the presence of an acid catalyst (CPSC 2010a). 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 et al. 2014). Worldwide production of DEHP is decreasing, mainly related to the regulations being enforced against certain uses of DEHP (Zolfaghari et al. 2014).

The Chemical Data Reporting (CDR) rule, which was enacted through the Toxic Substances Control Act (TSCA), requires manufacturers including importers of chemicals to provide EPA with information on the production and use of these chemicals in commerce. The Chemical Data Reporter indicated that there were 37 U.S.-based companies that either manufactured or imported DEHP to the United States in 2016 (CDR 2016). Most companies reported the production or import volume as confidential business information (CBI); however, in 2015 it was reported that at least 10,196,363 pounds were produced or imported from 19 companies.

Table 5-1 summarizes the number and location of U.S. facilities that reported the use and production of DEHP in 2018 (TRI18 2020). 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]
AL	1	1,000	9,999	8
AR	4	1,000	999,999	7, 8, 11
CA	8	100	9,999,999	7, 8, 14
CT	1	100	999	7
GA	3	100,000	999,999	8, 9
IL	2	1,000	99,999	7, 8
IN	5	100	9,999	7, 8, 12
LA	1	10,000	99,999	1, 5, 12
MA	4	10,000	999,999	8, 10, 11
MI	4	0	99	7
MO	6	100	999,999	7, 8
MS	4	1,000	99,999	7, 8
NC	10	0	999,999	1, 2, 3, 5, 7, 8, 13, 14
NJ	5	10,000	499,999,999	2, 3, 4, 7, 8, 9
NY	3	10,000	999,999	7, 8
OH	14	100	999,999	7, 8, 9, 12
OR	3	10,000	99,999	7, 8, 12
PA	3	10,000	999,999	2, 3, 7, 8
PR	3	1,000	999,999	8
RI	1	100,000	999,999	7, 14
SC	5	1,000	999,999	7, 8, 12, 14
TN	8	1,000	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
TX	7	1,000	999,999	7, 8, 10
VA	2	100,000	999,999	7, 8
WA	3	1,000	999,999	7, 8, 9
WI	6	100	999,999	7, 8, 9
WV	1	10,000	99,999	7, 8

[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: TRI18 2020 (Data are from 2018)

Decreasing demand for DEHP due to continued concern over health effects will impact future production volumes (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 2010a). The Chemical Data Reporter (CDR 2016) indicated a downward trend in annual imports, with estimated production or import of at least 28 million pounds in 2011 and 10 million pounds in 2015.

5.2.3 Use

DEHP was principally used as a plasticizer in the production of flexible PVC products, with about 97% of DEHP produced being used for this purpose (CPSC 2010a). DEHP is generally used to dissolve monomers to facilitate their crosslinking into polymers (e.g., the conversion of vinyl chloride into PVC) (Chaudhary et al. 2016). The polymerization process retains a portion of the plasticizer, and the retention of DEHP in polymers such as PVC increases flexibility, reduces hardness, and decreases tensile strength of the plastic (Chaudhary et al. 2016). Plastics made with DEHP can be found 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 2010a; NTP 1989). Current restrictions on the use of DEHP in PVC materials has led manufacturers to find alternatives to DEHP. In an effort to reduce use of DEHP, current or proposed replacement plasticizers that may reduce toxicity include citrate-based plasticizers, such as acetyl tri-*n*-butyl citrate (ATBC), as well as 1,2-cyclohexanedicarboxylic acid, diisononyl ester (DINCH), di(2-ethylhexyl) adipate (DEHA), trioctyltrimellitate (TOTM), and di(2-ethylhexyl) terephthalate (DEHT or DOTP) (CPSC 2010b; EPA 2012; Messerlian et al. 2017b; Tickner et al. 2001).

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 2010a). DEHP plasticizer use in medical devices and industrial/commercial products accounts for 25 and 45% of the overall consumption of DEHP, respectively (CPSC 2010a). In 2017, the European Union

passed the new Medical Device Regulation, which restricted the use of DEHP and other substances of very high concern by 2020 and encourages the use of alternatives (Hansen 2019).

Numerous nonplasticizer uses of DEHP have been reported and account for <3–5% of the national use of DEHP (CPSC 2010a). 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 2010a; Mannsville Chemical Products Corporation 1990; Messerlian et al. 2017b; 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 childcare 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 or surface lubricant for 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. 2017b).

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 2018, it was estimated that about 643,000 pounds of waste DEHP were transported from production facilities or points of usage for disposal, including publicly owned treatment works (TRI18

2020). 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 (TRI18 2020) are for releases in 2018 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 2018 were approximately 711,000 pounds (approximately 322 metric tons) (TRI18 2020).

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
AL	1	26,280	0	0	0	0	26,280	0	26,280
AR	4	1,738	7	0	2,354	0	2,494	1,604	4,098
CA	8	1,389	4	0	7,190	0	1,393	7,190	8,583
CT	1	0	0	0	0	311	0	311	311
GA	3	295	0	0	2,943	0	295	2,943	3,238
IL	2	29	0	0	1,900	0	29	1,900	1,929
IN	5	132	0	0	4,453	0	132	4,453	4,585
LA	1	0	0	0	0	0	0	0	0
MA	4	191	0	0	0	0	191	0	191
MI	4	250	33	0	0	0	250	33	283
MO	6	1,544	5	0	43,438	880	1,544	44,323	45,867
MS	4	42	0	0	98,260	0	42	98,260	98,301
NC	10	2,011	6	0	33,509	0	2,011	33,515	35,526
NJ	5	26	0	0	0	1,040	26	1,040	1,066
NY	3	2,143	0	0	0	0	2,143	0	2,143
OH	14	641	5	0	11,903	17,491	641	29,399	30,039
OR	3	60	0	0	19,688	0	19,748	0	19,748
PA	3	2	0	0	3,900	0	2	3,900	3,902
PR	3	24	0	0	0	0	24	0	24
RI	1	1,717	0	0	594	0	1,717	594	2,311
SC	5	201	1,564	5	142	250	201	1,961	2,162
TN	8	5,564	15	0	11,524	62	6,029	11,136	17,165
TX	7	6	0	395,800	0	0	6	395,800	395,806
VA	2	261	0	0	0	0	261	0	261
WA	3	1,603	0	0	0	0	1,603	0	1,603
WI	6	271	0	0	4,235	0	271	4,235	4,506
WV	1	255	10	0	500	0	510	255	765

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
Total	117	46,674	1,649	395,805	246,532	20,034	67,843	642,851	710,694

[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: TRI18 2020 (Data are from 2018)

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 46,674 pounds (~21 metric tons) of DEHP to the atmosphere from 117 domestic manufacturing and processing facilities in 2018, accounted for about 7% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). 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.

Emissions of DEHP to air can occur due to volatilization from sludge used in wastewater treatment plants. Lee et al. (2019c) collected sludge samples from 40 wastewater treatment facilities in South Korea and investigated the occurrence and emissions of phthalates from this source. DEHP was the dominant phthalate found in the sludge samples with levels ranging from 1,400 to 1,000,000 ng/g (71,000 ng/g mean). Using these data, an average emission of 1,310 kg/day was estimated from wastewater treatment plants in Korea.

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. Liang et al. (2019) developed a multi-media indoor fate model to estimate levels of phthalates such as DEHP in indoor air environments. The model accounted for emissions from common housing materials and sorption and resuspension from surfaces such as flooring, ceilings, furniture, and carpet. Steady-state DEHP levels in air from a typical residential home were estimated as 0.14 μg/m^3 and 80–46 000 μg/g in settled dust on various surfaces. Shinohara and Uchino (2020) measured the emissions of DEHP to indoor air and dust from a PVC sheet over a 2-week period using a passivize sampler. DEHP levels in the surface air on the PVC sheet were in the range of 2.6–3.3 μg/m^3. In a similar study, Shinohara et al. (2019) measured flux rates of DEHP from building

materials, such as vinyl floorings and wallpaper, using a passive flux sampler. They found that the rates were relatively constant over time, with fluxes in the range of 4.5–6.1 μg/m^2-hour. Cadogan et al. (1994) and Cadogan and Howick (2001) reported that an indoor flux of $2.3x10^{-4}$ mg/m^2-second (828 μg/m^2-hour) 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, the total end-use emission of DEHP to the air from indoor household uses in Western Europe in 1990 was 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 1,649 pounds (~0.75 metric tons) of DEHP to surface water from 117 domestic manufacturing and processing facilities in 2018, accounted for about 0.23% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). 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 246,532 pounds (~112 metric tons) of DEHP to soils from 117 domestic manufacturing and processing facilities in 2018, accounted for about 35% of the estimated total environmental releases from facilities required to report to the TRI (TRI18 2020). An additional 395,805 pounds (~180 metric tons), accounted for about 56% of the total environmental emissions, were released via underground injection (TRI18 2020). 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 5-8.

Land application of sewage sludge might also release DEHP to soil. The 1989 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 as biosolids. 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. In the 2009 National Sewage Sludge Survey, DEHP was detected in 84 samples collected from 74 treatment plants in 35 states, at concentrations ranging from 657 to 310,000 μg/kg (0.657–310 ppm) (EPA 2009a).

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 (Iannuzzi 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; Lunderberg et al. 2019), 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. The vapor pressure of DEHP is extremely low compared to water, indicating that volatilization is not a dominant transport process. Volatilization from water and soil may be expected, based on the Henry's law constant (estimated value 1.71x10^{-5} atm-m^3/mol; Staples et al. 1997); however, adsorption to soil and suspended particulate matter in the water column will attenuate the rate of volatilization. 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. 1980).

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. 1980). Distribution of DEHP between the water column and the sediments was modeled for several types of freshwater aquatic environments (Wolfe et al. 1980). 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). DEHP can undergo indirect photolysis in sunlit surface waters. Yu et al. (2019) demonstrated that nitrate or ferric ions facilitated the photodegradation of DEHP via oxidation with photochemically generated hydroxyl radicals and naturally occurring fulvic acids in water also promoted the photolysis of DEHP in surface waters via indirect photolysis whereby the fulvic acids absorb photons in the environmental ultraviolet (UV) spectrum and transfer energy from their excited state directly to DEHP resulting in the photodegradation of DEHP.

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 and Lin 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). The half-life of DEHP in a silt loam (38.6% sand, 45.0% silt, 16.4% clay, 3.8% organic carbon and pH = 6.0) ranged from 24.2 to 29.6 days (He et al. 2018). The half-life in a soil with low organic matter (38.7% sand, 44.4%, silt 16.9% clay, 0.6% organic carbon and pH = 5.8) was shown to be considerably longer, 94.1±4.3 days; however, the half-life tended to decrease as amendments such as compost and biochar were added, which increased the amount of organic matter in the soil.

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 (workplace) <1 ng/m^3 (outdoor)[b]	OSHA 1994 Thurén and Larsson 1990
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	23 µg/kg	Fernández-González et al. 2017
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.
[b]For a sampling volume of 300–400 m^3 collected at a flow rate of 4.5 m^3/day.

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	45.5	12.5	319	197
Soil (ppb)	9,300	14,600	20.3	305	190
Air (µg/m^3)	0.03	0.020	2.9	4	4

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). 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, 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. Its presence in atmospheric samples removed from point source indicates that DEHP is subject to long-range transport. The monitoring studies reported below appear to have taken reasonable efforts to eliminate contamination from their analyses.

Average atmospheric concentrations reported in the literature appear to be within a relatively narrow range regardless of sampling location. DEHP has been reported over the Pacific and Atlantic Oceans at mean levels of approximately 1.4 ng/m^3 with a range of 0.32–2.68 ng/m^3 (Atlas and Giam 1981; Giam et al. 1980). Within the continental United States, DEHP levels over the Great Lakes have been reported at a mean concentration of 2.0 ng/m^3 with a range of 0.50–5.0 ng/m^3 (Eisenreich et al. 1981). However, DEHP was not among the four phthalate esters detected in industrialized areas along the Niagara River (Hoff and Chan 1987). DEHP levels near Lake Chaohu, China were reported to range from 1.229 to 14.418 ng/m^3 (He et al. 2019).

DEHP has also been noted in outdoor air over Portland, Oregon at a mean level of 0.39 ng/m^3 with a range of 0.06–0.94 ng/m^3 (Ligocki et al. 1985a). The mean (± standard deviation) concentration of DEHP in outdoor air near a residence in Contra Costa County, California, was 3.4±0.4 ng/m^3 (Lunderberg et al. 2019). DEHP was detected in ambient air during a 7-month sampling period from a highly populated area of Mexico City, Mexico (Quintana-Belmares et al. 2018). DEHP levels ranged from 32.8 to

175.8 μg/g in PM_{10} particulates and from 21.5 to 229.7 μg/g in $PM_{2.5}$ particulates. DEHP has been noted in outdoor air in Sweden at a median concentration of 2.0 ng/m^3 with a range of 0.28–77.0 ng/m^3 (Thurén and Larsson 1990). In Germany above a forest, DEHP was detected but not quantified (Helmig et al. 1990).

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; 11,500 ng/m^3) observed in the workplace where plastics were melted. Szewczyńska et al. (2020) measured levels of DEHP in the workplace air of four companies in Poland involved in the manufacture of plastics and rubber products that could emit DEHP to the air. The maximum concentrations of DEHP in the respirable (aerodynamic diameter particles of <4 μm) and inhalable fractions were 1.25 and 6.47 μg/m^3, respectively.

Additional studies have quantified residential indoor DEHP air concentrations. In the spring of 2000, DEHP concentrations in five homes located in Tokyo, Japan ranged from 0.04 to 0.06 μg/m^3, with a concentration of 0.23 μg/m^3 reported in a sixth home (Otake et al. 2001). Thirty-two homes in New York City had a mean DEHP concentration of 0.09 μg/m^3 (90 ng/m^3), measured during a 2-week period (Adibi et al. 2008). In another study, Lunderberg et al. (2019) measured DEHP levels in indoor air in a single-family residential home in Contra Costa County, California, from December 7, 2017 to February 4, 2018. The mean (± standard deviation) DEHP level was 0.009±0.016 μg/m^3 when residents were home and 0.0014±0.0016 μg/m^3 when the home was vacant, suggesting that human activities can increase the levels of airborne DEHP.

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 2009b).

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). 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. 1985a).

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. 1985b; 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

Table 5-6. Concentration of DEHP in Food

	Concentration of DEHP (µg/g)		
Food	Minimum	Maximum	Median
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

Serrano et al. (2014) reviewed 17 studies measuring phthalate concentrations in United States and international foods and found DEHP levels in poultry, cooking oils, and cream-based dairy products often exceeded ≥300 µg/kg (0.300 µg/g). DEHP was detected in 74% of 72 individual food samples purchased in Albany, New York (Schecter et al. 2013). The mean and median values of DEHP in these food items are provided in Table 5-7.

Table 5-7. Mean and Median Values of DEHP in Food

Food item	Mean[a] (µg/g)	Median (µg/g)
Beverages	0.00385	0.00189
Milk	0.0486	0.0486
Other dairy	0.144	0.0928
Fish	0.0317	0.0396
Fruit/vegetables	0.00625	0.00185
Grain	0.0616	0.0506
Beef	0.00185	0.00185
Pork	0.300	0.0206
Poultry	0.0186	0.0148
Meat and meat products	0.101	0.007
Vegetable oils	0.117	0.0489
Condiments	0.0304	0.0206
Infant food	0.0751	0.0294

[a]Mean values were calculated substituting one-half the limit of detection for each non-detect.

Source: Schecter et al. 2013

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 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. 1981; Cole et al. 1981; Contreras et al. 1974; 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. 1981). 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. Newer circuits using other plasticizers such as trioctyltrimellitate (TOTM) have been shown to reduce exposure to DEHP; however, PVC priming bags that use DEHP as a plasticizer may still result in exposure (Fernandez-Canal et al. 2018).

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). In 2008, the Consumer Products Safety Commission (CPSC) tested 63 children's plastic toys purchased in the United States, 38 of which were composed of PVC (Babich et al. 2020). DEHP was detected in only 1 out these 38 toys. DEHP was detected above 0.1% in 11 out of 118 samples obtained from PVC composed children's toys in Switzerland (McCombie et al. 2017).

As presented in Section 5.5.2 above, Bauer and Herrmann (1997) reported that mixed household waste contained DEHP. Table 5-8 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 5-8. 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
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 off gassing 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 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-15, and 5-16 (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. (2009a) 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

Table 5-9. 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 5-9. 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	
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 5-9. 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	
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 5-10. Creatinine-Corrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2014

	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	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 5-10. Creatinine-Corrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2014

	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	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 5-10. Creatinine-Corrected Urinary MEHP Concentrations for the U.S. Population from NHANES 1999–2014

	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	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 5-11. 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 5-11. 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 5-11. 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 5-12. 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 5-12. 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 5-12. 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 5-13. 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 5-13. 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 5-13. 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 5-14. 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 5-14. 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 5-14. 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 5-15. 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 5-15. 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 5-15. 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; MECPP = mono-2-ethyl-5-carboxypentylphthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

Table 5-16. 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 5-16. 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 5-16. 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; MECPP = mono-2-ethyl-5-carboxypentylphthalate; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2018

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. Data obtained from a study in which phthalates were measured in 72 food items purchased in Albany, New York yielded an estimated mean adult intake of approximately 0.673 µg/kg/day for DEHP (Schecter et al. 2013).

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 workday of 5 mg/m^3 (OSHA 2019a, 2019b, 2019c).

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. (2009b, 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. 2009b). 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).

Children may be 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. 2009a); 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. 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. 1985b; 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). Kaestner et al. (2020) measured DEHP blood levels of ECMO patients hospitalized between May 2015 and December 2016. DEHP levels of patients receiving ECMO ranged from 31.5 to 1,009 μg/L (median 156.0 μg/L) while DEHP levels of a control group ranged from 19.4 to 75.3 μg/L (median 36.4 μg/L). 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
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

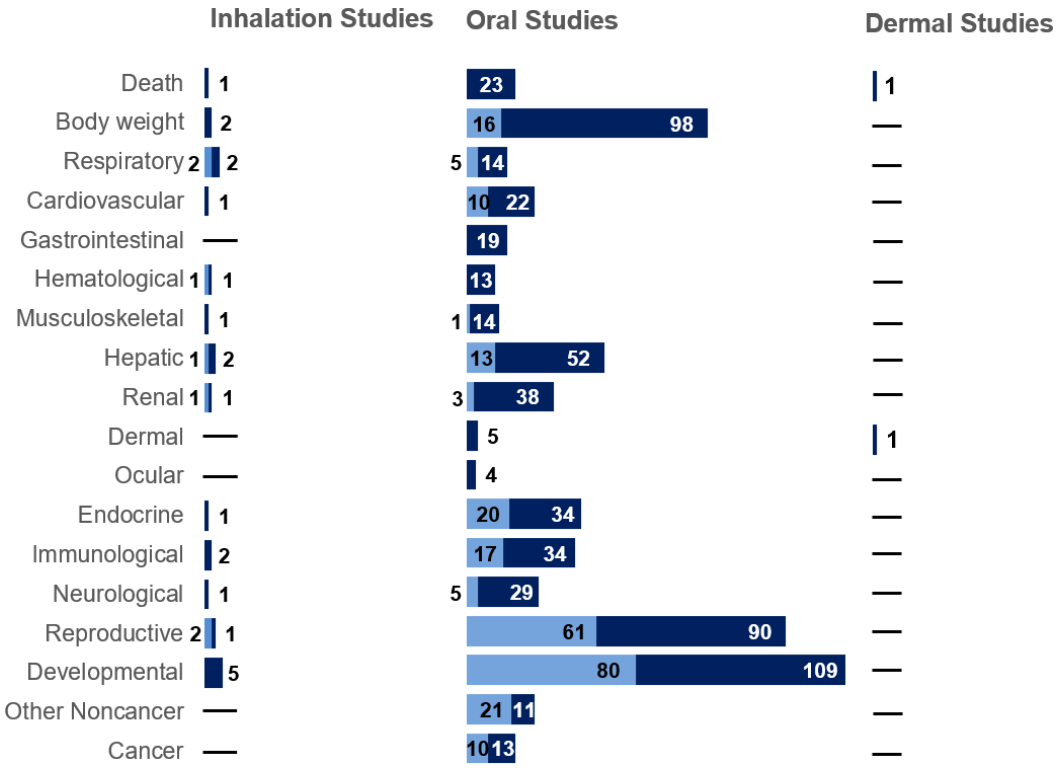
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to DEHP that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of DEHP. The number of human and animal 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 an MRL, a NOAEL value has not been established for the sensitive effect that serves as the basis of the MRL (altered glucose homeostasis in offspring). Additionally, NOAEL values have not been established for other sensitive effects following acute oral exposure (altered reproductive development in offspring, adult male reproductive effects). Similarly, potential adjuvant effects of DEHP, identified as a sensitive effect in longer-duration studies, have not been evaluated following acute oral exposure. Additional low-dose studies evaluating these endpoints could reduce uncertainty in the acute-duration oral MRL.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Ongoing Studies

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

Table 6-1. Ongoing Studies on DEHP

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

Table 6-1. Ongoing Studies on DEHP

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

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

Source: RePORTER 2021

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	Not evaluated	IRIS 1988
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	DWEL	0.7 mg/L	
	10^{-4} cancer risk	0.3 mg/L	
	National primary drinking water regulations		EPA 2009c
	Maximum contaminant level	0.006 mg/L	
	Public health goal	0	
	RfD	$2x10^{-2}$ mg/kg/day	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	Substances added to food[a]	Not listed	FDA 2020
	Indirect additives used in food contact substances[b]	Allowed for some uses	FDA 2019a
	Allowable level in bottled water	0.006 mg/L	FDA 2019b
	Tolerable intake value (oral)	0.04 mg/kg/day	FDA 2001
	Cancer		
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016
EPA	Carcinogenicity classification	Group B2[c]	IRIS 1988
IARC	Carcinogenicity classification	Group 2B[d]	IARC 2013

Table 7-1. Regulations and Guidelines Applicable to DEHP

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	5 mg/m^3	OSHA 2019a, 2019b, 2019c
NIOSH	REL (up to 10-hour TWA)	5 mg/m^3 [e]	NIOSH 2019
	STEL	10 mg/m^3	
	Emergency Criteria		
EPA	AEGLs-air	Not listed	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[f]	10 mg/m^3	
	PAC-2[f]	1,000 mg/m^3	
	PAC-3[f]	6,100 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]The Indirect Additives Used in Food Contact Substances list is a compilation of substances found in 21 CFR parts 175–178.
[c]Group B2: probable human carcinogen.
[d]Group 2B: possibly carcinogenic to humans.
[e]Potential occupational carcinogen.
[f]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; CFR = Code of Federal Regulations; 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; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; 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

Abdel-Maksoud FM, Knight R, Waler K, et al. 2018. Exposures of male rats to environmental chemicals [bisphenol A and di (2-ethylhexyl) phthalate] affected expression of several proteins in the developing epididymis. Andrology 6(1):214-222. http://doi.org/10.1111/andr.12451.

Abdel-Maksoud FM, Ali FAZ, Akingbemi BT. 2019. Prenatal exposures to bisphenol A and di (2-ethylhexyl) phthalate disrupted seminiferous tubular development in growing male rats. Reprod Toxicol 88:85-90. http://doi.org/10.1016/j.reprotox.2019.07.017.

Abe S, Sasaki M. 1977. Chromosome aberrations and sister chromatid exchanges in Chinese hamster cells exposed to various chemicals. J Natl Cancer Inst 58:1635-1641.

Absalan F, Saremy S, Mansori E, et al. 2017. Effects of mono-(2-ethylhexyl) phthalate and di-(2-ethylhexyl) phthalate administrations on oocyte meiotic maturation, apoptosis and gene quantification in mouse model. Cell J 18(4):503-513. http://doi.org/10.22074/cellj.2016.4717.

ACGIH. 2001. Di(2-ethylhexyl)phthalate. In: Documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1-6.

ACGIH. 2016. Di(2-ethylhexyl)phthalate. In: TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 27, 77.

Adachi K, Suemizu H, Murayama N, et al. 2015. Human biofluid concentrations of mono(2-ethylhexyl)phthalate extrapolated from pharmacokinetics in chimeric mice with humanized liver administered with di(2-ethylhexyl)phthalate and physiologically based pharmacokinetic modeling. Environ Toxicol Pharmacol 39(3):1067-1073. http://doi.org/10.1016/j.etap.2015.02.011.

Adibi JJ, Whyatt RM, Williams PL, et al. 2008. Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples. Environ Health Perspect 116(4):467-473. http://doi.org/10.1289/ehp.10749.

Adibi JJ, Hauser R, Williams PL, et al. 2009. Maternal urinary metabolites of di-(2-ethylhexyl) phthalate in relation to the timing of labor in a US multicenter pregnancy cohort study. Am J Epidemiol 169(8):1015-1024. http://doi.org/10.1093/aje/kwp001.

Adibi JJ, Lee MK, Naimi AI, et al. 2015. Human chorionic gonadotropin partially mediates phthalate association with male and female anogenital distance. J Clin Endocrinol Metab 100(9):E1216-E1224. http://doi.org/10.1210/jc.2015-2370.

Agarwal DK, Agarwal S, Seth PK. 1982. Interaction of di-(2-ethylhexyl) phthalate with the pharmacological response and metabolic aspects of ethanol in mice. Biochem Pharmacol 31:3419-3423.

Agarwal DK, Lawrence WH, Nunez LJ, et al. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites in Salmonella typhimurium cultures. J Toxicol Environ Health 16(1):61-69. http://doi.org/10.1080/15287398509530719.

Agarwal DK, Eustis S, Lamb JC, et al. 1986. Effects of di(2-ethylhexyl) phthalate on the gonadal pathophysiology, sperm morphology, and reproductive performance of male rats. Environ Health Perspect 65:343-350.

Agay-Shay K, Martinez D, Valvi D, et al. 2015. Exposure to endocrine-disrupting chemicals during pregnancy and weight at 7 years of age: A multi-pollutant approach. Environ Health Perspect 123(10):1030-1037. http://doi.org/10.1289/ehp.1409049.

Ahmad S, Khan MF, Parvez S, et al. 2017. Molecular docking reveals the potential of phthalate esters to inhibit the enzymes of the glucocorticoid biosynthesis pathway. J Appl Toxicol 37(3):265-277. http://doi.org/10.1002/jat.3355.

Ahmed RS, Price SC, Grasso P, et al. 1989. Effects of intermittent feeding of rats with di-2-ethylhexylphthalate. Biochem Soc Trans 17(6):1073-1074.

Akingbemi BT, Youker RT, Sottas CM, et al. 2001. Modulation of rat Leydig cell steroidogenic function by di(2-ethylhexyl)phthalate. Biol Reprod 65(4):1252-1259. http://doi.org/10.1095/biolreprod65.4.1252.

Akingbemi BT, Ge R, Klinefelter GR, et al. 2004. Phthalate-induced Leydig cell hyperplasia is associated with multiple endocrine disturbances. Proc Natl Acad Sci U S A 101(3):775-780. http://doi.org/10.1073/pnas.0305977101.

Albert O, Jégou B. 2014. A critical assessment of the endocrine susceptibility of the human testis to phthalates from fetal life to adulthood. Hum Reprod Update 20(2):231-249. http://doi.org/10.1093/humupd/dmt050.

Albro PW. 1986. Absorption, metabolism, and excretion of di(2-ethylhexyl) phthalate by rats and mice. Environ Health Perspect 65:293-298.

Albro PW, Thomas RO. 1973. Enzymatic hydrolysis of di-(2-ethylhexyl) phthalate by lipases. Biochim Biophys Acta 360(3):380-390.

Albro PW, Corbett JT. 1978. Distribution of di-and mono-(2-ethylhexyl) phthalate in human plasma. Transfusion 18:750-755.

Albro PW, Lavenhar SR. 1989. Metabolism of di(2-ethylhexyl)phthalate. Drug Metab Rev 21(1):13-34. http://doi.org/10.3109/03602538909029953.

Albro PW, Hass JR, Peck CC, et al. 1981. Identification of the metabolites of di-(2-ethylhexyl) phthalate in urine from the African green monkey. Drug Metab Dispos 9(3):223-225.

Albro PW, Corbett JT, Schroeder JL, et al. 1982a. Pharmacokinetics, interactions with macromolecules and species difference in metabolism of DEHP. Environ Health Perspect 45:19-25.

Albro PW, Hass JR, Peck CC, et al. 1982b. Applications of isotope differentiation for metabolic studies with di-(2-ethylhexyl) phthalate. J Environ Sci Health B 17(6):701-714.

Albro PW, Tondeur I, Marbury D, et al. 1983. Polar metabolites of di-(2-ethylhexyl)phthalate in the rat. Biochim Biophys Acta 760:283-292.

Alexander BM, Baxter CS. 2016. Flame-retardant contamination of firefighter personal protective clothing- a potential health risk for firefighters. J Occup Environ Hyg 13(9):D148-D155.

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

Al-Saleh I, Coskun S, Al-Doush I, et al. 2019a. The relationships between urinary phthalate metabolites, reproductive hormones and semen parameters in men attending in vitro fertilization clinic. Sci Total Environ 658:982-995. http://doi.org/10.1016/j.scitotenv.2018.12.261.

Al-Saleh I, Coskun S, Al-Doush I, et al. 2019b. Exposure to phthalates in couples undergoing in vitro fertilization treatment and its association with oxidative stress and DNA damage. Environ Res 169:396-408. http://doi.org/10.1016/j.envres.2018.11.018.

Al-Saleh I, Coskun S, Al-Doush I, et al. 2019c. Supplemental material: Exposure to phthalates in couples undergoing in vitro fertilization treatment and its association with oxidative stress and DNA damage. Environ Res 169. http://doi.org/10.1016/j.envres.2018.11.018.

Al-Saleh I, Coskun S, Al-Doush I, et al. 2019d. Couples exposure to phthalates and its influence on in vitro fertilization outcomes. Chemosphere 226:597-606. http://doi.org/10.1016/j.chemosphere.2019.03.146.

Andersen C, Krais AM, Eriksson AC, et al. 2018. Inhalation and dermal uptake of particle and gas-phase phthalates—a human exposure study. Environ Sci Technol 52(21):12792-12800. http://doi.org/10.1021/acs.est.8b03761.

Anderson SP, Cattley RC, Corton JC. 1999. Hepatic expression of acute-phase protein genes during carcinogenesis induced by peroxisome proliferators. Mol Carcinog 26:226-238.

Anderson WAC, Castle L, Scotter MJ, et al. 2001. A biomarker approach to measuring human dietary exposure to certain phthalate diesters. Food Addit Contam 18(12):1068-1074. http://doi.org/10.1080/02652030110050113.

Anderson WA, Castle L, Hird S, et al. 2011. A twenty-volunteer study using deuterium labelling to determine the kinetics and fractional excretion of primary and secondary urinary metabolites of di-2-

ethylhexylphthalate and di-iso-nonylphthalate. Food Chem Toxicol 49(9):2022-2029. http://doi.org/10.1016/j.fct.2011.05.013.

Andrade AJ, Grande SW, Talsness CE, et al. 2006a. A dose response study following in utero and lactational exposure to di-(2-ethylhexyl) phthalate (DEHP): Reproductive effects on adult male offspring rats. Toxicology 228(1):85-97. http://doi.org/10.1016/j.tox.2006.08.020.

Andrade AJ, Grande SW, Talsness CE, et al. 2006b. A dose-response study following in utero and lactational exposure to di-(2-ethylhexyl)-phthalate (DEHP): Non-monotonic dose-response and low dose effects on rat brain aromatase activity. Toxicology 227(3):185-192. http://doi.org/10.1016/j.tox.2006.07.022.

Andrade AJ, Grande SW, Talsness CE, et al. 2006c. A dose-response study following in utero and lactational exposure to di-(2-ethylhexyl) phthalate (DEHP): Effects on androgenic status, developmental landmarks and testicular histology in male offspring rats. Toxicology 225(1):64-74. http://doi.org/10.1016/j.tox.2006.05.007.

Araki A, Ait Bamai Y, Bastiaensen M, et al. 2020. Combined exposure to phthalate esters and phosphate flame retardants and plasticizers and their associations with wheeze and allergy symptoms among school children. Environ Res 183:109212. http://doi.org/10.1016/j.envres.2020.109212.

Arbuckle TE, MacPherson S, Barrett E, et al. 2019. Do stressful life events during pregnancy modify associations between phthalates and anogenital distance in newborns? Environ Res 177:108593. http://doi.org/10.1016/j.envres.2019.108593.

Arcadi FA, Costa C, Imperatore C, et al. 1998. Oral toxicity of bis(2-ethylhexyl) phthalate during pregnancy and suckling in the Long-Evans rat. Food Chem Toxicol 36(11):963-970. http://doi.org/10.1016/s0278-6915(98)00065-9.

Arzuaga X, Smith MT, Gibbons CF, et al. 2019. Proposed key characteristics of male reproductive toxicants as an approach for organizing and evaluating mechanistic evidence in human health hazard assessments. Environ Health Perspect 127(6):065001. http://doi.org/10.1289/ehp5045.

Ashari S, Karami M, Shokrzadeh M, et al. 2020. The implication of mitochondrial dysfunction and mitochondrial oxidative damage in di (2-ethylhexyl) phthalate induced nephrotoxicity in both in vivo and in vitro models. Toxicol Mech Methods 30(6):427-437. http://doi.org/10.1080/15376516.2020.1758980.

Ashley-Martin J, Dodds L, Levy AR, et al. 2015. Prenatal exposure to phthalates, bisphenol A and perfluoroalkyl substances and cord blood levels of IgE, TSLP and IL-33. Environ Res 140:360-368. http://doi.org/10.1016/j.envres.2015.04.010.

Astill BD. 1989. Metabolism of DEHP: Effects of prefeeding and dose variation, and comparative studies in rodents and the cynomolgus monkey (CMA studies). Drug Metab Rev 21(1):35-53.

Astill B, Barber E, Lington A, et al. 1986. Chemical industry voluntary test program for phthalate esters: Health effects studies. Environ Health Perspect 65:329-336.

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

ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Subtances and Disease Registry. Fed Regist 54(174):37618-37634.

ATSDR. 2010. Health consultation. Evaluation of contaminants in private residential well water, Fremont County, Pavillion, Wyoming. Agency For Toxic Substances and Disease Registry.

ATSDR. 2017. Di-(2-ethylhexyl)phthalate. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/SPL/resources/index.html. January 16, 2018.

ATSDR. 2019. Di-2-ethylhexyl phthalate. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry.

Attina TM, Trasande L. 2015. Association of exposure to di-2-ethylhexylphthalate replacements with increased insulin resistance in adolescents from NHANES 2009-2012. J Clin Endocrinol Metab 100(7):2640-2650. http://doi.org/10.1210/jc.2015-1686.

8. REFERENCES

Autian J. 1982. Antifertility effects and dominant lethal assays for mutagenic effects of DEHP. Environ Health Perspect 45:115-118.

Axelsson J, Rylander L, Rignell-Hydbom A, et al. 2015. Phthalate exposure and reproductive parameters in young men from the general Swedish population. Environ Int 85:54-60. http://doi.org/10.1016/j.envint.2015.07.005.

Aydemir D, Karabulut G, Şimşek G, et al. 2018. Impact of the di(2-ethylhexyl) phthalate administration on trace element and mineral levels in relation of kidney and liver damage in rats. Biol Trace Elem Res 186(2):474-488. http://doi.org/10.1007/s12011-018-1331-0.

Babich MA, Bevington C, Dreyfus MA. 2020. Plasticizer migration from children's toys, child care articles, art materials, and school supplies. Regul Toxicol Pharmacol 111:104574. http://doi.org/10.1016/j.yrtph.2019.104574.

Balalian AA, Whyatt RM, Liu X, et al. 2019. Prenatal and childhood exposure to phthalates and motor skills at age 11 years. Environ Res 171:416-427. http://doi.org/10.1016/j.envres.2019.01.046.

Barakat R, Lin PP, Rattan S, et al. 2017. Prenatal exposure to DEHP induces premature reproductive senescence in male mice. Toxicol Sci 156(1):96-108. http://doi.org/10.1093/toxsci/kfw248.

Barakat R, Lin PC, Park CJ, et al. 2018. Prenatal exposure to DEHP induces neuronal degeneration and neurobehavioral abnormalities in adult male mice. Toxicol Sci 164(2):439-452. http://doi.org/10.1093/toxsci/kfy103.

Barakat R, Lin PC, Park CJ, et al. 2020. Germline-dependent transmission of male reproductive traits induced by an endocrine disruptor, di-2-ethylhexyl phthalate, in future generations. Sci Rep 10(1):5705. http://doi.org/10.1038/s41598-020-62584-w.

Barber ED, Astill BD, Moran EJ, et al. 1987. Peroxisome induction studies on seven phthalate esters. Toxicol Ind Health 3(2):7-24. http://doi.org/10.1177/074823378700300203.

Barber ED, Teetsel NM, Kolberg KF, et al. 1992. A comparative study of the rats of *in vitro* percutaneous absorption of eight chemicals using rat and human skin. Fundam Appl Toxicol 19:493-497.

Barber ED, Fox JA, Giordano CJ. 1994. Hydrolysis, absorption and metabolism of di(2-ethylhexyl) terephthalate in the rat. Xenobiotica 24(5):441-450.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

Barrett ES, Parlett LE, Wang C, et al. 2014. Environmental exposure to di-2-ethylhexyl phthalate is associated with low interest in sexual activity in premenopausal women. Horm Behav 66(5):787-792. http://doi.org/10.1016/j.yhbeh.2014.10.003.

Barrett ES, Parlett LE, Sathyanarayana S, et al. 2016. Prenatal stress as a modifier of associations between phthalate exposure and reproductive development: Results from a multicentre pregnancy cohort study. Paediatr Perinat Epidemiol 30(2):105-114. http://doi.org/10.1111/ppe.12264.

Barrows ME, Petrocelli SR, Macek KJ. 1980. Bioconcentration and elimination of selected water pollutants by bluegill sunfish (*Lepomis macrochirus*). In: Haque R, ed. Dynamics, exposure and hazard assessment of toxic chemicals. Ann Arbor, MN: Ann Arbor Science Publishers, Inc., 379-392.

Barry YA, Labow RS, Keon WJ, et al. 1990. Atropine inhibition of the cardiodepressive effect of mono(2-ethylhexyl)phthalate on human myocardium. Toxicol Appl Pharmacol 106:48-52.

Bartles JR, Khuon S, Lin XH, et al. 1990. Peroxisome proliferator-induced alterations in the expression and modification of rat hepatocyte plasma membrane proteins. Cancer Res 50(3):669-676.

Basak S, Das MK, Duttaroy AK. 2020. Plastics derived endocrine-disrupting compounds and their effects on early development. Birth Defects Research 112(17):1308-1325. http://doi.org/10.1002/bdr2.1741.

Bastos Sales L, van Esterik JCJ, Hodemaekers HM, et al. 2018. Analysis of lipid metabolism, immune function, and neurobehavior in adult C57BL/6JxFVB mice after developmental exposure to di(2-ethylhexyl) phthalate. Front Endocrinol 9:684. http://doi.org/10.3389/fendo.2018.00684.

8. REFERENCES

Bauer MJ, Herrmann R. 1997. Estimation of the environmental contamination by phthalic acid esters leaching from household wastes. Sci Total Environ 208:49-57.

Beko G, Callesen M, Weschler CJ, et al. 2015. Phthalate exposure through different pathways and allergic sensitization in preschool children with asthma, allergic rhinoconjunctivitis and atopic dermatitis. Environ Res 137:432-439. http://doi.org/10.1016/j.envres.2015.01.012.

Bell FP. 1976. Inhibition of hepatic sterol and squalene biosynthesis in rats fed di-2-ethylhexyl phthalate. Lipids 11(10):769-773. http://doi.org/10.1007/bf02533053.

Bell FP. 1980. Effect of di-2-ethylhexyl phthalate in the female rat: Inhibition of hepatic and adrenal sterologenesis in vitro. Bull Environ Contam Toxicol 24:54-58.

Bell FP. 1982. Effects of phthalate esters on lipid metabolism in various tissues, cells and organelles in mammals. Environ Health Perspect 45(0):41-50.

Bell FP, Buthala DA. 1983. Biochemical changes in liver of rats fed the plasticizer di (2-ethylhexy) phthalate. Bull Environ Contam Toxicol 31(2):177-182. http://doi.org/10.1007/bf01607890.

Bellavia A, Hauser R, Seely EW, et al. 2017. Urinary phthalate metabolite concentrations and maternal weight during early pregnancy. Int J Hyg Environ Health 220:1347-1355.

Berger K, Eskenazi B, Kogut K, et al. 2018. Association of prenatal urinary concentrations of phthalates and bisphenol A and pubertal timing in boys and girls. Environ Health Perspect 126(9):97004. http://doi.org/10.1289/EHP3424.

Berk M, Williams LJ, Andreazza A, et al. 2014. Pop, heavy metal and the blues: secondary analysis of persistent organic pollutants (POP), heavy metals and depressive symptoms in the NHANES National Epidemiological Survey. Br Med J 4(7):e005142. http://doi.org/10.1136/bmjopen-2014-005142.

Berman E, Schlicht M, Moser VC, et al. 1995. A multidisciplinary approach to toxicological screening: I. Systemic toxicity. J Toxicol Environ Health 45(2):127-143. http://doi.org/10.1080/15287399509531986.

Bertelsen RJ, Carlsen KC, Calafat AM, et al. 2013. Urinary biomarkers for phthalates associated with asthma in Norwegian children. Environ Health Perspect 121(2):251-256. http://doi.org/10.1289/ehp.1205256.

Binder AM, Corvalan C, Calafat AM, et al. 2018a. Childhood and adolescent phenol and phthalate exposure and the age of menarche in Latina girls. Environ Health 17(1):32. http://doi.org/10.1186/s12940-018-0376-z.

Binder AM, Corvalan C, Calafat AM, et al. 2018b. Supplemental material: Childhood and adolescent phenol and phthalate exposure and the age of menarche in Latina girls. Environ Health 17. http://doi.org/10.1186/s12940-018-0376-z.

Bloom MS, Whitcomb BW, Chen Z, et al. 2015a. Associations between urinary phthalate concentrations and semen quality parameters in a general population. Hum Reprod 30(11):2645-2657. http://doi.org/10.1093/humrep/dev219.

Bloom MS, Whitcomb BW, Chen Z, et al. 2015b. Supplemental material: Associations between urinary phthalate concentrations and semen quality parameters in a general population. Hum Reprod 30. http://doi.org/10.1093/humrep/dev219.

Bloom MS, Wenzel AG, Brock JW, et al. 2019a. Racial disparity in maternal phthalates exposure; Association with racial disparity in fetal growth and birth outcomes. Environ Int 127:473-486. http://doi.org/10.1016/j.envint.2019.04.005.

Bloom MS, Wenzel AG, Brock JW, et al. 2019b. Supplemental material: Racial disparity in maternal phthalates exposure; Association with racial disparity in fetal growth and birth outcomes. Environ Int 127. http://doi.org/10.1016/j.envint.2019.04.005.

Bluthgen A. 2000. Organic migration agents into milk at farm level (illustrated with diethylhexylphthalate). Bull IDF 356:39-42.

Blystone C, Kissling G, Bishop J, et al. 2010. Determination of the di-(2-ethylhexyl) phthalate NOAEL for reproductive development in the rat: importance of the retention of extra animals to adulthood. Toxicol Sci 116(2):640-646. http://doi.org/10.1093/toxsci/kfq147.

Boas M, Frederiksen H, Feldt-Rasmussen U, et al. 2010. Childhood exposure to phthalates: Associations with thyroid function, insulin-like growth factor I, and growth. Environ Health Perspect 118(10):1458-1464. http://doi.org/10.1289/ehp.0901331.

Boerrigter ME. 2004. Mutagenicity of the peroxisome proliferators clofibrate, Wyeth 14,643 and di-2-ethylhexyl phthalate in the lacZ plasmid-based transgenic mouse mutation assay. J Carcinog 3(1):7. http://doi.org/10.1186/1477-3163-3-7.

Bolling AK, Holme JA, Bornehag CG, et al. 2013. Pulmonary phthalate exposure and asthma - is PPAR a plausible mechanistic link? EXCLI J 12:733-759.

Borch J, Metzdorff SB, Vinggaard AM, et al. 2006. Mechanisms underlying the anti-androgenic effects of diethylhexyl phthalate in fetal rat testis. Toxicology 223(1-2):144-155. http://doi.org/10.1016/j.tox.2006.03.015.

Bornehag CG, Lundgren B, Weschler CJ, et al. 2005. Phthalates in indoor dust and their association with building characteristics. Environ Health Perspect 113(10):1399-1404. http://doi.org/10.1289/ehp.7809.

Bornehag CG, Carlstedt F, Jonsson BA, et al. 2015. Prenatal phthalate exposures and anogenital distance in Swedish boys. Environ Health Perspect 123(1):101-107. http://doi.org/10.1289/ehp.1408163.

Braun JM, Smith KW, Williams PL, et al. 2012. Variability of urinary phthalate metabolite and bisphenol A concentrations before and during pregnancy. Environ Health Perspect 120(5):739-745. http://doi.org/10.1289/ehp.1104139.

Braun JM, Kalkbrenner AE, Just AC, et al. 2014. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study. Environ Health Perspect 122(5):513-520. http://doi.org/10.1289/ehp.1307261.

Braun JM, Bellinger DC, Hauser R, et al. 2017a. Prenatal phthalate, triclosan, and bisphenol A exposures and child visual-spatial abilities. Neurotoxicology 58:75-83. http://doi.org/10.1016/j.neuro.2016.11.009.

Braun JM, Bellinger DC, Hauser R, et al. 2017b. Supplemental material: Prenatal phthalate, triclosan, and bisphenol A exposures and child visual-spatial abilities. Neurotoxicology 58. http://doi.org/10.1016/j.neuro.2016.11.009.

Brehm E, Rattan S, Gao L, et al. 2018. Prenatal exposure to di(2-ethylhexyl) phthalate causes long-term transgenerational effects on female reproduction in mice. Endocrinology 159(2):795-809. http://doi.org/10.1210/en.2017-03004.

Brown KW, Donnelly KC. 1988. An estimation of risk associated with the organic constituents of hazardous and municipal waste landfill leachates. Haz Waste Haz Mater 5(1):1-30.

Buck Louis GM, Peterson CM, Chen Z, et al. 2013. Bisphenol A and phthalates and endometriosis: The Endometriosis: Natural History, Diagnosis and Outcomes Study. Fertil Steril 100(1):162-169. http://doi.org/10.1016/j.fertnstert.2013.03.026.

Buck Louis GM, Sundaram R, Sweeney AM, et al. 2014. Urinary bisphenol A, phthalates, and couple fecundity: the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Fertil Steril 101(5):1359-1366. http://doi.org/10.1016/j.fertnstert.2014.01.022.

Buckley JP, Engel SM, Braun JM, et al. 2016a. Prenatal phthalate exposures and body mass index among 4- to 7-year-old children: A pooled analysis. Epidemiology 27(3):449-458. http://doi.org/10.1097/ede.0000000000000436.

Buckley JP, Engel SM, Mendez MA, et al. 2016b. Prenatal phthalate exposures and childhood fat mass in a New York City cohort. Environ Health Perspect 124(4):507-513. http://doi.org/10.1289/ehp.1509788.

Buser MC, Murray HE, Scinicariello F. 2014. Age and sex differences in childhood and adulthood obesity association with phthalates: Analyses of NHANES 2007-2010. Int J Hyg Environ Health 217(6):687-694. http://doi.org/10.1016/j.ijheh.2014.02.005.

Busser MT, Lutz WK. 1987. Stimulation of DNA synthesis in rat and mouse liver by various tumor promoters. Carcinogenesis 8(10):1433-1437.

Bustamante-Montes LP, Hernández-Valero MA, Flores-Pimentel D, et al. 2013. Prenatal exposure to phthalates is associated with decreased anogenital distance and penile size in male newborns. J Dev Orig Health Dis 4(4):300-306. http://doi.org/10.1017/s2040174413000172.

Butterworth BE. 1984. The genetic toxicology of di(2-ethylhexyl)phthalate (DEHP). CIIT Activities 4(10):1-8.

Butterworth BE, Bermudez E, Smith-Oliver T, et al. 1984. Lack of genotoxic activity of di(2-ethylhexyl)phthalate (DEHP) in rat and human hepatocytes. Carcinogenesis 5(10):1329-1335.

Cadogan DF, Howick C. 2001. Plasticizers. In: Kirk-Othmer encyclopedia of chemical technology. John Wiley & Sons, http://doi.org/10.1002/0471238961.1612011903010415.a01.

Cadogan DF, Papez M, Poppe AC, et al. 1994. An assessment of the release, occurrence and possible effects of plasticisers in the environment. Prog Rubber Plast Technol 10:1-19.

Cahill TM, Cousins I, Mackay D. 2003. Development and application of a generalized physiologically based pharmacokinetic model for multiple environmental contaminants. Environ Toxicol Chem 22(1):26-34. http://doi.org/10.1002/etc.5620220104.

Cakmak S, Dales RE, Hebbern C, et al. 2014. The association between urinary phthalates and lung function. J Occup Environ Med 56(4):376-381. http://doi.org/10.1097/jom.0000000000000137.

Calafat AM, Slakman AR, Silva MJ, et al. 2004. Automated solid phase extraction and quantitative analysis of human milk for 13 phthalate metabolites. J Chromatogr 805(1):49-56. http://doi.org/10.1016/j.jchromb.2004.02.006.

Calafat AM, Brock JW, Silva MJ, et al. 2006. Urinary and amniotic fluid levels of phthalate monoesters in rats after the oral administration of di(2-ethylhexyl) phthalate and di-n-butyl phthalate. Toxicology 217(1):22-30. http://doi.org/10.1016/j.tox.2005.08.013.

Calafat AM, Longnecker MP, Koch HM, et al. 2015. Optimal exposure biomarkers for nonpersistent chemicals in environmental epidemiology. Environ Health Perspect 123(7):A166-A168.

Caldwell JC. 2012. DEHP: Genotoxicity and potential carcinogenic mechanisms-A review. Mutat Res 751(2):82-157. http://doi.org/10.1016/j.mrrev.2012.03.001.

Camacho L, Latendresse JR, Muskhelishvili L, et al. 2020. Effects of intravenous and oral di(2-ethylhexyl) phthalate (DEHP) and 20% Intralipid vehicle on neonatal rat testis, lung, liver, and kidney. Food Chem Toxicol 144:111497. http://doi.org/10.1016/j.fct.2020.111497.

Camann DE, Schultz ST, Yau AY, et al. 2013. Acetaminophen, pesticide, and diethylhexyl phthalate metabolites, anandamide, and fatty acids in deciduous molars: potential biomarkers of perinatal exposure. J Expo Sci Environ Epidemiol 23(2):190-196. http://doi.org/10.1038/jes.2012.71.

Canter LW, Sabatini DA. 1994. Contamination of public ground water supplies by Superfund sites. Int J Environ Stud 46:35-57.

Cantonwine DE, Meeker JD, Ferguson KK, et al. 2016. Urinary concentrations of bisphenol A and phthalate metabolites measured during pregnancy and risk of preeclampsia. Environ Health Perspect 124(10):1651-1655. http://doi.org/10.1289/EHP188.

Cao XL. 2010. Phthalate esters in foods: Sources, occurrence, and analytical methods. Compr Rev Food Sci Food Saf 9(1):21-43. http://doi.org/10.1111/j.1541-4337.2009.00093.x.

Carbone S, Szwarcfarb B, Ponzo O, et al. 2010. Impact of gestational and lactational phthalate exposure on hypothalamic content of amino acid neurotransmitters and FSH secretion in peripubertal male rats. Neurotoxicology 31(6):747-751. http://doi.org/10.1016/j.neuro.2010.06.006.

Carbone S, Samaniego YA, Cutrera R, et al. 2012. Different effects by sex on hypothalamic-pituitary axis of prepubertal offspring rats produced by in utero and lactational exposure to di-(2-ethylhexyl) phthalate (DEHP). Neurotoxicology 33(1):78-84. http://doi.org/10.1016/j.neuro.2011.11.009.

Carbone S, Ponzo OJ, Gobetto N, et al. 2013. Antiandrogenic effect of perinatal exposure to the endocrine disruptor di-(2-ethylhexyl) phthalate increases anxiety-like behavior in male rats during sexual maturation. Horm Behav 63(5):692-699. http://doi.org/10.1016/j.yhbeh.2013.01.006.

Carpenter CP, Weil CS, Smyth HF. 1953. Chronic oral toxicity of di-(2-ethylhexyl) phthalate of rats, guinea pigs, and dogs. AMA Arch Ind Hyg Occup Med 8(3):219-226.

Carrara SM, Morita DM, Boscov ME. 2011. Biodegradation of di(2-ethylhexyl)phthalate in a typical tropical soil. J Hazard Mater 197:40-48. http://doi.org/10.1016/j.jhazmat.2011.09.058.

Cartwright CD, Thompson IP, Burns G. 2000. Degradation and impact of phthalate plasticizers on soil microbial communities. Environ Toxicol Chem 19(5):1253-1261.

Casas M, Valvi D, Ballesteros-Gomez A, et al. 2016. Exposure to bisphenol A and phthalates during pregnancy and ultrasound measures of fetal growth in the INMA-Sabadell Cohort. Environ Health Perspect 124(4):521-528. http://doi.org/10.1289/ehp.1409190.

Caserta D, Bordi G, Ciardo F, et al. 2013. The influence of endocrine disruptors in a selected population of infertile women. Gynecol Endocrinol 29(5):444-447. http://doi.org/10.3109/09513590.2012.758702.

Castillo M, Oubina A, Barcelo D. 1998. Evaluation of ELISA kits followed by liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry for the determination of organic pollutants in industrial effluents. Environ Sci Technol 32:2180-2184.

Castle L, Mayo A, Gilbert J. 1989. Migration of plasticizers from printing inks into foods. Food Addit Contam 6(4):437-443.

Cathey A, Watkins DJ, Sánchez BN, et al. 2020a. Onset and tempo of sexual maturation is differentially associated with gestational phthalate exposure between boys and girls in a Mexico City birth cohort. Environ Int 136:105469. http://doi.org/10.1016/j.envint.2020.105469.

Cathey A, Watkins DJ, Sánchez BN, et al. 2020b. Supplemental material: Onset and tempo of sexual maturation is differentially associated with gestational phthalate exposure between boys and girls in a Mexico City birth cohort. Environ Int 136. http://doi.org/10.1016/j.envint.2020.105469.

Cattley RC, Glover SE. 1993. Elevated 8-hydroxydeoxyguanosine in hepatic DNA of rats following exposure to peroxisome proliferators: relationship to carcinogenesis and nuclear localization. Carcinogenesis 14(12):2495-2499.

Cattley RC, Richardson KK, Smith-Oliver T, et al. 1986. Effect of peroxisome proliferator carcinogens on unscheduled DNA synthesis in rat hepatocytes determined by autoradiography. Cancer Lett 33(3):269-277. http://doi.org/10.1016/0304-3835(86)90066-2.

Cattley RC, Conway JG, Popp JA. 1987. Association of persistent peroxisome proliferation and oxidative injury with hepatocarcinogenicity in female F-344 rats fed di(2-ethylhexyl)phthalate for 2 years. Cancer Lett 38(1-2):15-22. http://doi.org/10.1016/0304-3835(87)90195-9.

Cattley RC, Smith-Oliver T, Butterworth BE, et al. 1988. Failure of the peroxisome proliferator WY-14,643 to induce unscheduled DNA synthesis in rat hepatocytes following in vivo treatment. Carcinogenesis 9(7):1179-1183. http://doi.org/10.1093/carcin/9.7.1179.

Cavanagh JE, Trought K, Mitchell C, et al. 2018. Assessment of endocrine disruption and oxidative potential of bisphenol-A, triclosan, nonylphenol, diethylhexyl phthalate, galaxolide, and carbamazepine, common contaminants of municipal biosolids. Toxicol in Vitro 48:342-349. http://doi.org/10.1016/j.tiv.2018.02.003.

CDC. 2015. Fourth national report on human exposure to environmental chemicals. February 2015. Atlanta, GA: Centers for Disease Control and Prevention.

CDC. 2016. Biomonitoring summary. Phthalates overview. Centers for Disease Control and Prevention. https://www.cdc.gov/biomonitoring/DEHP_BiomonitoringSummary.html. June 06, 2017.

CDC. 2018. Fourth national report on human exposure to environmental chemicals. Updated Tables, March 2018, Volume One. Centers for Disease Control and Prevention.

CDR. 2016. Chemical data reporting: 2016 data. U.S. Environmental Protection Agency. https://www.epa.gov/chemical-data-reporting/access-cdr-data#2016. July 9, 2020.

Cerbulis J, Byler DM. 1986. Isolation and detection of dialkyl phthalates from pork. J Agric Food Chem 34:198-200.

Cha S, Jung K, Lee MY, et al. 2018. Nonmonotonic effects of chronic low-dose di(2-ethylhexyl) phthalate on gonadal weight and reproductive. Dev Reprod 22(1):85-94. http://doi.org/10.12717/dr.2018.22.1.085.

8. REFERENCES

Chang BV, Liao CS, Yuan SY. 2005. Anaerobic degradation of diethyl phthalate, di-n-butyl phthalate, and di-(2-ethylhexyl) phthalate from river sediment in Taiwan. Chemosphere 58(11):1601-1607. http://doi.org/10.1016/j.chemosphere.2004.11.031.

Chang WH, Li SS, Wu MH, et al. 2015. Phthalates might interfere with testicular function by reducing testosterone and insulin-like factor 3 levels. Hum Reprod 30(11):2658-2670. http://doi.org/10.1093/humrep/dev225.

Chang WH, Wu MH, Pan HA, et al. 2017a. Semen quality and insulin-like factor 3: Associations with urinary and seminal levels of phthalate metabolites in adult males. Chemosphere 173:594-602. http://doi.org/10.1016/j.chemosphere.2017.01.056.

Chang WH, Wu MH, Pan HA, et al. 2017b. Supplemental material: Semen quality and insulin-like factor 3: Associations with urinary and seminal levels of phthalate metabolites in adult males. Chemosphere 173. http://doi.org/10.1016/j.chemosphere.2017.01.056.

Chang YJ, Tseng CY, Lin PY, et al. 2017c. Acute exposure to DEHP metabolite, MEHP cause genotoxicity, mutagenesis and carcinogenicity in mammalian Chinese hamster ovary cells. Carcinogenesis 38(3):336-345. http://doi.org/10.1093/carcin/bgx009.

Chang WH, Tsai YS, Wang JY, et al. 2019a. Sex hormones and oxidative stress mediated phthalate-induced effects in prostatic enlargement. Environ Int 126:184-192. http://doi.org/10.1016/j.envint.2019.02.006.

Chang WH, Tsai YS, Wang JY, et al. 2019b. Supplemental material: Sex hormones and oxidative stress mediated phthalate-induced effects in prostatic enlargement. Environ Int 126. http://doi.org/10.1016/j.envint.2019.02.006.

Chang JW, Liao KW, Huang CY, et al. 2020. Phthalate exposure increased the risk of early renal impairment in Taiwanese without type 2 diabetes mellitus. Int J Hyg Environ Health 224:113414. http://doi.org/10.1016/j.ijheh.2019.10.009.

Chang-Liao WL, Hou ML, Chang LW, et al. 2013. Determination and pharmacokinetics of di-(2-ethylhexyl) phthalate in rats by ultra performance liquid chromatography with tandem mass spectrometry. Molecules 18(9):11452-11466. http://doi.org/10.3390/molecules180911452.

Chaudhary BI, Liotta CL, Cogen JM, et al. 2016. Plasticized PVC. In: Reference module in materials science and materials engineering. Elsevier Inc., 1-6.

Chauvigné F, Menuet A, Lesné L, et al. 2009. Time- and dose-related effects of di-(2-ethylhexyl) phthalate and its main metabolites on the function of the rat fetal testis in vitro. Environ Health Perspect 117(4):515-521. http://doi.org/10.1289/ehp.11870.

Chen S, Chen J, Cai X, et al. 2010. Perinatal exposure to di-(2-ethylhexyl) phthalate leads to restricted growth and delayed lung maturation in newborn rats. J Perinat Med 38(5):515-521. http://doi.org/10.1515/jpm.2010.083.

Chen J, Wu S, Wen S, et al. 2015. The mechanism of environmental endocrine disruptors (DEHP) induces epigenetic transgenerational inheritance of cryptorchidism. PLoS ONE 10(6):e0126403. http://doi.org/10.1371/journal.pone.0126403.

Chen SY, Hwang JS, Sung FC, et al. 2017. Mono-2-ethylhexyl phthalate associated with insulin resistance and lower testosterone levels in a young population. Environ Pollut 225:112-117. http://doi.org/10.1016/j.envpol.2017.03.037.

Chen CC, Wang YH, Chen WJ, et al. 2019. A benchmark dose study of prenatal exposure to di(2-ethylhexyl) phthalate and behavioral problems in children. Int J Hyg Environ Health 222(6):971-980. http://doi.org/10.1016/j.ijheh.2019.06.002.

Cheng HF, Lin JG. 2000. Biodegradation of di-(2-ethylhexyl)phthalate in sewage sludge. Water Sci Technol 41(12):1-6.

Cheon YP. 2020. Di-(2-ethylhexyl) phthalate (DEHP) and uterine histological characteristics. Dev Reprod 24(1):1-17. http://doi.org/10.12717/dr.2020.24.1.1.

Chevrier C, Petit C, Philippat C, et al. 2012. Maternal urinary phthalates and phenols and male genital anomalies. Epidemiology 23(2):353-356. http://doi.org/10.1097/EDE.0b013e318246073e.

Chiang C, Flaws JA. 2019. Subchronic exposure to di(2-ethylhexyl) phthalate and diisononyl phthalate during adulthood has immediate and long-term reproductive consequences in female mice. Toxicol Sci 168(2):620-631. http://doi.org/10.1093/toxsci/kfz013.

Chiang C, Lewis LR, Borkowski G, et al. 2020a. Late-life consequences of short-term exposure to di(2-ethylhexyl) phthalate and diisononyl phthalate during adulthood in female mice. Reprod Toxicol 93:28-42. http://doi.org/10.1016/j.reprotox.2019.12.006.

Chiang C, Lewis LR, Borkowski G, et al. 2020b. Exposure to di(2-ethylhexyl) phthalate and diisononyl phthalate during adulthood disrupts hormones and ovarian folliculogenesis throughout the prime reproductive life of the mouse. Toxicol Appl Pharmacol 393:114952. http://doi.org/10.1016/j.taap.2020.114952.

Ching NP, Jham GN, Subbarayan C, et al. 1981. Gas chromatographic-mass spectrometric detection of circulating plasticizers in surgical patients. J Chromatogr 222(2):171-177. http://doi.org/10.1016/s0378-4347(00)81050-6.

Chiu YH, Bellavia A, James-Todd T, et al. 2018a. Evaluating effects of prenatal exposure to phthalate mixtures on birth weight: A comparison of three statistical approaches. Environ Int 113:231-239. http://doi.org/10.1016/j.envint.2018.02.005.

Chiu YH, Bellavia A, James-Todd T, et al. 2018b. Supplemental material: Evaluating effects of prenatal exposure to phthalate mixtures on birth weight: A comparison of three statistical approaches. Environ Int 113 http://doi.org/10.1016/j.envint.2018.02.005.

Chiu CY, Sun SC, Chiang CK, et al. 2018c. Plasticizer di(2-ethylhexyl)phthalate interferes with osteoblastogenesis and adipogenesis in a mouse model. J Orthop Res 36(4):1124-1134. http://doi.org/10.1002/jor.23740.

Choi S, Park S, Jeong J, et al. 2010. Identification of toxicological biomarkers of di(2-ethylhexyl) phthalate in proteins secreted by HepG2 cells using proteomic analysis. Proteomics 10(9):1831-1846. http://doi.org/10.1002/pmic.200900674.

Choi K, Joo H, Campbell JL, et al. 2012. In vitro metabolism of di(2-ethylhexyl) phthalate (DEHP) by various tissues and cytochrome P450s of human and rat. Toxicol in Vitro 26(2):315-322. http://doi.org/10.1016/j.tiv.2011.12.002.

Choi K, Joo H, Campbell JL, et al. 2013. In vitro intestinal and hepatic metabolism of di(2-ethylhexyl) phthalate (DEHP) in human and rat. Toxicol in Vitro 27(5):1451-1457. http://doi.org/10.1016/j.tiv.2013.03.012.

Christiansen S, Scholze M, Dalgaard M, et al. 2009. Synergistic disruption of external male sex organ development by a mixture of four antiandrogens. Environ Health Perspect 117(12):1839-1846. http://doi.org/10.1289/ehp.0900689.

Christiansen S, Boberg J, Axelstad M, et al. 2010. Low-dose perinatal exposure to di(2-ethylhexyl) phthalate induces anti-androgenic effects in male rats. Reprod Toxicol 30(2):313-321. http://doi.org/10.1016/j.reprotox.2010.04.005.

Chu I, Dick D, Bronaugh R, et al. 1996. Skin reservoir formation and bioavailability of dermally administered chemicals in hairless guinea pigs. Food Chem Toxicol 34(3):267-276.

Chuang SC, Chen HC, Sun CW, et al. 2020. Phthalate exposure and prostate cancer in a population-based nested case-control study. Environ Res 181:108902. http://doi.org/10.1016/j.envres.2019.108902.

Cimini AM, Sulli A, Stefanini S, et al. 1994. Effects of di-(2-ethylhexyl)phthalate on peroxisomes of liver, kidney and brain of lactating rats and their pups. Cell Mol Biol 40(8):1063-1076.

Clara M, Windhofer G, Hartl W, et al. 2010. Occurrence of phthalates in surface runoff, untreated and treated wastewater and fate during wastewater treatment. Chemosphere 78(9):1078-1084. http://doi.org/10.1016/j.chemosphere.2009.12.052.

Clark KE, David RM, Guinn R, et al. 2011. Modeling human exposure to phthalate esters: A comparison of indirect and biomonitoring estimation methods. Hum Ecol Risk Assess 17(4):923-965. http://doi.org/10.1080/10807039.2011.588157.

Clayton GD, Clayton FE. 1981. Diethyl phthalate. In: Patty's industrial hygiene and toxicology. Vol. 2A. 3rd ed. New York, NY: John Wiley & Sons, 2344-2345.

Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

Clewell RA, Campbell JL, Ross SM, et al. 2010. Assessing the relevance of in vitro measures of phthalate inhibition of steroidogenesis for in vivo response. Toxicol in Vitro 24(1):327-334. http://doi.org/10.1016/j.tiv.2009.08.003.

CMA. 1986. Analysis of bis(2-ethylhexyl) phthalate (DEHP) by gas chromatography-mass spectrometry in dairy and meat products. Washington, DC: Chemical Manufacturer's Association.

Cobellis L, Latini G, De Felice C, et al. 2003. High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. Hum Reprod 18(7):1512-1515. http://doi.org/10.1093/humrep/deg254.

Cohen H, Charrier C, Sarfaty J. 1991. Extraction and identification of a plasticizer, di-(2-ethylhexyl)phthalate, from a plastic bag containing contaminated corn. Arch Environ Contam Toxicol 20:437-440.

Cole RS, Tocchi M, Whe E, et al. 1981. Contamination of commercial blood products by di-2-ethylhexyl phthalate and mono-2-ethylhexyl phthalate. Vox Sang 40:317-322.

Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the National Urban Runoff Program. J Water Pollut Control Fed 56(7):898-908.

Contreras TJ, Sheibley RH, Valeri CR. 1974. Accumulation of di-2-ethylhexyl phthalate (DEHP) in whole blood, platelet concentrates and platelet-poor plasma. Transfusion 14:34-46.

Conway JG, Tomaszewski KE, Olson MJ, et al. 1989. Relationship of oxidative damage to the hepatocarcinogenicity of the peroxisome proliferators di(2-ethylhexyl)phthalate and Wy-14,643. Carcinogenesis 10(3):513-519. http://doi.org/10.1093/carcin/10.3.513.

Corton JC, Peters JM, Klaunig JE. 2018. The PPARa-dependent rodent liver tumor response is not relevant to humans: Addressing misconceptions. Arch Toxicol 92:83-119.

CPSC. 1999. CPSC releases study on phthalates in teethers, rattles and other children's products. U.S. Consumer Product Safety Commission. http://cpsc.gov/cpscpub/prerel/prhtml99/99031.html. March 19, 2000.

CPSC. 2001. Chronic Hazard Advisory Panel on diisononyl phthalate (DINP). U.S. Consumer Product Safety Commission.

CPSC. 2010a. Memorandum to Michael Babich from Kent Carlson regarding the toxicity review of di(2-ethylhexyl) phthalate (DEHP). Bethesda, MD: U.S. Consumer Product Safety Commission.

CPSC. 2010b. Review of exposure and toxicity data for phthalate substitutes. Bethesda, MD: U.S. Consumer Product Safety Commission. https://www.cpsc.gov/s3fs-public/phthalsub.pdf. July 13, 2021.

CPSC. 2014. Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on phthalates and phthalate alternatives. Bethesda, MD: U.S. Consumer Product Safety Commission.

CPSIA. 2008. Consumer Product Safety Improvement Act of 2008. Public Law 11-314, 110th Congress. Title I- Children's product safety. Consumer Product Safety Improvement Act.

Culty M, Thuillier R, Li W, et al. 2008. In utero exposure to di-(2-ethylhexyl) phthalate exerts both short-term and long-lasting suppressive effects on testosterone production in the rat. Biol Reprod 78(6):1018-1028. http://doi.org/10.1095/biolreprod.107.065649.

Dales RE, Kauri LM, Cakmak S. 2018. The associations between phthalate exposure and insulin resistance, β-cell function and blood glucose control in a population-based sample. Sci Total Environ 612:1287-1292. http://doi.org/10.1016/j.scitotenv.2017.09.009.

Dalgaard M, Ostergaard G, Lam HR, et al. 2000. Toxicity study of di(2-ethylhexyl)phthalate (DEHP) in combination with acetone in rats. Pharmacol Toxicol 86(2):92-100. http://doi.org/10.1034/j.1600-0773.2000.pto860208.x.

Dalsenter PR, Santana GM, Grande SW, et al. 2006. Phthalate affect the reproductive function and sexual behavior of male Wistar rats. Hum Exp Toxicol 25(6):297-303. http://doi.org/10.1191/0960327105ht624oa.

Daniel JW, Bratt H. 1974. The absorption, metabolism and tissue distribution of di(2-ethylhexyl)phthalate in rats. Toxicology 2(1):51-65.

Daniel S, Balalian AA, Whyatt RM, et al. 2020. Perinatal phthalates exposure decreases fine-motor functions in 11-year-old girls: Results from weighted Quantile sum regression. Environ Int 136:105424. http://doi.org/10.1016/j.envint.2019.105424.

David RM, Moore MR, Cifone MA, et al. 1999. Chronic peroxisome proliferation and hepatomegaly associated with the hepatocellular tumorigenesis of di(2-ethylhexyl)phthalate and the effects of recovery. Toxicol Sci 50(2):195-205.

David RM, Moore MR, Finney DC, et al. 2000a. Chronic toxicity of di(2-ethylhexyl)phthalate in rats. Toxicol Sci 55(2):433-443.

David RM, Moore MR, Finney DC, et al. 2000b. Chronic toxicity of di(2-ethylhexyl)phthalate in mice. Toxicol Sci 58(2):377-385.

Deisinger PJ, Perry LG, Guest D. 1998. In vivo percutaneous absorption of [14C]DEHP from [14C]DEHP-plasticized polyvinyl chloride film in male Fischer 344 rats. Food Chem Toxicol 36:521-527.

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

Deng T, Xie X, Duan J, et al. 2019. Di-(2-ethylhexyl) phthalate induced an increase in blood pressure via activation of ACE and inhibition of the bradykinin-NO pathway. Environ Pollut 247:927-934. http://doi.org/10.1016/j.envpol.2019.01.099.

Deng T, Du Y, Wang Y, et al. 2020. The associations of urinary phthalate metabolites with the intermediate and pregnancy outcomes of women receiving IVF/ICSI treatments: A prospective single-center study. Ecotoxicol Environ Saf 188:109884. http://doi.org/10.1016/j.ecoenv.2019.109884.

Desdoits-Lethimonier C, Albert O, Le Bizec B, et al. 2012. Human testis steroidogenesis is inhibited by phthalates. Hum Reprod 27(5):1451-1459. http://doi.org/10.1093/humrep/des069.

Desideri PG, Lepri L, Checchini L, et al. 1994. Organic compounds in surface and deep Antarctic snow. Int J Environ Anal Chem 55:33-46.

Desideri PG, Lepri L, Udisti R, et al. 1998. Analysis of organic compounds in Antarctic snow and their origin. Int J Environ Anal Chem 7(3-4):331-351.

DeVault DS. 1985. Contaminants in fish from Great Lakes harbors and tributary mouths. Arch Environ Contam Toxicol 14:587-594.

Dhanya CR, Indu AR, Deepadevi KV, et al. 2003. Inhibition of membrane Na(+)-K+ ATPase of the brain, liver and RBC in rats administered di(2-ethyl hexyl) phthalate (DEHP) a plasticizer used in polyvinyl chloride (PVC) blood storage bags. Indian J Exp Biol 41(8):814-820.

Dine T, Luyckx M, Cazin M, et al. 1991. Rapid determination by high performance liquid chromatography of di-2-ethylhexyl phthalate in plasma stored in plastic bags. Biomed Chromatogr 5:94-97.

Dine T, Luychx M, Gressier B, et al. 2000. A pharmacokinetic interpretation of increasing concentrations of DEHP in haemodialysed patients. Med Eng Phys 22:157-165.

Ding Y, Gao K, Liu Y, et al. 2019. Transcriptome analysis revealed the mechanism of the metabolic toxicity and susceptibility of di-(2-ethylhexyl)phthalate on adolescent male ICR mice with type 2 diabetes mellitus. Arch Toxicol 93(11):3183-3206. http://doi.org/10.1007/s00204-019-02590-8.

Dirinck E, Dirtu AC, Geens T, et al. 2015. Urinary phthalate metabolites are associated with insulin resistance in obese subjects. Environ Res 137:419-423. http://doi.org/10.1016/j.envres.2015.01.010.

Dirtu AC, Geens T, Dirinck E, et al. 2013. Phthalate metabolites in obese individuals undergoing weight loss: Urinary levels and estimation of the phthalates daily intake. Environ Int 59:344-353. http://doi.org/10.1016/j.envint.2013.06.023.

Dirven HA, Theuws JL, Jongeneelen FJ, et al. 1991. Non-mutagenicity of 4 metabolites of di(2-ethylhexyl)phthalate (DEHP) and 3 structurally related derivatives of di(2-ethylhexyl)adipate (DEHA) in the Salmonella mutagenicity assay. Mutat Res 260(1):121-130. http://doi.org/10.1016/0165-1218(91)90088-4.

Diwan BA, Ward JM, Rice JM, et al. 1985. Tumor-promoting effects of di(2-ethylhexyl)phthalate in JB6 mouse epidermal cells and mouse skin. Carcinogenesis 6(3):343-347. http://doi.org/10.1093/carcin/6.3.343.

Do RP, Stahlhut RW, Ponzi D, et al. 2012. Non-monotonic dose effects of in utero exposure to di(2-ethylhexyl) phthalate (DEHP) on testicular and serum testosterone and anogenital distance in male mouse fetuses. Reprod Toxicol 34(4):614-621. http://doi.org/10.1016/j.reprotox.2012.09.006.

DOE. 2018a. Table 3: Protective Action Criteria (PAC) Rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. June 2018. Oak Ridge, TN: U.S. Department of Energy. https://edms.energy.gov/pac/docs/Revision_29A_Table3.pdf. April 12, 2020.

DOE. 2018b. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. Oak Ridge, TN: U.S. Department of Energy. https://edms.energy.gov/pac/. April 12, 2020.

Doherty BT, Engel SM, Buckley JP, et al. 2017. Prenatal phthalate biomarker concentrations and performances on the Bayles Scales of infant development-II in a population of young urban children. Environ Res 152:51-58.

Dombret C, Capela D, Poissenot K, et al. 2017. Neural mechanisms underlying the disruption of male courtship behavior by adult exposure to di(2-ethylhexyl) phthalate in mice. Environ Health Perspect 125(9):097001. http://doi.org/10.1289/ehp1443.

Dong X, Dong J, Zhao Y, et al. 2017. Effects of long-term in vivo exposure to di-2-ethylhexylphthalate on thyroid hormones and the TSH/TSHR signaling pathways in Wistar rats. Int J Environ Res Public Health 14:44. http://doi.org/10.3390/ijerph14010044.

Dong J, Cong Z, You M, et al. 2019. Effects of perinatal di (2-ethylhexyl) phthalate exposure on thyroid function in rat offspring. Environ Toxicol Pharmacol 67:53-60. http://doi.org/10.1016/j.etap.2019.01.012.

Dorman DC, Chiu W, Hales BF, et al. 2018. Systematic reviews and meta-analyses of human and animal evidence of prenatal diethylhexyl phthalate exposure and changes in male anogenital distance. J Toxicol Environ Health 21(4):207-226. http://doi.org/10.1080/10937404.2018.1505354.

Dostal LA, Jenkins WL, Schwetz BA. 1987. Hepatic peroxisome proliferation and hypolipidemic effects of di(2-ethylhexyl) phthalate in neonatal and adult rats. Toxicol Appl Pharmacol 87:81-90.

Dostal LA, Chapin RE, Stefanski SA, et al. 1988. Testicular toxicity and reduced Sertoli cell numbers in neonatal rats by di(2-ethylhexyl) phthalate and the recovery of fertility as adults. Toxicol Appl Pharmacol 95(1):104-121. http://doi.org/10.1016/s0041-008x(88)80012-7.

Douglas GR, Hugenholtz AP, Blakey DH. 1986. Genetic toxicology of phthalate esters: Mutagenic and other genotoxic effects. Environ Health Perspect 65:255-262.

Doull J, Cattley R, Elcombe C, et al. 1999. A cancer risk assessment of di(2-ethylhexyl)phthalate: Application of the new U.S. EPA Risk Assessment Guidelines. Regul Toxicol Pharmacol 29(3):327-357. http://doi.org/10.1006/rtph.1999.1296.

Doyle TJ, Bowman JL, Windell VL, et al. 2013. Transgenerational effects of di-(2-ethylhexyl) phthalate on testicular germ cell associations and spermatogonial stem cells in mice. Biol Reprod 88(5):112. http://doi.org/10.1095/biolreprod.112.106104.

Du YY, Fang YL, Wang YX, et al. 2016. Follicular fluid and urinary concentrations of phthalate metabolites among infertile women and associations with in vitro fertilization parameters. Reprod Toxicol 61:142-150. http://doi.org/10.1016/j.reprotox.2016.04.005.

Du ZP, Feng S, Li YL, et al. 2020. Di-(2-ethylhexyl) phthalate inhibits expression and internalization of transthyretin in human placental trophoblastic cells. Toxicol Appl Pharmacol 394:114960. http://doi.org/10.1016/j.taap.2020.114960.

Eckel W, Ross B, Isensee R. 1993. Pentobarbitol found in ground water. Ground Water 31:801-804.

Edlund C, Ericsson J, Dallner G. 1987. Changes in hepatic dolichol and dolichyl monophosphate caused by treatment of rats with inducers of the endoplasmic reticulum and peroxisomes and during ontogeny. Chem Biol Interact 62(2):191-208. http://doi.org/10.1016/0009-2797(87)90090-1.

Egestad B, Sjoberg P. 1992. Glucosidation as a new conjugation pathway for metabolites of bis(2-ethylhexyl) phthalate. Drug Metab Dispos 20(3):470-472.

Egestad B, Green G, Sjoberg P, et al. 1996. Chromatographic fractionation and analysis by mass spectrometry of conjugated metabolites of bis(2-ethylhexyl)phthalate in urine. J Chromatogr 677(1):99-109. http://doi.org/10.1016/0378-4347(95)00439-4.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1):30-38.

Ellington JJ. 1999. Octanol/water partition coefficients and water solubilities of phthalate esters. J Chem Eng Data 44:1414-1418.

Elliott BM, Elcombe CR. 1987. Lack of DNA damage or lipid peroxidation measured in vivo in the rat liver following treatment with peroxisomal proliferators. Carcinogenesis 8(9):1213-1218. http://doi.org/10.1093/carcin/8.9.1213.

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

Emoto C, Murayama N, Rostami-Hodjegan A, et al. 2009. Utilization of estimated physicochemical properties as an integrated part of predicting hepatic clearance in the early drug-discovery stage: Impact of plasma and microsomal binding. Xenobiotica 39(3):227-235. http://doi.org/10.1080/00498250802668863.

Engel SM, Villanger GD, Nethery RC, et al. 2018. Prenatal phthalates, maternal thyroid function, and risk of attention-deficit hyperactivity disorder in the Norwegian mother and child cohort. Environ Health Perspect 126(5):057004. http://doi.org/10.1289/EHP2358.

EPA. 1979. Water-related environmental fate of 129 priority pollutants. Vol. II. Halogenated aliphatic hydrocarbons, halogenated ethers, monocyclic aromatics, phthalate esters, polycyclic aromatic hydrocarbons, nitrosamines, and miscellaneous compounds. Washington, DC: U.S. Environmental Protection Agency. EPA440479029a. PB80204373.

EPA. 1980. Ambient water quality criteria for phthalate esters. Washington, DC: U.S. Environmental Protection Agency. EPA440479029a. PB80204373.

EPA. 1981. An exposure and risk assessment for phthalate esters: Di(2-ethylhexyl) phthalate, di-n-butyl phthalate, dimethyl phthalate, diethyl phthalate, di-n-octyl phthalate, butyl benzyl phthalate. Washington, DC: U.S. Environmental Protection Agency. EPA440481020. PB85211936.

EPA. 1984. GC/MS analysis of organics in drinking water concentrates and advanced waste treatment concentrates: Volume I: Analysis results for 17 drinking water, 16 advanced waste treatment and 3 process blank concentrates. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600184020a. PB85128221.

EPA. 1986. Method 8060: Phthalate esters. Test methods for evaluating solid waste. U.S. Environmental Protection Agency. SW-846.

EPA. 1990. Table 1-11: Pollutant concentration estimates from the National Sewage Sludge Survey. U.S. Environmental Protection Agency. Fed Regist 55:47229.

EPA. 1995. Method 525.2. Determination of organic compounds in drinking water by liquid-solid extraction and capillary column gas chromatography/mass spectrometry. Selected analytical methods for environmental remediation and recovery (SAM). Cincinnati, OH: U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2015-06/documents/epa-525.2.pdf. April 15, 2021.

EPA. 1996. Method 8061A. Phthalate esters by gas chromatography with electron capture detection (GC/ECD). Test methods for evaluation solid waste. U.S. Environmental Protection Agency. SW-846.

EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the

Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. EPA260B05001.

EPA. 2009a. Targeted national sewage sludge survey sampling and analysis technical report. Washington, DC: U.S. Environmental Protection Agency. EPA822R08016. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1003RL8.txt. July 31, 2020.

EPA. 2009b. The analysis of regulated contaminant occurrence data from public water systems in support of the second six-year review of National Primary Drinking Water Regulations. U.S. Environmental Protection Agency.

EPA. 2009c. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. September 7, 2017.

EPA. 2012. Phthalates action plan. Revised 3/14/2012. Washington, DC: U.S. Environmental Protection Agency. https://www.epa/gov/sites/production/files/2015-09/documents/phthalates_actionplan_revised 2012-03-14.pdf. July 9, 2018.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822S12001. https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf. July 25, 2018.

EPA. 2018b. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

Eriksson P, Darnerud PO. 1985. Distribution and retention of some chlorinated hydrocarbons and a phthalate in the mouse brain during the preweaning period. Toxicology 37:189-203.

Erkekoğlu P, Rachidi W, De Rosa V, et al. 2010a. Protective effect of selenium supplementation on the genotoxicity of di(2-ethylhexyl)phthalate and mono(2-ethylhexyl)phthalate treatment in LNCaP cells. Free Radic Biol Med 49(4):559-566. http://doi.org/10.1016/j.freeradbiomed.2010.04.03.

Erkekoglu P, Giray B, Durmaz E, et al. 2010b. Evaluation of the correlation between plasma amylase and lipase levels and phthalate exposure in pubertal gynecomastia patients. Turk Pediatri Arsivi 45(4):366-370. http://doi.org/10.4274/tpa.45.366.

Erythropel HC, Maric M, Nicell JA, et al. 2014. Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure. Appl Microbiol Biotechnol 98(24):9967-9981. http://doi.org/10.1007/s00253-014-6183-8.

Exxon Chemical Americas. 1990. An investigation of the effect of di-(2-ethylhexyl) phthalate on rat hepatic peroxisomes with cover letter. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0530399. 86-91000007729. TSCATS/414999.

Factor-Litvak P, Insel B, Calafat AM, et al. 2014. Persistent associations between maternal prenatal exposure to phthalates on child IQ at age 7 years. PLoS ONE 9(12):e114003. http://doi.org/10.1371/journal.pone.0114003.

Fahrig R, Steinkamp-Zucht A. 1996. Co-recombinogenic and anti-mutagenic effects of diethylhexylphthalate, inactiveness of pentachlorophenol in the spot test with mice. Mutat Res 354(1):59-67. http://doi.org/10.1016/0027-5107(96)00036-x.

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

Fan Y, Qin Y, Chen M, et al. 2020. Prenatal low-dose DEHP exposure induces metabolic adaptation and obesity: Role of hepatic thiamine metabolism. J Hazard Mater 385:121534. http://doi.org/10.1016/j.jhazmat.2019.121534.

Faouzi MA, Dine T, Luyckx M, et al. 1994. Leaching of diethylhexyl phthalate from PVC bags into intravenous teniposide solution. Int J Pharm 105(1):89-93.

Faouzi MA, Dine T, Gressier B, et al. 1999. Exposure of hemodialysis patients to di-2-ethylhexyl phthalate. Int J Pharm 180(1):113-121. http://doi.org/10.1016/s0378-5173(98)00411-6.

Fayad NM, Sheikheldin SY, Al-Malack MH, et al. 1997. Migration of vinyl chloride monomer (VCM) and additives into PVC bottled drinking water. J Environ Sci Health A Environ Sci Eng Toxic Hazard A32(4):1065-1083.

FDA. 1999a. Subpart B-Substances for use only as components of adhesives. Adhesives. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105.

FDA. 1999b. Cellophane. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 177.1200.

FDA. 1999c. Acrylic and modified acrylic plastics, semirigid and rigid. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 177.1010.

FDA. 1999d. Surface lubricants used in the manufacture of metallic articles. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 178.3910.

FDA. 1999e. Defoaming agents used in the manufacture of paper and paper-board. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 176.210.

FDA. 1999f. Plasticizers. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 181.27.

FDA. 1999g. Resinous and polymeric coatings. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.300.

FDA. 2001. Safety assessment of di(2-ethylhexyl)phthalate (DEHP) released from PVC medical devices. Rockville, MD: U.S. Food and Drug Administration.

FDA. 2016. Subpart B- Requirements for specific standardized beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.55AppA. June 06, 2017.

FDA. 2019a. Di(2-ethylhexyl) phthalate. Indirect additives used in food contact substances. Washington, DC: U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives&id=DIPHTHALATE. August 26, 2020.

FDA. 2019b. Subpart B - Requirements for specific standardized beverages. Bottled water. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 165.110. https://www.govinfo.gov/content/pkg/CFR-2019-title21-vol2/pdf/CFR-2019-title21-vol2-part165.pdf. December 5, 2019.

FDA. 2020. Substances added to food. Washington, DC: U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances. April 12, 2020.

Feng W, Liu Y, Ding Y, et al. 2020. Typical neurobehavioral methods and transcriptome analysis reveal the neurotoxicity and mechanisms of di(2-ethylhexyl) phthalate on pubertal male ICR mice with type 2 diabetes mellitus. Arch Toxicol 94(4):1279-1302. http://doi.org/10.1007/s00204-020-02683-9.

Ferguson KK, Loch-Caruso R, Meeker JD. 2012. Exploration of oxidative stress and inflammatory markers in relation to urinary phthalate metabolites: NHANES 1999-2006. Environ Sci Technol 46(1):477-485. http://doi.org/10.1021/es202340b.

Ferguson KK, Peterson KE, Lee JM, et al. 2014a. Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. Reprod Toxicol 47:70-76. http://doi.org/10.1016/j.reprotox.2014.06.002.

Ferguson KK, McElrath TF, Meeker JD. 2014b. Environmental phthalate exposure and preterm birth. JAMA Pediatrics 168(1):61. http://doi.org/10.1001/jamapediatrics.2013.3699.

Ferguson KK, McElrath TF, Ko Y, et al. 2014c. Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. Environ Int 70:118-124. http://doi.org/10.1016/j.envint.2014.05.016.

Ferguson KK, Peterson KE, Lee JM, et al. 2014d. Supplemental material: Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. Reprod Toxicol 47. http://doi.org/10.1016/j.reprotox.2014.06.002.

Ferguson KK, McElrath TF, Chen YH, et al. 2015. Urinary phthalate metabolites and biomarkers of oxidative stress in pregnant women: A repeated measures analysis. Environ Health Perspect 123(3):210-216. http://doi.org/10.1289/ehp.1307996.

Ferguson KK, Chen YH, VanderWeele TJ, et al. 2017. Mediation of the relationship between maternal phthalate exposure and preterm birth by oxidative stress with repeated measurements across pregnancy. Environ Health Perspect 125(3):488-494. http://doi.org/0.1289/ehp282.

Ferguson KK, Rosen EM, Barrett ES, et al. 2019a. Joint impact of phthalate exposure and stressful life events in pregnancy on preterm birth. Environ Int 133(Pt B):105254. http://doi.org/10.1016/j.envint.2019.105254.

Ferguson KK, Rosen EM, Barrett ES, et al. 2019b. Supplemental material: Joint impact of phthalate exposure and stressful life events in pregnancy on preterm birth. Environ Int 133. http://doi.org/10.1016/j.envint.2019.105254.

Ferguson KK, Rosen EM, Rosario Z, et al. 2019c. Environmental phthalate exposure and preterm birth in the PROTECT birth cohort. Environ Int 132:105099. http://doi.org/10.1016/j.envint.2019.105099.

Fernandez-Canal C, Pinta PG, Eljezi T, et al. 2018. Patients' exposure to PVC plasticizers from ECMO circuits. Expert Rev Med Devices 15(5):377-383. http://doi.org/10.1080/17434440.2018.1462698.

Fernández-González V, Moscoso-Pérez C, Muniategui-Lorenzo S, et al. 2017. Reliable, rapid and simple method for the analysis of phthalates in sediments by ultrasonic solvent extraction followed by head space-solid phase microextraction gas chromatography mass spectrometry determination. Talanta 162:648-653. http://doi.org/10.1016/j.talanta.2016.10.068.

Fiandanese N, Borromeo V, Berrini A, et al. 2016. Maternal exposure to a mixture of di(2-ethylhexyl) phthalate (DEHP) and polychlorinated biphenyls (PCBs) causes reproductive dysfunction in adult male mouse offspring. Reprod Toxicol 65:123-132. http://doi.org/10.1016/j.reprotox.2016.07.004.

Fong JP, Lee FJ, Lu IS, et al. 2015. Relationship between urinary concentrations of di(2-ethylhexyl) phthalate (DEHP) metabolites and reproductive hormones in polyvinyl chloride production workers. Occup Environ Med 72(5):346-353. http://doi.org/10.1136/oemed-2014-102532.

Franken C, Lambrechts N, Govarts E, et al. 2017. Phthalate-induced oxidative stress and association with asthma-related airway inflammation in adolescents. Int J Hyg Environ Health 220(2 Pt B):468-477. http://doi.org/10.1016/j.ijheh.2017.01.006.

Friedman GM, Mukhopadhyay PK, Moch A, et al. 2000. Waters and organic-rich waste near dumping grounds in New York Bight. Int J Coal Geol 42:325-355.

Furr JR, Lambright CS, Wilson VS, et al. 2014. A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicol Sci 140(2):403-424. http://doi.org/10.1093/toxsci/kfu081.

Ganning AE, Brunk U, Edlund C, et al. 1987. Effects of prolonged administration of phthalate ester on the liver. Environ Health Perspect 73(0):251-258.

Ganning AE, Olsson MJ, Peterson E, et al. 1989. Fatty acid oxidation in hepatic peroxisomes and mitochondria after treatment of rats with di(2-ethylhexyl)phthalate. Pharmacol Toxicol 65(4):265-268. http://doi.org/10.1111/j.1600-0773.1989.tb01170.x.

Ganning AE, Olsson MJ, Brunk U, et al. 1991. Effects of prolonged treatment with phthalate ester on rat liver. Pharmacol Toxicol 68:392-401.

Gao X, Yang B, Tang Z, et al. 2014. Determination of phthalates released from paper packaging materials by solid-phase extraction-high-performance liquid chromatography. J Chromatogr Sci 52(5):383-389. http://doi.org/10.1093/chromsci/bmt046.

Gao HT, Xu R, Cao WX, et al. 2016. Food emulsifier glycerin monostearate increases internal exposure levels of six priority controlled phthalate esters and exacerbates their male reproductive toxicities in rats. PLoS ONE 11(8):e0161253. http://doi.org/10.1371/journal.pone.0161253.

Gao H, Xu YY, Huang K, et al. 2017. Cumulative risk assessment of phthalates associated with birth outcomes in pregnant Chinese women: A prospective cohort study. Environ Pollut 222:549-556. http://doi.org/10.1016/j.envpol.2016.11.026.

Gao H, Wang YF, Huang K, et al. 2019. Prenatal phthalate exposure in relation to gestational age and preterm birth in a prospective cohort study. Environ Res 176:108530. http://doi.org/10.1016/j.envres.2019.108530.

Gascon M, Casas M, Morales E, et al. 2015a. Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy. J Allergy Clin Immunol 135(2):370-378. http://doi.org/10.1016/j.jaci.2014.09.030.

Gascon M, Valvi D, Forns J, et al. 2015b. Prenatal exposure to phthalates and neuropsychological development during childhood. Int J Hyg Environ Health 218(6):550-558. http://doi.org/10.1016/j.ijheh.2015.05.006.

Ge RS, Chen GR, Dong Q, et al. 2007. Biphasic effects of postnatal exposure to diethylhexylphthalate on the timing of puberty in male rats. J Androl 28(4):513-520. http://doi.org/10.2164/jandrol.106.001909.

Gejlsbjerg B, Klinge C, Madsen T. 2001. Mineralization of organic contaminants in sludge-soil mixtures. Environ Toxicol Chem 20(4):698-705.

Genuis SJ, Beesoon S, Lobo RA, et al. 2012. Human elimination of phthalate compounds: Blood, urine, and sweat (BUS) study. Sci World J 2012:615068. http://doi.org/10.1100/2012/615068.

Gerbracht U, Einig C, Oesterle D, et al. 1990. Di(2-ethylhexyl)phthalate alters carbohydrate enzyme activities and foci incidence in rat liver. Carcinogenesis 11(12):2111-2115.

Ghassemi M, Quinlivan S, Bachmaier J. 1984. Characteristics of leachates from hazardous waste landfills. J Environ Sci Health A Environ Sci Eng Toxic Hazard 19:579-620.

Giam CS, Wong MK. 1987. Plasticizers in food. J Food Prot 50(9):769-782.

Giam CS, Chan HS, Neff GS. 1975. Sensitive method for determination of phthalate ester plasticizers in open-ocean biota samples. Anal Chem 47:2225-2228.

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

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

Gong M, Zhang Y, Weschler CJ. 2014. Measurement of phthalates in skin wipes: Estimating exposure from dermal absorption. Environ Sci Technol 48(13):7428-7435. http://doi.org/10.1021/es501700u.

Goodman M, Lakind JS, Mattison DR. 2014. Do phthalates act as obesogens in humans? A systematic review of the epidemiological literature. Crit Rev Toxicol 44(2):151-175. http://doi.org/10.3109/10408444.2013.860076.

Goodrich JM, Ingle ME, Domino SE, et al. 2019. First trimester maternal exposures to endocrine disrupting chemicals and metals and fetal size in the Michigan Mother-Infant Pairs study. J Dev Orig Health Dis 10(4):447-458. http://doi.org/10.1017/S204017441800106X.

Gramiccioni L, Milana MR, DiMarzio S, et al. 1990. Experimental evaluation about the actual release of DEHP from caps to packaged foods. Rass Chim 42:3-7.

Grande SW, Andrade AJ, Talsness CE, et al. 2006. A dose-response study following in utero and lactational exposure to di(2-ethylhexyl)phthalate: effects on female rat reproductive development. Toxicol Sci 91(1):247-254. http://doi.org/10.1093/toxsci/kfj128.

Grande SW, Andrade AJ, Talsness CE, et al. 2007. A dose-response study following in utero and lactational exposure to di-(2-ethylhexyl) phthalate (DEHP): reproductive effects on adult female offspring rats. Toxicology 229(1-2):114-122. http://doi.org/10.1016/j.tox.2006.10.005.

Grasso P, Heindel JJ, Powell CJ, et al. 1993. Effects of mono(2-ethylhexyl) phthalate, a testicular toxicant, on follicle-stimulating hormone binding to membranes from cultured rat Sertoli cells. Biol Reprod 48(3):454-459.

Gray TJB, Beamand JA. 1984. Effect of some phthalate esters and other testicular toxins on primary cultures of testicular cells. Food Chem Toxicol 22(2):123-131. http://doi.org/10.1016/0278-6915(84)90092-9.

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

Gray TJ, Butterworth KR, Gaunt IF, et al. 1977. Short-term toxicity study of di-(2-ethylhexyl) phthalate in rats. Food Chem Toxicol 15(5):389-399. http://doi.org/10.1016/s0015-6264(77)80003-5.

Gray L, Barlow N, Howdeshell K, et al. 2009. Transgenerational effects of di (2-ethylhexyl) phthalate in the male CRL:CD(SD) rat: added value of assessing multiple offspring per litter. Toxicol Sci 110(2):411-425. http://doi.org/10.1093/toxsci/kfp109.

Greifenstein M, White DW, Stubner A, et al. 2013. Impact of temperature and storage duration on the chemical and odor quality of military packaged water in polyethylene terephthalate bottles. Sci Total Environ 456-457:376-383. http://doi.org/10.1016/j.scitotenv.2013.03.092.

Grindler NM, Allsworth JE, Macones GA, et al. 2015. Persistent organic pollutants and early menopause in U.S. women. PLoS ONE 10(1):e0116057. http://doi.org/10.1371/journal.pone.0116057.

Gu H, Liu Y, Wang W, et al. 2016. In utero exposure to di-(2-ethylhexyl) phthalate induces metabolic disorder and increases fat accumulation in visceral depots of C57BL/6J mice offspring. Exp Ther Med 12(6):3806-3812. http://doi.org/10.3892/etm.2016.3820.

Guo J, Han B, Qin L, et al. 2012. Pulmonary toxicity and adjuvant effect of di-(2-exylhexyl) phthalate in ovalbumin-immunized BALB/c mice. PLoS ONE 7(6):e39008. http://doi.org/10.1371/journal.pone.0039008.

Guo J, Li XW, Liang Y, et al. 2013. The increased number of Leydig cells by di(2-ethylhexyl) phthalate comes from the differentiation of stem cells into Leydig cell lineage in the adult rat testis. Toxicology 306:9-15. http://doi.org/10.1016/j.tox.2013.01.021.

Guo Y, Weck J, Sundaram R, et al. 2014. Urinary concentrations of phthalates in couples planning pregnancy and its association with 8-hydroxy-2'-deoxyguanosine, a biomarker of oxidative stress: longitudinal investigation of fertility and the environment study. Environ Sci Technol 48(16):9804-9811. http://doi.org/10.1021/es5024898.

Gupta RC, Goel SK, Earley K, et al. 1985. 32P-Postlabeling analysis of peroxisome proliferator-DNA adduct formation in rat liver in vivo and hepatocytes in vitro. Carcinogenesis 6(6):933-936. http://doi.org/10.1093/carcin/6.6.933.

Gupta C, Hattori A, Shinozuka H. 1988. Suppression of EGF binding in rat liver by the hypolipidemic peroxisome proliferators, 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio-(N-beta-hydroxyethyl)acetamide and di(2-ethylhexyl)phthalate. Carcinogenesis 9(1):167-169. http://doi.org/10.1093/carcin/9.1.167.

Guyton KZ, Chiu WA, Bateson TF, et al. 2009. A reexamination of the PPAR-alpha activation mode of action as a basis for assessing human cancer risks of environmental contaminants. Environ Health Perspect 117(11):1664-1672. http://doi.org/10.1289/ehp.0900758.

Hall AP, Elcombe CR, Foster J, et al. 2012. Liver hypertrophy: A review of the adaptive (adverse and non-adverse changes- conclusions from the 3rd International ESTP Expert Workshop. Toxicol Pathol 40(7):971-994.

Han Y, Wang X, Chen G, et al. 2014a. Di-(2-ethylhexyl) phthalate adjuvantly induces imbalanced humoral immunity in ovalbumin-sensitized BALB/c mice ascribing to T follicular helper cells hyperfunction. Toxicology 324:88-97. http://doi.org/10.1016/j.tox.2014.07.011.

Han X, Cui Z, Zhou N, et al. 2014b. Urinary phthalate metabolites and male reproductive function parameters in Chongqing general population, China. Int J Hyg Environ Health 217(2-3):271-278. http://doi.org/10.1016/j.ijheh.2013.06.006.

Han H, Lee HA, Park B, et al. 2019. Associations of phthalate exposure with lipid levels and insulin sensitivity index in children: A prospective cohort study. Sci Total Environ 662:714-721. http://doi.org/10.1016/j.scitotenv.2019.01.151.

Hanioka N, Isobe T, Ohkawara S, et al. 2019. Hydrolysis of di(2-ethylhexyl) phthalate in humans, monkeys, dogs, rats, and mice: An in vitro analysis using liver and intestinal microsomes. Toxicol in Vitro 54:237-242. http://doi.org/10.1016/j.tiv.2018.10.006.

Hannas BR, Lambright CS, Furr J, et al. 2011. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl

phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol Sci 123(1):206-216. http://doi.org/10.1093/toxsci/kfr146.

Hannon PR, Peretz J, Flaws JA. 2014. Daily exposure to di(2-ethylhexyl) phthalate alters estrous cyclicity and accelerates primordial follicle recruitment potentially via dysregulation of the phosphatidylinositol 3-kinase signaling pathway in adult mice. Biol Reprod 90(6):136. http://doi.org/10.1095/biolreprod.114.119032.

Hansen OG. 2019. Does it really make sense to develop PVC-free materials? Plastics Today. https://www.plasticstoday.com/medical/does-it-really-make-sense-develop-pvc-free-materials. July 9, 2021.

Hansen JF, Bendtzen K, Boas M, et al. 2015. Influence of phthalates on cytokine production in monocytes and macrophages: a systematic review of experimental trials. PLoS ONE 10(3):e0120083. http://doi.org/10.1371/journal.pone.0120083.

Hao C, Cheng X, Xia H, et al. 2012. The endocrine disruptor mono-(2-ethylhexyl) phthalate promotes adipocyte differentiation and induces obesity in mice. Biosci Rep 32:619-629.

Harley KG, Berger K, Rauch S, et al. 2017. Association of prenatal urinary phthalate metabolite concentrations and childhood BMI and obesity. Pediatr Res 82(3):405-415.

Hasegawa M, Kawai K, Mitsui T, et al. 2011. The reconstituted 'humanized liver' in TK-NOG mice is mature and functional. Biochem Biophys Res Commun 405(3):405-410. http://doi.org/10.1016/j.bbrc.2011.01.042.

Hasmall SC, James NH, Macdonald N, et al. 2000. Species differences in response to diethylhexylphthalate: suppression of apoptosis, induction of DNA synthesis and peroxisome proliferator activated receptor alpha-mediated gene expression. Arch Toxicol 74(2):85-91. http://doi.org/10.1007/s002040050657.

Hatch EE, Nelson JW, Qureshi MM, et al. 2008. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002. Environ Health 7:27. http://doi.org/10.1186/1476-069x-7-27.

Hauser TR, Bromberg SM. 1982. EPA's monitoring program at Love Canal 1980. Environ Monit Assess 2(3):249-272. http://doi.org/10.1007/bf00394456.

Hauser R, Williams P, Altshul L, et al. 2005. Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. Environ Health Perspect 113(4):425-430. http://doi.org/10.1289/ehp.7305.

Hauser R, Meeker JD, Duty S, et al. 2006. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. Epidemiology 17(6):682-691. http://doi.org/10.1097/01.ede.0000235996.89953.d7.

Hauser R, Meeker JD, Singh NP, et al. 2007. DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. Hum Reprod 22(3):688-695. http://doi.org/10.1093/humrep/del428.

Hauser R, Gaskins AJ, Souter I, et al. 2016. Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: Results from the EARTH study. Environ Health Perspect 124(6):831-839. http://doi.org/10.1289/ehp.1509760.

Hayashi F, Tamura H, Yamada J, et al. 1994. Characteristics of the hepatocarcinogenesis caused by dehydroepiandrosterone, a peroxisome proliferator, in male F-344 rats. Carcinogenesis 15(10):2215-2219. http://doi.org/10.1093/carcin/15.10.2215.

Hayashi F, Motoki Y, Tamura H, et al. 1998. Induction of hepatic poly(ADP-ribose) polymerase by peroxisome proliferators, non-genotoxic hepatocarcinogens. Cancer Lett 127(1-2):1-7.

Hayashi Y, Ito Y, Yanagiba Y, et al. 2012. Differences in metabolite burden of di(2-ethylhexyl)phthalate in pregnant and postpartum dams and their offspring in relation to drug-metabolizing enzymes in mice. Arch Toxicol 86(4):563-569. http://doi.org/10.1007/s00204-011-0790-2.

Haynes WM. 2014. Physical constants of organic compounds. Bis(2-ethylhexyl) phthalate. In: CRC handbook of chemistry and physics. 95th ed. Boca Raton, FL: CRC Press, 3-54.

He L, Fan S, Müller K, et al. 2018. Comparative analysis biochar and compost-induced degradation of di-(2-ethylhexyl) phthalate in soils. Sci Total Environ 625:987-993. http://doi.org/10.1016/j.scitotenv.2018.01.002.

He Y, Wang Q, He W, et al. 2019. Phthalate esters (PAEs) in atmospheric particles around a large shallow natural lake (Lake Chaohu, China). Sci Total Environ 687:297-308. http://doi.org/10.1016/j.scitotenv.2019.06.034.

Health Canada. 1998. Risk assessment on diisononyl phthalate in vinyl children's products. Ottawa, ON: Health Canada.

Heggeseth BC, Holland N, Eskenazi B, et al. 2019a. Heterogeneity in childhood body mass trajectories in relation to prenatal phthalate exposure. Environ Res 175:22-33. http://doi.org/10.1016/j.envres.2019.04.036.

Heggeseth BC, Holland N, Eskenazi B, et al. 2019b. Supplementary data: Heterogeneity in childhood body mass trajectories in relation to prenatal phthalate exposure. Environ Res 175. http://doi.org/10.1016/j.envres.2019.04.036.

Heindel JJ, Powell CJ. 1992. Phthalate ester effects on rat Sertoli cell function in vitro: Effects of phthalate side chain and age of animal. Toxicol Appl Pharmacol 115(1):116-123. http://doi.org/10.1016/0041-008x(92)90374-2.

Hellwig J, Freudenberger H, Jäckh R. 1997. Differential prenatal toxicity of branched phthalate esters in rats. Food Chem Toxicol 35(5):501-512. http://doi.org/10.1016/s0278-6915(97)00008-2.

Helmig D, Bauer A, Mueller J, et al. 1990. Analysis of particulate organics in a forest atmosphere by thermodesorption GC/MS. Atmos Environ 24(1):179-184. http://doi.org/10.1016/0960-1686(90)90454-u.

Herr C, zur Nieden A, Koch HM, et al. 2009. Urinary di(2-ethylhexyl)phthalate (DEHP)--metabolites and male human markers of reproductive function. Int J Hyg Environ Health 212(6):648-653. http://doi.org/10.1016/j.ijheh.2009.08.001.

Hill SS, Shaw BR, Wu AH. 2001. The clinical effects of plasticizers, antioxidants, and other contaminants in medical polyvinylchloride tubing during respiratory and non-respiratory exposure. Clin Chim Acta 304:1-8.

Hines EP, Calafat AM, Silva MJ, et al. 2009a. Concentrations of phthalate metabolites in milk, urine, saliva, and serum of lactating North Carolina women. Environ Health Perspect 117(1):86-92. http://doi.org/10.1289/ehp.11610.

Hines CJ, Nilsen Hopf NB, Deddens JA, et al. 2009b. Urinary phthalate metabolite concentrations among workers in selected industries: a pilot biomonitoring study. Ann Occup Hyg 53(1):1-17. http://doi.org/10.1093/annhyg/men066.

Hines C, Hopf N, Deddens J, et al. 2011. Estimated daily intake of phthalates in occupationally exposed groups. J Expo Sci Environ Epidemiol 21(2):133-141. http://doi.org/10.1038/jes.2009.62.

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

Hites RA. 1973. Analysis of trace organic compounds in New England rivers. J Chromatogr Sci 11(11):570-574.

Hodgson JR. 1987. Results of peroxisome induction studies on tri(2-ethylhexyl)trimellitate and 2-ethylhexanol. Toxicol Ind Health 3(2):49-61. http://doi.org/10.1177/074823378700300205.

Hodgson JR, Myhr BC, McKeon M, et al. 1982. Evaluation of di-(2-ethylhexyl)phthalate and its major metabolites in the primary rat hepatocyte unscheduled DNA synthesis assay. Environ Mutagen 4(3):388.

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

Holmes AK, Koller KR, Kieszak SM, et al. 2014. Case-control study of breast cancer and exposure to synthetic environmental chemicals among Alaska Native women. Int J Circumpolar Health 73:25760.

Hopf NB, Berthet A, Vernez D, et al. 2014. Skin permeation and metabolism of di(2-ethylhexyl) phthalate (DEHP). Toxicol Lett 224(1):47-53. http://doi.org/10.1016/j.toxlet.2013.10.004.

Hoppin JA, Ulmer R, London SJ. 2004. Phthalate exposure and pulmonary function. Environ Health Perspect 112(5):571-574.

Hoppin JA, Jaramillo R, London SJ, et al. 2013. Phthalate exposure and allergy in the U.S. population: Results from NHANES 2005-2006. Environ Health Perspect 121(10):1129-1134. http://doi.org/10.1289/ehp.1206211.

Hou JW, Lin CL, Tsai YA, et al. 2015a. The effects of phthalate and nonylphenol exposure on body size and secondary sexual characteristics during puberty. Int J Hyg Environ Health 218(7):603-615. http://doi.org/10.1016/j.ijheh.2015.06.004.

Hou JW, Lin CL, Tsai YA, et al. 2015b. Supplemental data: The effects of phthalate and nonylphenol exposure on body size and secondary sexual characteristics during puberty. Int J Hyg Environ Health 218.

Howard PH. 1989. Large production and priority pollutants. In: Handbook of environmental fate and exposure data of environmental chemicals. Vol. 1. Chelsea, MA: Lewis Publishers Inc., 279-285.

Howard PH, Meylan WM. 1997. Di(2-ethylhexyl)phthalate. In: Handbook of physical properties of organic chemicals. Boca Raton, FL: CRC Press, Inc., 226.

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

Howarth JA, Price SC, Dobrota M, et al. 2001. Effects on male rats of di-(2-ethylhexyl) phthalate and di-n-hexylphthalate administered alone or in combination. Toxicol Lett 121(1):35-43.

Howdeshell KL, Furr J, Lambright CR, et al. 2007. Cumulative effects of dibutyl phthalate and diethylhexyl phthalate on male rat reproductive tract development: Altered fetal steroid hormones and genes. Toxicol Sci 99(1):190-202. http://doi.org/10.1093/toxsci/kfm069.

Howdeshell KL, Wilson VS, Furr J, et al. 2008. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicol Sci 105(1):153-165. http://doi.org/10.1093/toxsci/kfn077.

Hoyer BB, Lenters V, Giwercman A, et al. 2018. Impact of di-2-ethylhexyl phthalate metabolites on male reproductive function: A systematic review of human evidence. Current Environmental Health Reports 5(1):20-33. http://doi.org/10.1007/s40572-018-0174-3.

Hsu NY, Lee CC, Wang JY, et al. 2012. Predicted risk of childhood allergy, asthma and reported symptoms using measured phthalate exposure in dust and urine. Indoor Air 22(3):186-199. http://doi.org/10.1111/j.1600-0668.2011.00753.x.

Hsu PC, Kuo YT, Leon Guo Y, et al. 2016. The adverse effects of low-dose exposure to di(2-ethylhexyl) phthalate during adolescence on sperm function in adult rats. Environ Toxicol 31(6):706-712. http://doi.org/10.1002/tox.22083.

Hsu JW, Yeh SC, Tsai FY, et al. 2019. Fibroblast growth factor 21 secretion enhances glucose uptake in mono(2-ethylhexyl)phthalate-treated adipocytes. Toxicol in Vitro 59:246-254. http://doi.org/10.1016/j.tiv.2019.04.021.

Hsu JW, Nien CY, Yeh SC, et al. 2020. Phthalate exposure causes browning-like effects on adipocytes in vitro and in vivo. Food Chem Toxicol 142:111487. http://doi.org/10.1016/j.fct.2020.111487.

Hu JMY, Arbuckle TE, Janssen P, et al. 2020. Associations of prenatal urinary phthalate exposure with preterm birth: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. Can J Public Health 111(3):333-341. http://doi.org/10.17269/s41997-020-00322-5.

Huang PC, Kuo PL, Guo YL, et al. 2007. Associations between urinary phthalate monoesters and thyroid hormones in pregnant women. Hum Reprod 22(10):2715-2722. http://doi.org/10.1093/humrep/dem205.

Huang PC, Tsai EM, Li WF, et al. 2010. Association between phthalate exposure and glutathione S-transferase M1 polymorphism in adenomyosis, leiomyoma and endometriosis. Hum Reprod 25(4):986-994. http://doi.org/10.1093/humrep/deq015.

Huang LP, Lee CC, Fan JP, et al. 2014a. Urinary metabolites of di(2-ethylhexyl) phthalate relation to sperm motility, reactive oxygen species generation, and apoptosis in polyvinyl chloride workers. Int Arch Occup Environ Health 87(6):635-646. http://doi.org/10.1007/s00420-013-0905-6.

Huang T, Saxena AR, Isganaitis E, et al. 2014b. Gender and racial/ethnic differences in the associations of urinary phthalate metabolites with markers of diabetes risk: National Health and Nutrition Examination Survey 2001-2008. Environ Health 13(1):6. http://doi.org/10.1186/1476-069x-13-6.

Huang HB, Chen HY, Su PH, et al. 2015. Fetal and childhood exposure to phthalate diesters and cognitive function in children up to 12 years of age: Taiwanese maternal and infant cohort study. PLoS ONE 10(6):e0131910. http://doi.org/10.1371/journal.pone.0131910.

Huang HB, Pan WH, Chang JW, et al. 2017. Does exposure to phthalates influence thyroid function and growth hormone homeostasis? The Taiwan Environmental Survey for Toxicants (TEST) 2013. Environ Res 153:63-72. http://doi.org/10.1016/j.envres.2016.11.014.

Huang HB, Kuo PL, Chang JW, et al. 2018. Longitudinal assessment of prenatal phthalate exposure on serum and cord thyroid hormones homeostasis during pregnancy- Tainan birth cohort study (TBCS). Sci Total Environ 619-620:1058-1065.

Huang HB, Kuo PH, Su PH, et al. 2019. Prenatal and childhood exposure to phthalate diesters and neurobehavioral development in a 15-year follow-up birth cohort study. Environ Res 172:569-577. http://doi.org/10.1016/j.envres.2019.02.029.

Huang PC, Waits A, Chen HC, et al. 2020a. Mediating role of oxidative/nitrosative stress biomarkers in the associations between phthalate exposure and thyroid function in Taiwanese adults. Environ Int 140:105751. http://doi.org/10.1016/j.envint.2020.105751.

Huang PC, Chang WH, Wu MT, et al. 2020b. Characterization of phthalate exposure in relation to serum thyroid and growth hormones, and estimated daily intake levels in children exposed to phthalate-tainted products: A longitudinal cohort study. Environ Pollut 264:114648. http://doi.org/10.1016/j.envpol.2020.114648.

Huber W, Grasl-Kraupp B, Schulte-Hermann R. 1996. Hepatocarcinogenic potential of di(2-ethylhexyl)phthalate in rodents and its implications on human risk. Crit Rev Toxicol 26(4):365-481. http://doi.org/10.3109/10408449609048302.

Hunt BG, Wang Y, Chen M, et al. 2017. Maternal diethylhexyl phthalate exposure affects adiposity and insulin tolerance in offspring in a PCNA-dependent manner. Environ Res 159:588-594.

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

Iannuzzi TJ, Huntley SL, Schmidt CW, et al. 1997. Combined sewer overflows (CSOs) as sources of sediment contamination in the lower Passaic River, New Jersey. I. Priority pollutants and inorganic chemicals. Chemosphere 34(2):213-231.

IARC. 1982. Di(2-ethylhexyl)phthalate. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans: Some industrial chemicals and dyestuffs. Lyon, France: International Agency for Research on Cancer. Vol. 29, 269-294.

IARC. 2012. Di(2-ethylhexyl)phthalate. IARC Monographs. Some chemicals present in industrial and consumer products, food and drinking-water. International Agency for Research on Cancer.

IARC. 2013. Di(2-ethylhexyl)phthalate. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 101: Some chemicals present in industrial and consumer products, food and drinking-water. Lyon, France: International Agency for Research on Cancer.

IARC. 2013. Di(2-ethylhexyl)phthalate. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 101: Some chemicals present in industrial and consumer products, food and drinking-water. Lyon, France: International Agency for Research on Cancer. 149-284. https://publications.iarc.fr/125. April 27, 2017.

IARC. 2017. Agents classified by the IARC Monographs, Volumes 1-118. Lyon, France: International Agency for Research on Cancer.

ICI Americas Inc. 1982. Bis(2-ethylhexyl)phthalate: A comparative subacute toxicity study in the rat and marmoset with cover letter dated 032283. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS215194. 878220040. TSCATS/020230.

Ikeda GJ, Sapienza PP, Couvillion JL, et al. 1980. Comparative distribution, excretion and metabolism of di-(2-ethylhexyl) phthalate in rats, dogs and miniature pigs. Food Cosmet Toxicol 18(6):637-642. http://doi.org/10.1016/s0015-6264(80)80012-5.

Inoue K, Kawaguchi M, Yamanaka R, et al. 2005. Evaluation and analysis of exposure levels of di(2-ethylhexyl) phthalate from blood bags. Clin Chim Acta 358(1-2):159-166. http://doi.org/10.1016/j.cccn.2005.02.019.

Ipapo KN, Factor-Litvak P, Whyatt RM, et al. 2017. Maternal prenatal urinary phthalate metabolite concentrations and visual recognition memory among infants at 27 weeks. Environ Res 155:7-14. http://doi.org/10.1016/j.envres.2017.01.019.

IRIS. 1988. Di(2-ethylhexyl)phthalate (DEHP); CASRN 117-81-7. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0014_summary.pdf. April 27, 2017.

Isenberg JS, Kamendulis LM, Smith JH, et al. 2000. Effects of di-2-ethlhexyl phthalate (DEHP) on gap-junctional intercellular communication (GJIC), DNA synthesis, and peroxisomal beta oxidation (PBOX) in rat, mouse, and hamster liver. Toxicol Sci 56:73-85.

Isenberg JS, Kamendulis L, Ackley D, et al. 2001. Reversibility and persistence of di-2-ethylhexyl phthalate (DEHP)- and phenobarbital-induced hepatocellular changes in rodents. Toxicol Sci 64(2):192-199. http://doi.org/10.1093/toxsci/64.2.192.

Ito Y, Yokota H, Wang R, et al. 2005. Species differences in the metabolism of di(2-ethylhexyl) phthalate (DEHP) in several organs of mice, rats, and marmosets. Arch Toxicol 79(3):147-154. http://doi.org/10.1007/s00204-004-0615-7.

Ito Y, Kamijima M, Hasegawa C, et al. 2014. Species and inter-individual differences in metabolic capacity of di(2-ethylhexyl)phthalate (DEHP) between human and mouse livers. Environ Health Prev Med 19(2):117-125. http://doi.org/10.1007/s12199-013-0362-6.

Ito Y, Kamijima M, Nakajima T. 2019. Di(2-ethylhexyl) phthalate-induced toxicity and peroxisome proliferator-activated receptor alpha: a review. Environ Health Prev Med 24(1):47. http://doi.org/10.1186/s12199-019-0802-z.

Itoh H, Iwasaki M, Hanaoka T, et al. 2009. Urinary phthalate monoesters and endometriosis in infertile Japanese women. Sci Total Environ 408(1):37-42. http://doi.org/10.1016/j.scitotenv.2009.09.012.

Jaeger RJ, Rubin RJ. 1972. Migration of a phthalate ester plasticizer from polyvinyl chloride blood bags into stored human blood and its localization in human tissues. N Engl J Med 287:1114-1118.

Jaimes R, McCullough D, Siegel B, et al. 2019. Plasticizer interaction with the heart: Chemicals used in plastic medical devices can interfere with cardiac electrophysiology. Circ Arrhythm Electrophysiol 12(7):e007294. http://doi.org/10.1161/circep.119.007294.

James-Todd T, Stahlhut R, Meeker JD, et al. 2012. Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001-2008. Environ Health Perspect 120(9):1307-1313. http://doi.org/10.1289/ehp.1104717.

James-Todd TM, Huang T, Seely EW, et al. 2016a. The association between phthalates and metabolic syndrome: the National Health and Nutrition Examination Survey 2001-2010. Environ Health 15:52. http://doi.org/10.1186/s12940-016-0136-x.

James-Todd TM, Meeker JD, Huang T, et al. 2016b. Pregnancy urinary phthalate metabolite concentrations and gestational diabetes risk factors. Environ Int 96:118-126. http://doi.org/10.1016/j.envint.2016.09.009.

James-Todd TM, Chiu YH, Messerlian C, et al. 2018. Trimester-specific phthalate concentrations and glucose levels among women from a fertility clinic. Environ Health 17(1):55. http://doi.org/10.1186/s12940-018-0399-5.

Jarfelt K, Dalgaard M, Hass U, et al. 2005. Antiandrogenic effects in male rats perinatally exposed to a mixture of di(2-ethylhexyl) phthalate and di(2-ethylhexyl) adipate. Reprod Toxicol 19(4):505-515. http://doi.org/10.1016/j.reprotox.2004.11.005.

Jensen TK, Frederiksen H, Kyhl HB, et al. 2016. Prenatal exposure to phthalates and anogenital distance in male infants from a low-exposed Danish cohort (2010-2012). Environ Health Perspect 124(7):1107-1113. http://doi.org/10.1289/ehp.1509870.

Joensen UN, Frederiksen H, Blomberg Jensen M, et al. 2012. Phthalate excretion pattern and testicular function: a study of 881 healthy Danish men. Environ Health Perspect 120(10):1397-1403. http://doi.org/10.1289/ehp.1205113.

Joensen UN, Jorgensen N, Meldgaard M, et al. 2014. Associations of filaggrin gene loss-of-function variants with urinary phthalate metabolites and testicular function in young Danish Men. Environ Health Perspect 122(4):345-350. http://doi.org/10.1289/ehp.1306720.

Jøhnk C, Høst A, Husby S, et al. 2020. Maternal phthalate exposure and asthma, rhinitis and eczema in 552 children aged 5 years; a prospective cohort study. Environ Health 19(1):32. http://doi.org/10.1186/s12940-020-00586-x.

Johns LE, Ferguson KK, Soldin OP, et al. 2015. Urinary phthalate metabolites in relation to maternal serum thyroid and sex hormone levels during pregnancy: a longitudinal analysis. Reprod Biol Endocrinol 13:4. http://doi.org/10.1186/1477-7827-13-4.

Johns LE, Ferguson KK, McElrath TF, et al. 2016. Associations between repeated measures of maternal urinary phthalate metabolites and thyroid hormone parameters during pregnancy. Environ Health Perspect 124(11):1808-1815. http://doi.org/10.1289/ehp170.

Johns LE, Ferguson KK, Cantonwine DE, et al. 2017. Urinary BPA and phthalate metabolite concentrations and plasma vitamin D levels in pregnant women: A repeated measures analysis. Environ Health Perspect 125(8):087026. http://doi.org/10.1289/EHP1178.

Johnson BT, Heitkamp MA, Jones JR. 1977. Dynamics of phthalic acid esters in aquatic organisms. Fate of pollutants in the air and water environments: Part 2. Chemical and biological fate of pollutants in the environment. New York, NY: John Wiley & Sons. 283-300

Johnson BT, Heitkamp MA, Jones JR. 1984. Environmental and chemical factors influencing the biodegradation of phthalic-acid esters in freshwater sediments. Environ Pollut 8(2):101-118. http://doi.org/10.1016/0143-148x(84)90021-1.

Jones HB, Garside DA, Liu R, et al. 1993. The influence of phthalate esters on Leydig cell structure and function in vitro and in vivo. Exp Mol Pathol 58(3):179-193. http://doi.org/10.1006/exmp.1993.1016.

Jones DL, Burklin CE, Seaman JC, et al. 1996. Models to estimate volatile organic hazardous air pollutant emissions from municipal sewer systems. J Air Waste Manage Assoc 46:657-666.

Jones S, Boisvert A, Duong TB, et al. 2014. Disruption of rat testis development following combined in utero exposure to the phytoestrogen genistein and antiandrogenic plasticizer di-(2-ethylhexyl) phthalate. Biol Reprod 91(3):64. http://doi.org/10.1095/biolreprod.114.120907.

Jones S, Boisvert A, Francois S, et al. 2015. In utero exposure to di-(2-ethylhexyl) phthalate induces testicular effects in neonatal rats that are antagonized by genistein cotreatment. Biol Reprod 93(4):92. http://doi.org/10.1095/biolreprod.115.129098.

Jones S, Boisvert A, Naghi A, et al. 2016. Stimulatory effects of combined endocrine disruptors on MA-10 Leydig cell steroid production and lipid homeostasis. Toxicology 355-356:21-30. http://doi.org/10.1016/j.tox.2016.05.008.

Jonsson BAG, Richthoff J, Rylander L, et al. 2005. Urinary phthalate metabolites and biomarkers of reproductive function in young men. Epidemiology 16(4):487-493. http://doi.org/10.1097/01.ede.0000164555.19041.01.

Juberg DR, Alfano K, Coughlin RJ, et al. 2001. An observational study of object mouthing behavior by young children. Pediatrics 107:135-142.

Jukic AM, Calafat AM, McConnaughey DR, et al. 2016. Urinary concentrations of phthalate metabolites and bisphenol A and associations with follicular-phase length, luteal-phase length, fecundability, and early pregnancy loss. Environ Health Perspect 124(3):321-328. http://doi.org/10.1289/ehp.1408164.

Jurewicz J, Radwan M, Sobala W, et al. 2013. Human urinary phthalate metabolites level and main semen parameters, sperm chromatin structure, sperm aneuploidy and reproductive hormones. Reprod Toxicol 42:232-241. http://doi.org/10.1016/j.reprotox.2013.10.001.

Just AC, Whyatt RM, Miller RL, et al. 2012. Children's urinary phthalate metabolites and fractional exhaled nitric oxide in an urban cohort. Am J Respir Crit Care Med 186(9):830-837. http://doi.org/10.1164/rccm.201203-0398OC.

Kaestner F, Seiler F, Rapp D, et al. 2020. Exposure of patients to di(2-ethylhexy)phthalate (DEHP) and its metabolite MEHP during extracorporeal membrane oxygenation (ECMO) therapy. PLoS ONE 15(1):e0224931. http://doi.org/10.1371/journal.pone.0224931.

Kambia K, Dine T, Gressier B, et al. 2001. High-performance liquid chromatographic method for the determination of di(2-ethylhexyl) phthalate in total parenteral nutrition and in plasma. J Chromatogr 755(1-2):297-303. http://doi.org/10.1016/s0378-4347(01)00125-6.

Kamijo Y, Hora K, Nakajima T, et al. 2007. Peroxisome proliferator-activated receptor alpha protects against glomerulonephritis induced by long-term exposure to the plasticizer di-(2-ethylhexyl)phthalate. J Am Soc Nephrol 18(1):176-188. http://doi.org/10.1681/asn.2006060597.

Kang Y, Park J, Youn K. 2019. Association between urinary phthalate metabolites and obesity in adult Korean population: Korean National Environmental Health Survey (KoNEHS), 2012-2014. Ann Occup Environ Med 31:e23. http://doi.org/10.35371/aoem.2019.31.e23.

Kanki K, Nishikawa A, Masumura K, et al. 2005. In vivo mutational analysis of liver DNA in gpt delta transgenic rats treated with the hepatocarcinogens N-nitrosopyrrolidine, 2-amino-3-methylimidazo[4,5-f]quinoline, and di(2-ethylhexyl)phthalate. Mol Carcinog 42(1):9-17. http://doi.org/10.1002/mc.20061.

Kanode R, Chandra S, Sharma S. 2017. Application of bacterial reverse mutation assay for detection of non-genotoxic carcinogens. Toxicol Mech Methods 27(5):376-381. http://doi.org/10.1080/15376516.2017.1300616.

Karabulut G, Barlas N. 2018. Genotoxic, histologic, immunohistochemical, morphometric and hormonal effects of di-(2-ethylhexyl)-phthalate (DEHP) on reproductive systems in pre-pubertal male rats. Toxicology Research 7(5):859-873. http://doi.org/10.1039/c8tx00045j.

Kardas F, Bayram AK, Demirci E, et al. 2016. Increased serum phthalates (MEHP, DEHP) and bisphenol A concentrations in children with autism spectrum disorder: The role of endocrine disruptors in autism etiopathogenesis. J Child Neurol 31(5):629-635. http://doi.org/10.1177/0883073815609150.

Karle VA, Short BL, Martin GR, et al. 1997. Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethylhexyl)phthalate. Crit Care Med 25:696-703.

Kato K, Silva MJ, Reidy JA, et al. 2004. Mono(2-ethyl-5-hydroxyhexyl) phthalate and mono-(2-ethyl-5-oxohexyl) phthalate as biomarkers for human exposure assessment to di-(2-ethylhexyl) phthalate. Environ Health Perspect 112(3):327-330. http://doi.org/10.1289/ehp.6663.

Kaun-Yu L, Tseng FW, Wu CJ, et al. 2004. Suppression by phthalates of the calcium signaling of human nicotinic acetylcholine receptors in human neuroblastoma SH-SY5Y cells. Toxicology 200(2-3):113-121. http://doi.org/10.1016/j.tox.2004.03.018.

Kenaga EE. 1980. Predicted bioconcentration factors and soil sorption coefficient of pesticides and other chemicals. Ecotoxicol Environ Saf 4:26-38.

Kessler W, Numtip W, Grote K, et al. 2004. Blood burden of di(2-ethylhexyl) phthalate and its primary metabolite mono(2-ethylhexyl) phthalate in pregnant and nonpregnant rats and marmosets. Toxicol Appl Pharmacol 195(2):142-153. http://doi.org/10.1016/j.taap.2003.11.014.

Kessler W, Numtip W, Völkel W, et al. 2012. Kinetics of di(2-ethylhexyl) phthalate (DEHP) and mono(2-ethylhexyl) phthalate in blood and of DEHP metabolites in urine of male volunteers after

single ingestion of ring-deuterated DEHP. Toxicol Appl Pharmacol 264(2):284-291. http://doi.org/10.1016/j.taap.2012.08.009.

Keys DA, Wallace DG, Kepler TB, et al. 1999. Quantitative evaluation of alternative mechanisms of blood and testes disposition of di(2-ethylhexyl) phthalate and mono(2-ethylhexyl) phthalate in rats. Toxicol Sci 49(2):172-185.

Khedr A. 2013. Optimized extraction method for LC-MS determination of bisphenol A, melamine and di(2-ethylhexyl) phthalate in selected soft drinks, syringes, and milk powder. J Chromatogr 930:98-103. http://doi.org/10.1016/j.jchromb.2013.04.040.

Kickham P, Otton SV, Moore MM, et al. 2012. Relationship between biodegradation and sorption of phthalate esters and their metabolites in natural sediments. Environ Toxicol Chem 31(8):1730-1737. http://doi.org/10.1002/etc.1903.

Kim JH, Hong YC. 2014. HSP70-hom gene polymorphisms modify the association of diethylhexyl phthalates with insulin resistance. Environ Mol Mutagen 55(9):727-734. http://doi.org/10.1002/em.21884.

Kim SH, Park MJ. 2014. Phthalate exposure and childhood obesity. Ann Pediatr Endocrinol Metab 19(2):69-75. http://doi.org/10.6065/apem.2014.19.2.69.

Kim Y, Ha EH, Kim EJ, et al. 2011. Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. Environ Health Perspect 119(10):1495-1500. http://doi.org/10.1289/ehp.1003178.

Kim JH, Park HY, Bae S, et al. 2013. Diethylhexyl phthalates is associated with insulin resistance via oxidative stress in the elderly: a panel study. PLoS ONE 8(8):e71392. http://doi.org/10.1371/journal.pone.0071392.

Kim SH, Cho S, Ihm HJ, et al. 2015. Possible role of phthalate in the pathogenesis of endometriosis: in vitro, animal, and human data. J Clin Endocrinol Metab 100(12):E1502-E1511. http://doi.org/10.1210/jc.2015-2478.

Kim JH, Park H, Lee J, et al. 2016a. Association of diethylhexyl phthalate with obesity-related markers and body mass change from birth to 3 months of age. J Epidemiol Community Health 70(5):466-472. http://doi.org/10.1136/jech-2015-206315.

Kim KN, Choi YH, Lim YH, et al. 2016b. Urinary phthalate metabolites and depression in an elderly population: National Health and Nutrition Examination Survey 2005-2012. Environ Res 145:61-67. http://doi.org/10.1016/j.envres.2015.11.021.

Kim S, Kim S, Won S, et al. 2017a. Considering common sources of exposure in association studies - Urinary benzophenone-3 and DEHP metabolites are associated with altered thyroid hormone balance in the NHANES 2007-2008. Environ Int 107:25-32. http://doi.org/10.1016/j.envint.2017.06.013.

Kim S, Kim S, Won S, et al. 2017b. Supplemental material: Considering common sources of exposure in association studies - Urinary benzophenone-3 and DEHP metabolites are associated with altered thyroid hormone balance in the NHANES 2007-2008. Environ Int 107. http://doi.org/10.1016/j.envint.2017.06.013.

Kim SH, On JW, Pyo H, et al. 2018a. Percentage fractions of urinary di(2-ethylhexyl) phthalate metabolites: Association with obesity and insulin resistance in Korean girls. PLoS ONE 13(11):e0208081. http://doi.org/10.1371/journal.pone.0208081.

Kim HS, Cheon YP, Lee SH. 2018b. Hershberger assays for di-2-ethylhexyl phthalate and its substitute candidates. Dev Reprod 22(1):19-27. http://doi.org/10.12717/dr.2018.22.1.019.

Kim M, Jeong JS, Kim H, et al. 2018c. Low dose exposure to di-2-ethylhexylphthalate in juvenile rats alters the expression of genes related with thyroid hormone regulation. Biomol Ther (Seoul) 26(5):512-519. http://doi.org/10.4062/biomolther.2018.076.

Kim M, Jeong JS, Kim H, et al. 2018d. Supplemental material: Low dose exposure to di-2-ethylhexylphthalate in juvenile rats alters the expression of genes related with thyroid hormone regulation. Biomol Ther (Seoul) 26. http://doi.org/10.4062/biomolther.2018.076.

Kim YM, Kim J, Cheong HK, et al. 2018e. Exposure to phthalates aggravates pulmonary function and airway inflammation in asthmatic children. PLoS ONE 13(12):e0208553. http://doi.org/10.1371/journal.pone.0208553.

Kim S, Eom S, Kim HJ, et al. 2018f. Association between maternal exposure to major phthalates, heavy metals, and persistent organic pollutants, and the neurodevelopmental performances of their children at 1 to 2years of age- CHECK cohort study. Sci Total Environ 624:377-384. http://doi.org/10.1016/j.scitotenv.2017.12.058.

Kim J, Cha S, Lee MY, et al. 2018g. Chronic low-dose nonylphenol or di-(2-ethylhexyl) phthalate has a different estrogen-like response in mouse uterus. Dev Reprod 22(4):379-391. http://doi.org/10.12717/dr.2018.22.4.379.

Kim S, Park GY, Yoo YJ, et al. 2019a. Di-2-ethylhexylphthalate promotes thyroid cell proliferation and DNA damage through activating thyrotropin-receptor-mediated pathways in vitro and in vivo. Food Chem Toxicol 124:265-272. http://doi.org/10.1016/j.fct.2018.12.010.

Kim J, Cha S, Lee MY, et al. 2019b. Chronic and low dose exposure to nonlyphenol or di(2-ethylhexyl) phthalate alters cell proliferation and the localization of steroid hormone receptors in uterine endometria in mice. Dev Reprod 23(3):263-275. http://doi.org/10.12717/dr.2019.23.3.263.

Kirby PE, Pizzarello RF, Lawlor TE, et al. 1983. Evaluation of di-(2-ethylhexyl)phthalate and its major metabolites in the Ames test and L5178Y mouse lymphoma mutagenicity assay. Environ Mutagen 5(5):657-663. http://doi.org/10.1002/em.2860050504.

Kitaoka M, Hirai S, Terayama H, et al. 2013. Effects on the local immunity in the testis by exposure to di-(2-ethylhexyl) phthalate (DEHP) in mice. J Reprod Dev 59(5):485-490. http://doi.org/10.1262/jrd.2012-180.

Klaunig JE, Babich MA, Baetcke KP, et al. 2003. PPARalpha agonist-induced rodent tumors: Modes of action and human relevance. Crit Rev Toxicol 33(6):655-780. http://doi.org/10.1080/713608372.

Kleinsasser NH, Harreus UA, Kastenbauer ER, et al. 2004. Mono(2-ethylhexyl)phthalate exhibits genotoxic effects in human lymphocytes and mucosal cells of the upper aerodigestive tract in the comet assay. Toxicol Lett 148(1-2):83-90. http://doi.org/10.1016/j.toxlet.2003.12.013.

Klimisch HJ, Hellwig J, Kauffmann W, et al. 1991. Di-(2-ethylhexyl)phthalate (DEHP): Investigation of inhalation toxicity in rats after repeated exposure (28 d). Hum Exp Toxicol 10:68.

Klimisch HJ, Gamer AO, Hellwig J, et al. 1992. Di-(2-ethylhexyl) phthalate: A short-term repeated inhalation toxicity study including fertility assessment. Food Chem Toxicol 30(11):915-919. http://doi.org/10.1016/0278-6915(92)90175-k.

Klinefelter GR, Laskey JW, Winnik WM, et al. 2012. Novel molecular targets associated with testicular dysgenesis induced by gestational exposure to diethylhexyl phthalate in the rat: a role for estradiol. Reproduction 144(6):747-761. http://doi.org/10.1530/rep-12-0266.

Klopcic I, Kolsek K, Dolenc MS. 2015. Glucocorticoid-like activity of propylparaben, butylparaben, diethylhexyl phthalate and tetramethrin mixtures studied in the MDA-kb2 cell line. Toxicol Lett 232(2):376-383. http://doi.org/10.1016/j.toxlet.2014.11.019.

Kluwe WM, Haseman JK, Douglas JF, et al. 1982a. The carcinogenicity of dietary di(2-ethylhexyl) phthalate (DEHP) in Fischer 344 rats and B6C3F1 mice. J Toxicol Environ Health 10(4-5):797-815. http://doi.org/10.1080/15287398209530296.

Kluwe WM, McConnell EE, Huff JE, et al. 1982b. Carcinogenicity testing of phthalate esters and related compounds by the National Toxicology Program and the National Cancer Institute. Environ Health Perspect 45:129-133. http://doi.org/10.2307/3429396.

Kluwe WM, Huff JE, Matthews HB, et al. 1985. Comparative chronic toxicities and carcinogenic potentials of 2-ethylhexyl-containing compounds in rats and mice. Carcinogenesis 6(11):1577-1583. http://doi.org/10.1093/carcin/6.11.1577.

Ko NY, Lo YC, Huang PC, et al. 2019. Changes in insulin resistance mediate the associations between phthalate exposure and metabolic syndrome. Environ Res 175:434-441. http://doi.org/10.1016/j.envres.2019.04.022.

Ko C, Benedict RT. 2020. Personal communication: Animal numbers used in Barakat et al. 2017 "Prenatal exposure to DEHP induces premature reproductive senescence in male" Toxicol Sci 156(1):96-108. University of Illinois at Urbana-Champaign. Agency for Toxic Substances and Disease Registry. December 2020.

Kobayashi K, Miyagawa M, Wang RS, et al. 2006. Effects of in utero and lactational exposure to di(2-ethylhexyl)phthalate on somatic and physical development in rat offspring. Ind Health 44(4):652-660.

Kobrosly RW, Evans S, Miodovnik A, et al. 2014. Prenatal phthalate exposures and neurobehavioral development scores in boys and girls at 6-10 years of age. Environ Health Perspect 122(5):521-528. http://doi.org/10.1289/ehp.1307063.

Koch HM, Bolt HM, Angerer J. 2004. Di(2-ethylhexyl)phthalate (DEHP) metabolites in human urine and serum after a single oral dose of deuterium-labelled DEHP. Arch Toxicol 78(3):123-130. http://doi.org/10.1007/s00204-003-0522-3.

Koch HM, Bolt HM, Preuss R, et al. 2005a. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Arch Toxicol 79(7):367-376. http://doi.org/10.1007/s00204-004-0642-4.

Koch HM, Bolt HM, Preuss R, et al. 2005b. Intravenous exposure to di(2-ethylhexyl)phthalate (DEHP): metabolites of DEHP in urine after a voluntary platelet donation. Arch Toxicol 79(12):689-693. http://doi.org/10.1007/s00204-005-0004-x.

Koch HM, Lorber M, Christensen KLY, et al. 2013. Identifying sources of phthalate exposure with human biomonitoring: Results of a 48h fasting study with urine collection and personal activity patterns. Int J Hyg Environ Health 216(6):672-681. http://doi.org/10.1016/j.ijheh.2012.12.002.

Kolena B, Petrovicova I, Pilka T, et al. 2014. Phthalate exposure and health-related outcomes in specific types of work environment. Int J Environ Res Public Health 11(6):5628-5639. http://doi.org/10.3390/ijerph110605628.

Kolena B, Petrovicova I, Sidlovska M, et al. 2020. Occupational hazards and risks associated with phthalates among Slovakian firefighters. Int J Environ Res Public Health 17(7) http://doi.org/10.3390/ijerph17072483.

Koo HJ, Lee BM. 2007. Toxicokinetic relationship between di(2-ethylhexyl) phthalate (DEHP) and mono(2-ethylhexyl) phthalate in rats. J Toxicol Environ Health 70(5):383-387. http://doi.org/10.1080/15287390600882150.

Kornbrust DJ, Barfknecht TR, Ingram P, et al. 1984. Effect of di(2-ethylhexyl) phthalate on DNA repair and lipid peroxidation in rat hepatocytes and on metabolic cooperation in Chinese hamster V-79 cells. J Toxicol Environ Health 13(1):99-116. http://doi.org/10.1080/15287398409530484.

Kozumbo WJ, Kroll R, Rubin RJ. 1982. Assessment of the mutagenicity of phthalate esters. Environ Health Perspect 45:103-109. http://doi.org/10.2307/3429391.

Krais AM, Andersen C, Eriksson AC, et al. 2018. Excretion of urinary metabolites of the phthalate esters DEP and DEHP in 16 volunteers after inhalation and dermal exposure. Int J Environ Res Public Health 15(11) http://doi.org/10.3390/ijerph15112514.

Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Ku HY, Su PH, Wen HJ, et al. 2015. Prenatal and postnatal exposure to phthalate esters and asthma: a 9-year follow-up study of a Taiwanese birth cohort. PLoS ONE 10(4):e0123309. http://doi.org/10.1371/journal.pone.0123309.

Ku HY, Tsai TL, Wang PL, et al. 2020. Prenatal and childhood phthalate exposure and attention deficit hyperactivity disorder traits in child temperament: A 12-year follow-up birth cohort study. Sci Total Environ 699:134053. http://doi.org/10.1016/j.scitotenv.2019.134053.

Kuo FC, Su SW, Wu CF, et al. 2015. Relationship of urinary phthalate metabolites with serum thyroid hormones in pregnant women and their newborns: a prospective birth cohort in Taiwan. PLoS ONE 10(6):e0123884. http://doi.org/10.1371/journal.pone.0123884.

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.

Kurane R. 1986. Microbial degradation of phthalate esters. Microbiol Sci 3(3):92-95.

Kurata Y, Kidachi F, Yokoyama M, et al. 1998. Subchronic toxicity of di(2-ethylhexyl)phthalate in common marmosets: lack of hepatic peroxisome proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia. Toxicol Sci 42(1):49-56. http://doi.org/10.1006/toxs.1997.2414.

Kurata Y, Makinodan F, Shimamura N, et al. 2012a. Metabolism of di (2-ethylhexyl) phthalate (DEHP): comparative study in juvenile and fetal marmosets and rats. J Toxicol Sci 37(1):33-49. http://doi.org/10.2131/jts.37.33.

Kurata Y, Shimamura N, Katoh M. 2012b. Metabolite profiling and identification in human urine after single oral administration of DEHP. J Toxicol Sci 37(2):401-414.

Kushman ME, Kraft AD, Guyton KZ, et al. 2013. A systematic approach for identifying and presenting mechanistic evidence in human health assessments. Regul Toxicol Pharmacol 67(2):266-277. http://doi.org/10.1016/j.yrtph.2013.08.005.

La Rocca C, Tait S, Guerranti C, et al. 2014. Exposure to endocrine disrupters and nuclear receptor gene expression in infertile and fertile women from different Italian areas. Int J Environ Res Public Health 11(10):10146-10164. http://doi.org/10.3390/ijerph111010146.

Lacey S, Alexander BM, Baxter CS. 2014. Plasticizer contamination of firefighter personal protective clothing--a potential factor in increased health risks in firefighters. J Occup Environ Hyg 11(5):D43-48. http://doi.org/10.1080/15459624.2013.877142.

Lagos-Cabré R, Moreno RD. 2012. Contribution of environmental pollutants to male infertility: a working model of germ cell apoptosis induced by plasticizers. Biol Res 45(1):5-14. http://doi.org/10.1590/s0716-97602012000100001.

Lake BG, Brantom PG, Gangolli SD, et al. 1976. Studies on the effects of orally administered di-(2-ethylhexyl) phthalate in the ferret. Toxicology 6(3):341-356.

Lake BG, Gray TJ, Foster JR, et al. 1984. Comparative studies on di-(2-ethylhexyl) phthalate-induced hepatic peroxisome proliferation in the rat and hamster. Toxicol Appl Pharmacol 72(1):46-60. http://doi.org/10.1016/0041-008x(84)90248-5.

Lake B, Kozlen S, Evans J, et al. 1987. Effect of prolonged administration of clofibric acid and di-(2-ethylhexyl)phthalate on hepatic enzyme activities and lipid peroxidation in the rat. Toxicology 44(2):213-228.

Lamb J, Chapin R, Teague J, et al. 1987. Reproductive effects of four phthalic acid esters in the mouse. Toxicol Appl Pharmacol 88(2):255-269. http://doi.org/10.1016/0041-008x(87)90011-1.

Larranaga MD, Lewis RJ, Lewis RA. 2016. Di(2-ethylhexyl) phthalate. In: Hawley's condensed chemical dictionary. 16th ed. Hoboken, NJ: John Wiley & Sons, Inc., 470-471.

Larsen ST, Hansen JS, Hansen EW, et al. 2007. Airway inflammation and adjuvant effect after repeated airborne exposures to di-(2-ethylhexyl)phthalate and ovalbumin in BALB/c mice. Toxicology 235(1-2):119-129. http://doi.org/10.1016/j.tox.2007.03.010.

Latini G. 2000. Potential hazards of exposure to di-(2-ethylhexyl)-phthalate in babies. Biol Neonate 78:269-276.

Latini G, Avery GB. 1999. Materials degradation in endotracheal tubes: a potential contributor to bronchopulmonary dysplasia. Acta Paediatr 88(10):1174-1175. http://doi.org/10.1111/j.1651-2227.1999.tb01011.x.

Laurenzana EM, Coslo DM, Vigilar MV, et al. 2016. Activation of the constitutive androstane receptor by monophthalates. Chem Res Toxicol 29(10):1651-1661. http://doi.org/10.1021/acs.chemrestox.6b00186.

Lay JO, Miller BJ. 1987. Plasticizers in pacifiers: Direct determination by FAB-MS. Anal Chem 59(22):1323-1325.

Le Hegarat L, Mourot A, Huet S, et al. 2014. Performance of comet and micronucleus assays in metabolic competent HepaRG cells to predict in vivo genotoxicity. Toxicol Sci 138(2):300-309. http://doi.org/10.1093/toxsci/kfu004.

Leboeuf RA, Kerckaert GA, Aardema MJ, et al. 1996. The pH 6.7 Syrian hamster embryo cell transformation assay for assessing the carcinogenic potential of chemicals. Mutat Res 356(1):85-127. http://doi.org/10.1016/0027-5107(95)00199-9.

Lee BM, Koo HJ. 2007. Hershberger assay for antiandrogenic effects of phthalates. J Toxicol Environ Health 70(15-16):1365-1370. http://doi.org/10.1080/15287390701432285.

Lee PC, Borysewicz R, Raab K, et al. 1993. Development of lipolytic activity in gastric aspirates from premature infants. J Pediatr Gastroenterol Nutr 17:291-297.

Lee S, Martinez-Arguelles DB, Campioli E, et al. 2017. Fetal exposure to low levels of the plasticizer DEHP predisposes the adult male adrenal gland to endocrine disruption. Endocrinology 158(2):304-318. http://doi.org/10.1210/en.2016-1604.

Lee KS, Lim YH, Kim KN, et al. 2018. Urinary phthalate metabolites concentrations and symptoms of depression in an elderly population. Sci Total Environ 625:1191-1197. http://doi.org/10.1016/j.scitotenv.2017.12.219.

Lee DG, Kim KM, Lee HS, et al. 2019a. Peroxiredoxin 5 prevents diethylhexyl phthalate-induced neuronal cell death by inhibiting mitochondrial fission in mouse hippocampal HT-22 cells. Neurotoxicology 74:242-251. http://doi.org/10.1016/j.neuro.2019.08.003.

Lee JW, Lee SJ, Gye MC, et al. 2019b. Genotoxicity and glucose tolerance induction by acetyltriethylcitrate, substitute plasticizer compared to di(2-ethylhexyl)phthalate. Sci Rep 9(1):12237. http://doi.org/10.1038/s41598-019-48599-y.

Lee YS, Lee S, Lim JE, et al. 2019c. Occurrence and emission of phthalates and non-phthalate plasticizers in sludge from wastewater treatment plants in Korea. Sci Total Environ 692:354-360. http://doi.org/10.1016/j.scitotenv.2019.07.301.

Lee DW, Lim YH, Shin CH, et al. 2020. Prenatal exposure to di-(2-ethylhexyl) phthalate and decreased skeletal muscle mass in 6-year-old children: A prospective birth cohort study. Environ Res 182:109020. http://doi.org/10.1016/j.envres.2019.109020.

Letinski DJ, Connelly MJ, Peterson DR, et al. 2002. Slow-stir water solubility measurements of selected alcohols and diesters. Chemosphere 48(3):257-265.

Leyder F, Boulanger P. 1983. Ultraviolet absorption, aqueous solubility, and octanol-water partition for several phthalates. Bull Environ Contam Toxicol 30:152-157.

Lhuguenot JC, Mitchell AM, Elcombe CR. 1988. The metabolism of mono-(2-ethylhexyl) phthalate (MEHP) and liver peroxisome proliferation in the hamster. Toxicol Ind Health 4(4):431-441. http://doi.org/10.1177/074823378800400402.

Lhuguenot JC, Mitchell AM, Milner G, et al. 1985. The metabolism of di(2-ethylhexyl) phthalate (DEHP) and mono-(2-ethylhexyl) phthalate (MEHP) in rats: in vivo and in vitro dose and time dependency of metabolism. Toxicol Appl Pharmacol 80(1):11-22. http://doi.org/10.1016/0041-008x(85)90096-1.

Li H, Kim KH. 2003. Effects of mono-(2-ethylhexyl) phthalate on fetal and neonatal rat testis organ cultures. Biol Reprod 69(6):1964-1972. http://doi.org/10.1095/biolreprod.103.018895.

Li LH, Jester WF, Orth JM. 1998. Effects of relatively low levels of mono-(2-ethylhexyl) phthalate on cocultured Sertoli cells and gonocytes from neonatal rats. Toxicol Appl Pharmacol 153(2):258-265. http://doi.org/10.1006/taap.1998.8550.

Li LH, Jester WF, Laslett AL, et al. 2000. A single dose of di-(2-ethylhexyl) phthalate in neonatal rats alters gonocytes, reduces Sertoli cell proliferation, and decreases cyclin D2 expression. Toxicol Appl Pharmacol 166(3):222-229. http://doi.org/10.1006/taap.2000.8972.

Li XW, Liang Y, Su Y, et al. 2012a. Adverse effects of di-(2-ethylhexyl) phthalate on Leydig cell regeneration in the adult rat testis. Toxicol Lett 215(2):84-91. http://doi.org/10.1016/j.toxlet.2012.10.001.

Li N, Liu T, Zhou L, et al. 2012b. Di-(2-ethylhcxyl) phthalate reduces progesterone levels and induces apoptosis of ovarian granulosa cell in adult female ICR mice. Environ Toxicol Pharmacol 34(3):869-875. http://doi.org/10.1016/j.etap.2012.08.013.

Li R, Yu C, Gao R, et al. 2012c. Effects of DEHP on endometrial receptivity and embryo implantation in pregnant mice. J Hazard Mater 241-242:231-240. http://doi.org/10.1016/j.jhazmat.2012.09.038.

Li L, Zhang T, Qin XS, et al. 2014. Exposure to diethylhexyl phthalate (DEHP) results in a heritable modification of imprint genes DNA methylation in mouse oocytes. Mol Biol Rep 41(3):1227-1235. http://doi.org/10.1007/s11033-013-2967-7.

Li L, Liu JC, Lai FN, et al. 2016. Di (2-ethylhexyl) phthalate exposure impairs growth of antral follicle in mice. PLoS ONE 11(2):e0148350. http://doi.org/10.1371/journal.pone.0148350.

Li W, Zhang W, Chang M, et al. 2018. Quadrupole orbitrap mass spectrometer-based metabonomic elucidation of influences of short-term di(2-ethylhexyl) phthalate exposure on cardiac metabolism in male mice. Chem Res Toxicol 31(11):1185-1194. http://doi.org/10.1021/acs.chemrestox.8b00184.

Li MC, Mínguez-Alarcón L, Bellavia A, et al. 2019a. Serum beta-carotene modifies the association between phthalate mixtures and insulin resistance: The National Health and Nutrition Examination Survey 2003-2006. Environ Res 178:108729. http://doi.org/10.1016/j.envres.2019.108729.

Li MC, Mínguez-Alarcón L, Bellavia A, et al. 2019b. Supplemental material: Serum beta-carotene modifies the association between phthalate mixtures and insulin resistance: The National Health and Nutrition Examination Survey 2003-2006. Environ Res 178. http://doi.org/10.1016/j.envres.2019.108729.

Li YL, Lv J, Du ZP, et al. 2020. The levels of phthalate exposure and associations with obesity in an elderly population in China. Ecotoxicol Environ Saf 201:110749. http://doi.org/10.1016/j.ecoenv.2020.110749.

Liang Y, Bi C, Wang X, et al. 2019. A general mechanistic model for predicting the fate and transport of phthalates in indoor environments. Indoor Air 29(1):55-69. http://doi.org/10.1111/ina.12514.

Lien YJ, Ku HY, Su PH, et al. 2015. Prenatal exposure to phthalate esters and behavioral syndromes in children at 8 years of age: Taiwan Maternal and Infant Cohort Study. Environ Health Perspect 123(1):95-100. http://doi.org/10.1289/ehp.1307154.

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

Ligocki MP, Leuenberger C, Pankow JF. 1985b. Trace organic compounds in rain-III. Particle scavenging of neutral organic compounds. Atmos Environ 19(10):1619-1626.

Lin H, Ge R, Chen G, et al. 2008. Involvement of testicular growth factors in fetal Leydig cell aggregation after exposure to phthalate in utero. Proc Natl Acad Sci U S A 105(20):7218-7222. http://doi.org/10.1073/pnas.0709260105.

Lin H, Lian Q, Hu G, et al. 2009. In utero and lactational exposures to diethylhexyl-phthalate affect two populations of Leydig cells in male Long-Evans rats. Biol Reprod 80(5):882-888. http://doi.org/10.1095/biolreprod.108.072975.

Lin Y, Wei J, Li Y, et al. 2011. Developmental exposure to di(2-ethylhexyl) phthalate impairs endocrine pancreas and leads to long-term adverse effects on glucose homeostasis in the rat. Am J Physiol Endocrinol Metab 301(3):E527-538. http://doi.org/10.1152/ajpendo.00233.2011.

Lin CY, Hsieh CJ, Lo SC, et al. 2016. Positive association between concentration of phthalate metabolites in urine and microparticles in adolescents and young adults. Environ Int 92-93:157-164. http://doi.org/10.1016/j.envint.2016.04.006.

Lin LY, Tsai MS, Chen MH, et al. 2018. Childhood exposure to phthalates and pulmonary function. Sci Total Environ 615:1282-1289. http://doi.org/10.1016/j.scitotenv.2017.08.318.

Lin CY, Lee HL, Hwang YT, et al. 2020. The association between urine di-(2-ethylhexyl) phthalate metabolites, global DNA methylation, and subclinical atherosclerosis in a young Taiwanese population. Environ Pollut 265(Pt B):114912. http://doi.org/10.1016/j.envpol.2020.114912.

Lioy PJ, Hauser R, Gennings C, et al. 2015. Assessment of phthalates/phthalate alternatives in children's toys and childcare articles: Review of the report including conclusions and recommendations of Chronic Hazard Advisory Panel of the Consumer Product Safety Commission. J Expo Sci Environ Epidemiol 25:343-353.

Liss GM, Albro PW, Hartle RW, et al. 1985. Urine phthalate determinations as an index of occupational exposure to phthalic anhydride and di(2-ethylhexyl)phthalate. Scand J Work Environ Health 11(5):381-387.

Liu X, He D, Zhang D, et al. 2008. Di(2-ethylhexyl) phthalate (DEHP) increases transforming growth factor-beta1 expression in fetal mouse genital tubercles. J Toxicol Environ Health 71(19):1289-1294. http://doi.org/10.1080/15287390802114915.

Liu L, Bao H, Liu F, et al. 2012. Phthalates exposure of Chinese reproductive age couples and its effect on male semen quality, a primary study. Environ Int 42:78-83. http://doi.org/10.1016/j.envint.2011.04.005.

Liu L, Wang H, Tian M, et al. 2017. Phthalate metabolites related to infertile biomarkers and infertility in Chinese men. Environ Pollut 231(Pt 1):291-300. http://doi.org/10.1016/j.envpol.2017.08.018.

Liu T, Wang Y, Yang M, et al. 2018a. Di-(2-ethylhexyl) phthalate induces precocious puberty in adolescent female rats. Iran J Basic Med Sci 21(8):848-855. http://doi.org/10.22038/ijbms.2018.28489.6905.

Liu H, Guo Y, Yang T, et al. 2018b. Intervention effect of gamma aminobutyric acid on anxiety behavior induced by phthalate (2-ethylhexyl ester) in rats. Int J Neurosci 128(10):928-934. http://doi.org/10.1080/00207454.2017.1405952.

Liu C, Deng YL, Zheng TZ, et al. 2020. Urinary biomarkers of phthalates exposure and risks of thyroid cancer and benign nodule. J Hazard Mater 383:121189. http://doi.org/10.1016/j.jhazmat.2019.121189.

Ljungvall K, Tienpont B, David F, et al. 2004. Kinetics of orally administered di(2-ethylhexyl) phthalate and its metabolite, mono(2-ethylhexyl) phthalate, in male pigs. Arch Toxicol 78(7):384-389. http://doi.org/10.1007/s00204-004-0558-z.

Loff S, Kabs F, Witt J, et al. 2000. Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers. J Pediatr Surg 35(12):1775-1781.

Lopes TJ, Furlong ET. 2001. Occurrence and potential adverse effects of semivolatile organic compounds in streambed sediment, United States, 1992-1995. Environ Toxicol Chem 20(4):727-737.

Lopes TJ, Furlong ET, Pritt JW. 1997. Occurrence and distribution of semivolatile organic compounds in stream bed sediments, United States, 1992-95. In: Little EE, Greenberg BM, DeLonay AJ, eds. Environmental toxicology and risk assessment. Vol. 7. West Conshohocken, PA: American Society for Testing and Materials, 105-119. http://doi.org/10.1520/STP12158S.

Lopez-Carrillo L, Hernandez-Ramirez RU, Calafat AM, et al. 2010. Exposure to phthalates and breast cancer risk in northern Mexico. Environ Health Perspect 118(4):539-544. http://doi.org/10.1289/ehp.0901091.

Lorber M, Calafat AM. 2012. Dose reconstruction of di(2-ethylhexyl) phthalate using a simple pharmacokinetic model. Environ Health Perspect 120(12):1705-1710. http://doi.org/10.1289/ehp.1205182.

Lorber M, Angerer J, Koch H. 2010. A simple pharmacokinetic model to characterize exposure of Americans to di-2-ethylhexyl phthalate. J Expo Sci Environ Epidemiol 20(1):38-53. http://doi.org/10.1038/jes.2008.74.

Lovekamp-Swan T, Davis BJ. 2003. Mechanisms of phthalate ester toxicity in the female reproductive system. Environ Health Perspect 111(2):139-145.

Lu Z, Zhang C, Han C, et al. 2019. Plasticizer bis(2-ethylhexyl) phthalate causes meiosis defects and decreases fertilization ability of mouse oocytes in vivo. J Agric Food Chem 67(12):3459-3468. http://doi.org/10.1021/acs.jafc.9b00121.

Lunderberg DM, Kristensen K, Liu Y, et al. 2019. Characterizing airborne phthalate concentrations and dynamics in a normally occupied residence. Environ Sci Technol 53(13):7337-7346. http://doi.org/10.1021/acs.est.9b02123.

Luo Q, Liu ZH, Yin H, et al. 2018. Migration and potential risk of trace phthalates in bottled water: A global situation. Water Res 147:362-372. http://doi.org/10.1016/j.watres.2018.10.002.

Lutz WK. 1986. Investigation of the potential for binding of di(2-ethylhexyl) phthalate (DEHP) to rat liver DNA in vivo. Environ Health Perspect 65:267-269.

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. http://doi.org/10.1093/toxsci/kfl036.

Machtinger R, Gaskins AJ, Racowsky C, et al. 2018. Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environ Int 111:23-31. http://doi.org/10.1016/j.envint.2017.11.011.

Mackintosh CE, Maldonado J, Hongwu J, et al. 2004. Distribution of phthalate esters in a marine aquatic food web: Comparison to polychlorinated biphenyls. Environ Sci Technol 38(7):2011-2020.

Maloney EK, Waxman DJ. 1999. trans-Activation of PPARα and PPARγ by structurally diverse environmental chemicals. Toxicol Appl Pharmacol 161(2):209-218. http://doi.org/10.1006/taap.1999.8809.

Mangala Priya V, Mayilvanan C, Akilavalli N, et al. 2014. Lactational exposure of phthalate impairs insulin signaling in the cardiac muscle of F1 female albino rats. Cardiovasc Toxicol 14(1):10-20. http://doi.org/10.1007/s12012-013-9233-z.

Mannsville Chemical Products Corporation. 1990. Chemical products synopsis: Dioctyl phthalate. Asbury Park, NY: Mannsville Chemical Products Corp.

Maranghi F, Lorenzetti S, Tassinari R, et al. 2010. In utero exposure to di-(2-ethylhexyl) phthalate affects liver morphology and metabolism in post-natal CD-1 mice. Reprod Toxicol 29(4):427-432. http://doi.org/10.1016/j.reprotox.2010.03.002.

Maresca MM, Hoepner LA, Hassoun A, et al. 2016. Prenatal exposure to phthalates and childhood body size in an urban cohort. Environ Health Perspect 124(4):514-520. http://doi.org/10.1289/ehp.1408750.

Marie C, Vendittelli F, Sauvant-Rochat MP. 2015. Obstetrical outcomes and biomarkers to assess exposure to phthalates: A review. Environ Int 83:116-136. http://doi.org/10.1016/j.envint.2015.06.003.

Marotta V, Russo G, Gambardella C, et al. 2019. Human exposure to bisphenol AF and diethylhexylphthalate increases susceptibility to develop differentiated thyroid cancer in patients with thyroid nodules. Chemosphere 218:885-894. http://doi.org/10.1016/j.chemosphere.2018.11.084.

Marsman DS, Cattley RC, Conway JG, et al. 1988. Relationship of hepatic peroxisome proliferation and replicative DNA synthesis to the hepatocarcinogenicity of the peroxisome proliferators di(2-ethylhexyl)phthalate and [4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid (Wy-14,643) in rats. Cancer Res 48(23):6739-6744.

Martínez MA, Rovira J, Sharma RP, et al. 2017. Prenatal exposure estimation of BPA and DEHP using integrated external and internal dosimetry: A case study. Environ Res 158:566-575. http://doi.org/10.1016/j.envres.2017.07.016.

Martínez MA, Rovira J, Prasad Sharma R, et al. 2018. Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: A Catalonia (Spain) case study. Environ Res 166:25-34. http://doi.org/10.1016/j.envres.2018.05.008.

Martínez MA, Rovira J, Sharma RP, et al. 2020. Reconstruction of phthalate exposure and DINCH metabolites from biomonitoring data from the EXHES cohort of Tarragona, Spain: A case study on estimated vs reconstructed DEHP using the PBPK model. Environ Res 186:109534. http://doi.org/10.1016/j.envres.2020.109534.

Martinez-Arguelles DB, Papadopoulos V. 2015. Mechanisms mediating environmental chemical-induced endocrine disruption in the adrenal gland. Front Endocrinol (Lausanne) 6:29. http://doi.org/10.3389/fendo.2015.00029.

Martinez-Arguelles DB, Guichard T, Culty M, et al. 2011. In utero exposure to the antiandrogen di-(2-ethylhexyl) phthalate decreases adrenal aldosterone production in the adult rat. Biol Reprod 85(1):51-61. http://doi.org/10.1095/biolreprod.110.089920.

Martinez-Arguelles DB, Mcintosh M, Rohlicek CV, et al. 2013. Maternal in utero exposure to the endocrine disruptor di-(2-ethylhexyl) phthalate affects the blood pressure of adult male offspring. Toxicol Appl Pharmacol 266(1):95-100. http://doi.org/10.1016/j.taap.2012.10.027.

Martinez-Nava GA, Burguete-Garcia AI, Lopez-Carrillo L, et al. 2013. PPARgamma and PPARGC1B polymorphisms modify the association between phthalate metabolites and breast cancer risk. Biomarkers 18(6):493-501. http://doi.org/10.3109/1354750x.2013.816776.

Martino-Andrade AJ, Morais RN, Botelho GGK, et al. 2009. Coadministration of active phthalates results in disruption of foetal testicular function in rats. Int J Androl 32(6):704-712. http://doi.org/10.1111/j.1365-2605.2008.00939.x.

Martino-Andrade AJ, Liu F, Sathyanarayana S, et al. 2016. Timing of prenatal phthalate exposure in relation to genital endpoints in male newborns. Andrology 4(4):585-593. http://doi.org/10.1111/andr.12180.

Marx J. 1990. Animal carcinogen testing challenged. Science 250:743-745.

Mauthe RJ, Gibson DP, Bunch RT, et al. 2001. The Syrian hamster embryo (SHE) cell transformation assay: review of the methods and results. Toxicol Pathol 29 Suppl:138-146

McCombie G, Biedermann S, Suter G, et al. 2017. Survey on plasticizers currently found in PVC toys on the Swiss market: Banned phthalates are only a minor concern. J Environ Sci Health A Environ Sci Eng Toxic Hazard 52(5):491-496. http://doi.org/10.1080/10934529.2016.1274176.

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

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

McKee RH. 2000. The role of inhibition of gap junctional intercellular communication in rodent liver tumor induction by phthalates: review of data on selected phthalates and the potential relevance to man. Regul Toxicol Pharmacol 32(1):51-55. http://doi.org/10.1006/rtph.2000.1407.

Meeker JD, Ferguson KK. 2011. Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007-2008. Environ Health Perspect 119(10):1396-1402. http://doi.org/10.1289/ehp.1103582.

Meeker JD, Calafat AM, Hauser R. 2007. Di(2-ethylhexyl) phthalate metabolites may alter thyroid hormone levels in men. Environ Health Perspect 115(7):1029-1034. http://doi.org/10.1289/ehp.9852.

Meeker JD, Hu H, Cantonwine DE, et al. 2009a. Urinary phthalate metabolites in relation to preterm birth in Mexico city. Environ Health Perspect 117(10):1587-1592. http://doi.org/10.1289/ehp.0800522.

Meeker JD, Calafat AM, Hauser R. 2009b. Urinary metabolites of di(2-ethylhexyl) phthalate are associated with decreased steroid hormone levels in adult men. J Androl 30(3):287-297. http://doi.org/10.2164/jandrol.108.006403.

Meeker JD, Ferguson KK. 2014. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. J Clin Endocrinol Metab 99(11):4346-4352. http://doi.org/10.1210/jc.2014-2555.

Melnick RL. 2001. Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl) phthalate (DEHP)? Environ Health Perspect 109(5):437-442.

Mendiola J, Jørgensen N, Andersson AM, et al. 2011. Associations between urinary metabolites of di(2-ethylhexyl) phthalate and reproductive hormones in fertile men. Int J Androl 34(4 Pt. 1):369378. http://doi.org/10.1111/j.1365-2605.2010.01095.x.

Mendiola J, Meeker JD, Jørgensen N, et al. 2012. Urinary concentrations of di(2-ethylhexyl) phthalate metabolites and serum reproductive hormones: Pooled analysis of fertile and infertile men. J Androl 33(3):488-198. http://doi.org/10.2164/jandrol.111.013557.

Meng F, Yin X, Ma X, et al. 2013. Assessment of the value of serum cholinesterase as a liver function test for cirrhotic patients. Biomed Rep 1:265-268. http://doi.org/10.3892/br.2013.60.

Mérida-Ortega Á, Hernández-Alcaraz C, Hernández-Ramírez RU, et al. 2016. Phthalate exposure, flavonoid consumption and breast cancer risk among Mexican women. Environ Int 96:167-172. http://doi.org/10.1016/j.envint.2016.08.023.

Merkle J, Klimisch HJ, Jäckh R. 1988. Developmental toxicity in rats after inhalation exposure of di-2-ethylhexylphthalate (DEHP). Toxicol Lett 42(2):215-223. http://doi.org/10.1016/0378-4274(88)90080-x.

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

Messerlian C, Souter I, Gaskins AJ, et al. 2016a. Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Hum Reprod 31(1):75-83. http://doi.org/10.1093/humrep/dev292.

Messerlian C, Wylie BJ, Minguez-Alarcon L, et al. 2016b. Urinary concentrations of phthalate metabolites and pregnancy loss among women conceiving with medically assisted reproduction. Epidemiology 27(6):879-888. http://doi.org/10.1097/ede.0000000000000525.

Messerlian C, Braun JM, Minguez-Alarcon L, et al. 2017a. Paternal and maternal urinary phthalate metabolite concentrations and birth weight of singletons conceived by subfertile couples. Environ Int 107:55-64. http://doi.org/10.1016/j.envint.2017.06.015.

Messerlian C, Mustieles V, Wylie BJ, et al. 2017b. Ultrasound gel as an unrecognized source of exposure to phthalates and phenols among pregnant women undergoing routine scan. Int J Hyg Environ Health 220:1285-1294.

Meylan WM, Howard PH. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. Chemosphere 26(12):2293-2299.

Miao H, Liu X, Li J, et al. 2020. Associations of urinary phthalate metabolites with risk of papillary thyroid cancer. Chemosphere 241:125093. http://doi.org/10.1016/j.chemosphere.2019.125093.

Mikalsen S-O, Holen I, Sanner T. 1990. Morphological transformation and catalase activity of Syrian hamster embryo cells treated with hepatic peroxisome proliferators, TPA and nickel sulphate. Cell Biol Toxicol 6(1):1-14.

Minguez-Alarcon L, Williams PL, Chiu YH, et al. 2018a. Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: Identifying potential predictors. Environ Int 121(Pt 2):1297-1303. http://doi.org/10.1016/j.envint.2018.10.052.

Minguez-Alarcon L, Williams PL, Chiu YH, et al. 2018b. Supplementary data: Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: Identifying potential predictors. Environ Int 121(Pt 2) http://doi.org/10.1016/j.envint.2018.10.052.

Miodovnik A, Engel SM, Zhu C, et al. 2011. Endocrine disruptors and childhood social impairment. Neurotoxicology 32(2):261-267. http://doi.org/10.1016/j.neuro.2010.12.009.

Miodovnik A, Edwards A, Bellinger DC, et al. 2014. Developmental neurotoxicity of ortho-phthalate diesters: review of human and experimental evidence. Neurotoxicology 41:112-122. http://doi.org/10.1016/j.neuro.2014.01.007.

Mitchell FE, Price SC, Hinton RH, et al. 1985. Time and dose-response study of the effects on rats of the plasticizer di(2-ethylhexyl) phthalate. Toxicol Appl Pharmacol 81(3 Pt. 1):371-392.

Mittermeier A, Volkel W, Fromme H. 2016. Kinetics of the phthalate metabolites mono-2-ethylhexyl phthalate (MEHP) and mono-n-butyl phthalate (MnBP) in male subjects after a single oral dose. Toxicol Lett 252:22-28. http://doi.org/10.1016/j.toxlet.2016.04.009.

Morelli-Cardoso MHW, Lachter ER, Tabak D, et al. 1999. Determination of the specific migration of DEHP into food stimulants using high performance liquid chromatography. J High Resolut Chromatogr 22(1):70-72.

Morgan M, Deoraj A, Felty Q, et al. 2017. Environmental estrogen-like endocrine disrupting chemicals and breast cancer. Mol Cell Endocrinol 457:89-102. http://doi.org/10.1016/j.mce.2016.10.003.

Morgenstern R, Whyatt RM, Insel BJ, et al. 2017. Phthalates and thyroid function in preschool age children: Sex specific associations. Environ Int 106:11-18. http://doi.org/10.1016/j.envint.2017.05.007.

Morrissey RE, CLJ, Schwetz BA, et al. 1988. Association of sperm, vaginal cytology, and reproductive organ weight data with results of continuous breeding reproduction studies in swiss (CD-1) mice. Fundam Appl Toxicol 11(2):359-371.

Moser VC, Cheek BM, Macphail RC. 1995. A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity. J Toxicol Environ Health 45(2):173-210. http://doi.org/10.1080/15287399509531988.

Moser VC, Macphail RC, Gennings C. 2003. Neurobehavioral evaluations of mixtures of trichloroethylene, heptachlor, and di(2-ethylhexyl)phthalate in a full-factorial design. Toxicology 188(2-3):125-137. http://doi.org/10.1016/s0300-483x(03)00083-0.

Moss EJ, Cook MW, Thomas LV, et al. 1988. The effect of mono-(2-ethylhexyl) phthalate and other phthalate esters on lactate production by Sertoli cells in vitro. Toxicol Lett 40(1):77-84. http://doi.org/10.1016/0378-4274(88)90185-3.

Mu D, Gao F, Fan Z, et al. 2015a. Levels of phthalate metabolites in urine of pregnant women and risk of clinical pregnancy loss. Environ Sci Technol 49(17):10651-10657. http://doi.org/10.1021/acs.est.5b02617.

Mu X, Liao X, Chen X, et al. 2015b. DEHP exposure impairs mouse oocyte cyst breakdown and primordial follicle assembly through estrogen receptor-dependent and independent mechanisms. J Hazard Mater 298:232-240. http://doi.org/10.1016/j.jhazmat.2015.05.052.

Muhlenkamp CR, Gill SS. 1998. A glucose-regulated protein, GRP58, is down-regulated in C57B6 mouse liver after diethylhexyl phthalate exposure. Toxicol Appl Pharmacol 148(1):101-108. http://doi.org/10.1006/taap.1997.8323.

Murphy CJ, Stermer AR, Richburg JH. 2014. Age- and species-dependent infiltration of macrophages into the testis of rats and mice exposed to mono-(2-Ethylhexyl) phthalate (MEHP). Biol Reprod 91(1):18. http://doi.org/10.1095/biolreprod.113.115527.

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

Mustieles V, Minguez-Alarcon L, Christou G, et al. 2019. Placental weight in relation to maternal and paternal preconception and prenatal urinary phthalate metabolite concentrations among subfertile couples. Environ Res 169:272-279. http://doi.org/10.1016/j.envres.2018.11.022.

Myers BA. 1992a. A subchronic (4-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in B6C3F1 mice (final report) with attachments and cover letter dated 040392. Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535432. EPA 86-920000874.

Myers BA. 1992b. Subchronic (13-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in Fischer 344 rats (final report) w-attachments and letter dated 040392 (missing pages 304 to 386). Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0535433. 86-920000875.

Nair N, Kurup CKR. 1986. Investigations on the mechanism of the hypocholesterolemic action of diethylhexyl phthalate in rats. Biochem Pharmacol 35(20):3441-3447.

Nair N, Kurup CK. 1987a. Effect of administration of diethylhexyl phthalate on the function and turnover of rat hepatic mitochondria. Biochim Biophys Acta 925(3):332-340. http://doi.org/10.1016/0304-4165(87)90199-1.

Nair N, Kurup CKR. 1987b. Increase in hepatic ubiquinone on administration of diethylhexyl phthalate to the rat. J Biosci 11(1-4):391-397.

Nakamura Y, Yagi Y, Tomita I, et al. 1979. Teratogenicity of di-(2-ethylhexyl)phthalate in mice. Toxicol Lett 4(2):113-117. http://doi.org/10.1016/0378-4274(79)90084-5.

Nardelli TC, Albert O, Lalancette C, et al. 2017. In utero and lactational exposure study in rats to identify replacements for di(2-ethylhexyl) phthalate. Sci Rep 7(1):3862. http://doi.org/10.1038/s41598-017-03979-0.

Narotsky MG, Kavlock RJ. 1995. A multidisciplinary approach to toxicological screening: II. Developmental toxicity. J Toxicol Environ Health 45(2):145-171. http://doi.org/10.1080/15287399509531987.

NAS. 2008. Phthalates and cumulative risk assessment. The tasks ahead. National Academy of Sciences. http://dels.nas.edu/dels/rpt_briefs/phthalates_final.pdf. June 19, 2018.

NAS. 2017. NAS systematic review: Application of systematic review methods in overall strategy for evaluating low-dose toxicity from endocrine active chemicals. Washington, DC: National Academy of Sciences. http://nap.edu/24758. June 05, 2018.

NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences. National Research Council. 15-35.

Nasu M, Goto M, Oshima Y, et al. 2001. Study on endocrine disrupting chemicals in wastewater treatment plants. Water Sci Technol 43(2):101-208.

Ng KME, Chu I, Bronaugh RL, et al. 1992. Percutaneous absorption and metabolism of pyrene, benzo[a]pyrene, and di(2-ethylhexyl) phthalate: comparison of in vitro and in vivo results in the hairless guinea pig. Toxicol Appl Pharmacol 115(2):216-223. http://doi.org/10.1016/0041-008x(92)90326-n.

Niino T, Ishibashi T, Itho T, et al. 2001. Monoester formation by hydrolysis of dialkyl phthalate migrating from polyvinyl chloride products in human saliva. J Health Sci 47(3):318-322.

NIOSH. 2001. Di-sec octyl phthalate. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health.

NIOSH. 2016. Di-sec octyl phthalate. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health.

NIOSH. 2019. Di-sec octyl phthalate. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0236.html. August 26, 2020.

NOES. 1990. National occupational exposure survey. Cincinnati, OH: National Institute of Occupational Safety and Health.

Noriega NC, Howdeshell KL, Furr J, et al. 2009. Pubertal administration of DEHP delays puberty, suppresses testosterone production, and inhibits reproductive tract development in male Sprague-Dawley and Long-Evans rats. Toxicol Sci 111(1):163-178. http://doi.org/10.1093/toxsci/kfp129.

NPS. 2016. Screening for contaminants of emerging concern in waters of the northern Colorado plateau network. 2015 Surface water data. National Park Service. NPS 960/133371, June 2016.

NTP. 1982. Carcinogenesis bioassay of di(2-ethylhexyl)phthalate (CAS No. 117-81-7) in F344 rats and B6C3F1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program. NTP-TR-217. NTP-80-37. NIH Publication No. 82-1773.

NTP. 1984. Diethylhexyl phthalate (DEHP). Reproduction and fertility assessment in CD-1 mice when administered in the feed. Research Triangle Park, NC: National Toxicology Program. PB84181734.

NTP. 1988. Reproduction and fertility evaluation of diethylhexyl phthalate (CAS no 117-81-7) in CD-1 mice exposed during gestation. NTP 88. Jefferson, AK: U.S. National Toxicology Program. PB88204300. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB88204300.xhtml. April 15, 2020.

NTP. 1989. Fifth annual report on carcinogens: Summary 1989. Research Triangle Park, NC: National Toxicology Program.

NTP. 2000. NTP-CERHR expert panel report on di(2-ethylhexyl)phthalate. National Toxicology Program. NTP-CERHR-DEHP-00. http://cerhr.niehs.nih.gov/news/index.html. May 11, 2000.

NTP. 2005. Diethylhexylphthalate: Multigenerational reproductive assessment by continuous breeding when administered to Sprague-Dawley rats in the diet. Research Triangle Park, NC: National Toxicology Program. PB2005107575. TRC Study No 7244-200. NTP-RACB-98-004.

NTP. 2006. NTP-CERHR monograph on the potential human reproductive and developmental effects of di(2-ethylhexyl) phthalate (DEHP). National Toxicology Program. NIH Publication No. 06-4476.

NTP. 2016. Di(2-ethylhexyl) phthalate. In: Report on carcinogens. 14th ed. Research Triangle Park, NC: National Toxicology Program, https://ntp.niehs.nih.gov/ntp/roc/content/profiles/diethylhexylphthalate.pdf. August 27, 2020.

NYDEC. 2014. Water quality monitoring data for pesticides on Long Island, NY. New York State Department of Environmental Conservation.

Nyssen GA, Miller EC, Glass TF, et al. 1987. Solubilities of hydrophobic compounds in aqueous-organic solvent mixtures. Environ Monit Assess 9:1-11.

Oberly T, Bewsey B, Probst G. 1985. Tests for the induction of forward mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells in culture. Prog Mutat Res 5:569-582.

O'Connor GA. 1996. Organic compounds in sludge-amended soils and their potential for uptake by crop plants. Sci Total Environ 185(1-3):71-81. http://doi.org/10.1016/0048-9697(95)05043-4.

O'Connor OA, Rivera MD, Young LY. 1989. Toxicity and biodegradation of phthalic acid esters under methanogenic conditions. Environ Toxicol Chem 8(7):569-576.

O'Grady DP, Howard PH, Werner AF. 1985. Activated sludge biodegradation of 12 commercial phthalate esters. Appl Environ Microbiol 49(2):443-445.

Oie L, Hersoug LG, Madsen JO. 1997. Residential exposure to plasticizers and its possible role in the pathogenesis of asthma. Environ Health Perspect 105(9):972-978.

Oishi S. 1989. Effects of co-administration of di(2-ethylhexyl)phthalate and testosterone on several parameters in the testis and pharmacokinetics of its mono-de-esterified metabolite. Arch Toxicol 63(4):289-295.

Oishi S. 1990. Effects of phthalic acid esters on testicular mitochondrial functions in the rat. Arch Toxicol 64(2):143-147.

Okai Y, Higashi-Okai K. 2000. Enhancing effect of a plastic plasticizer, di-2-ethylhexyl phthalate on umu C gene expression in Salmonella typhimurium (TA 1535/pSK 1002). J UOEH 22(4):305-315.

Olesen TS, Bleses D, Andersen HR, et al. 2018a. Prenatal phthalate exposure and language development in toddlers from the Odense Child Cohort. Neurotoxicol Teratol 65:34-41. http://doi.org/10.1016/j.ntt.2017.11.004.

Olesen TS, Bleses D, Andersen HR, et al. 2018b. Supplementary data: Prenatal phthalate exposure and language development in toddlers from the Odense Child Cohort. Neurotoxicol Teratol 65. http://doi.org/10.1016/j.ntt.2017.11.004.

OSHA. 1994. Method 104. Dimethyl Phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), di-2-ethylhexyl phthalate (DEHP), di-n-octyl phthalate (DNOP). Sampling and analytical methods. Occupational Safety and Health Administration.

OSHA. 2019a. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1: Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1000TABLEZ1. October 25, 2019.

OSHA. 2019b. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.osha.gov/laws-regs/regulations/standardnumber/1915/1915.1000. October 25, 2019.

OSHA. 2019c. Safety and health regulations for construction. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55 Appendix A. https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.55AppA. October 25, 2019.

Otake T, Yoshinaga J, Yanagisawa Y. 2001. Analysis of organic esters of plasticizer in indoor air by GC-MS and GC-FPD. Environ Sci Technol 2001(35):3099-3102.

Oudir M, Chader H, Bouzid B, et al. 2018. Male rat exposure to low dose of di(2-ethylhexyl) phthalate during pre-pubertal, pubertal and post-pubertal periods: Impact on sperm count, gonad histology and testosterone secretion. Reprod Toxicol 75:33-39. http://doi.org/10.1016/j.reprotox.2017.11.004.

Ozaki H, Sugihara K, Watanabe Y, et al. 2017. Comparative study of hydrolytic metabolism of dimethyl phthalate, dibutyl phthalate and di(2-ethylhexyl) phthalate by microsomes of various rat tissues. Food Chem Toxicol 100:217-224. http://doi.org/10.1016/j.fct.2016.12.019.

Pan G, Hanaoka T, Yoshimura M, et al. 2006. Decreased serum free testosterone in workers exposed to high levels of di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP), a cross-sectional study in China. Environ Health Perspect 114(11):1643-1648. http://doi.org/10.1289/ehp.9016.

Pan Y, Jing J, Dong F, et al. 2015. Association between phthalate metabolites and biomarkers of reproductive function in 1066 Chinese men of reproductive age. J Hazard Mater 300:729-736. http://doi.org/10.1016/j.jhazmat.2015.08.011.

Pant K, Sly J, Bruce S, et al. 2010. Syrian Hamster Embryo (SHE) cell transformation assay with and without X-ray irradiation of feeder cells using di(2-ethylhexyl)phthalate (DEHP) and N-nitroso-N-methylnitroguanidine (MNNG). Mutat Res 698(1-2):6-10. http://doi.org/10.1016/j.mrgentox.2010.02.017.

Park SY, Choi J. 2007. Cytotoxicity, genotoxicity and ecotoxicity assay using human cell and environmental species for the screening of the risk from pollutant exposure. Environ Int 33(6):817-822. http://doi.org/10.1016/j.envint.2007.03.014.

Park HY, Kim JH, Lim YH, et al. 2013. Influence of genetic polymorphisms on the association between phthalate exposure and pulmonary function in the elderly. Environ Res 122:18-24. http://doi.org/10.1016/j.envres.2012.11.004.

Park S, Kim BN, Cho SC, et al. 2014. Association between urine phthalate levels and poor attentional performance in children with attention-deficit hyperactivity disorder with evidence of dopamine gene-phthalate interaction. Int J Environ Res Public Health 11(7):6743-6756. http://doi.org/10.3390/ijerph110706743.

Park C, Choi W, Hwang M, et al. 2017. Associations between urinary phthalate metabolites and bisphenol A levels, and serum thyroid hormones among the Korean adult population - Korean National Environmental Health Survey (KoNEHS) 2012-2014. Sci Total Environ 584-585:950-957. http://doi.org/10.1016/j.scitotenv.2017.01.144.

Parks LG, Ostby JS, Lambright CR, et al. 2000. The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. Toxicol Sci 58:339-349.

Parmar D, Srivastava SP, Srivastava SP, et al. 1985. Hepatic mixed function oxidases and cytochrome P-450 contents in rat pups exposed to di-(2-ethylhexyl)phthalate through mother's milk. Drug Metab Dispos 13(3):368-370.

Parmar D, Srivastava SP, Singh GB, et al. 1987. Effect of testosterone on the testicular atrophy caused by di(2-ethylhexyl)phthalate (DEHP). Toxicol Lett 36(3):297-308. http://doi.org/10.1016/0378-4274(87)90199-8.

Parmar D, Srivastava SP, Seth PK. 1988. Effect of di(2-ethylhexyl)phthalate (DEHP) on hepatic mixed function oxidases in different animal species. Toxicol Lett 40(3):209-217.

Parmar D, Srivastava SP, Seth PK. 1994. Age related effects of di(2-ethylhexyl)phthalate on hepatic cytochrome P450 monooxygenases in Wistar rats. Pharmacol Toxicol 75:177-180.

Parmar D, Srivastava SP, Singh GB, et al. 1995. Testicular toxicity of di(2-ethylhexyl)phthalate in developing rats. Vet Hum Toxicol 37(4):310-313.

Parra-Forero LY, Veloz-Contreras A, Vargas-Marín S, et al. 2019. Alterations in oocytes and early zygotes following oral exposure to di(2-ethylhexyl) phthalate in young adult female mice. Reprod Toxicol 90:53-61. http://doi.org/10.1016/j.reprotox.2019.08.012.

Parry JM, Arni P, Brooks TM, et al. 1985. Summary report on the performance of the yeast and Aspergillus assays. Prog Mutat Res 5:25-46.

Parsanathan R, Maria Joseph A, Karundevi B. 2019. Postnatal exposure to di-(2-ethylhexyl)phthalate alters cardiac insulin signaling molecules and GLUT4(Ser488) phosphorylation in male rat offspring. J Cell Biochem 120(4):5802-5812. http://doi.org/10.1002/jcb.27866.

Peck J, Sweeney A, Symanski E, et al. 2010. Intra- and inter-individual variability of urinary phthalate metabolite concentrations in Hmong women of reproductive age. J Expo Sci Environ Epidemiol 20(1):90-100. http://doi.org/10.1038/jes.2009.4.

Pegg D. 1982. Disposition of di-2-ethylhexyl phthalate following inhalation and peroral exposure in rats. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86910000683. OTS0530339.

Percy Z, Xu Y, Sucharew H, et al. 2016. Gestational exposure to phthalates and gender-related play behaviors in 8-year-old children: An observational study. Environ Health 15:87. http://doi.org/19.1186/s12940-016-0171-7.

Perera MIR, Katyal SL, Shinozuka H. 1986. Suppression of choline-deficient diet-induced hepatocyte membrane lipid peroxidation in rats by the peroxisome proliferators 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio(N-beta-hydroxyethyl)acetamide and di(2-ethylhexyl)phthalate. Cancer Res 46:3304-3308.

Pérez PA, Toledo J, Sosa LDV, et al. 2020. The phthalate DEHP modulates the estrogen receptors α and β increasing lactotroph cell population in female pituitary glands. Chemosphere 258:127304. http://doi.org/10.1016/j.chemosphere.2020.127304.

Perng W, Watkins DJ, Cantoral A, et al. 2017. Exposure to phthalates is associated with lipid profile in peripubertal Mexican youth. Environ Res 154:311-317. http://doi.org/10.1016/j.envres.2017.01.033.

Perng W, Kasper NM, Watkins DJ, et al. 2020. Exposure to endocrine-disrupting chemicals during pregnancy is associated with weight change through 1 year postpartum among women in the early-life exposure in Mexico to Environmental Toxicants Project. J Womens Health 29(11):1419-1426. http://doi.org/10.1089/jwh.2019.8078.

Peters JM, Cheung C, Gonzalez FJ. 2005. Peroxisome proliferator-activated receptor-a and liver cancer: where do we stand? J Mol Med 83:774-785. http://doi.org/10.1007/s00109-005-0678-9.

Petersen JH, Breindahl T. 2000. Plasticizers in total diet samples, baby food and infant formulae. Food Addit Contam 17(2):133-141.

Philippat C, Bennett DH, Krakowiak P, et al. 2015. Phthalate concentrations in house dust in relation to autism spectrum disorder and developmental delay in the CHildhood Autism Risks from Genetics and the Environment (CHARGE) study. Environ Health 14:56. http://doi.org/10.1186/s12940-015-0024-9.

Phillips BJ, James TE, Gangolli SD. 1982. Genotoxicity studies of di(2-ethylhexyl)phthalate and its metabolites in CHO cells. Mutat Res 102(3):297-304. http://doi.org/10.1016/0165-1218(82)90139-2.

Phillips BJ, Anderson D, Gangolli SD. 1986. Studies on the genetic effects of phthalic acid esters on cells in culture. Environ Health Perspect 65:263-266. http://doi.org/10.2307/3430192.

Piepenbrink M, Hussain I, Marsh J, et al. 2005. Developmental immunotoxicology of di-(2-Ethylhexyl)phthalate (DEHP): Age-based assessment in the female rat. J Immunotoxicol 2(1):21-31. http://doi.org/10.1080/15363750490429435.

Plichta V, Volkel W, Fembacher L, et al. 2019. Bioavailability of phthalate and DINCH(R) plasticizers, after oral administration of dust to piglets. Toxicol Lett 314:82-88. http://doi.org/10.1016/j.toxlet.2019.07.018.

Plonait SL, Nau H, Maier RF, et al. 1993. Exposure of newborn infants to di-(2-ethylhexyl)-phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters. Transfusion 33:598-605.

Plumb RH. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. Ground Water Monit Rev 7:94-100.

Pocar P, Fiandanese N, Secchi C, et al. 2012. Exposure to di(2-ethyl-hexyl) phthalate (DEHP) in utero and during lactation causes long-term pituitary-gonadal axis disruption in male and female mouse offspring. Endocrinology 153(2):937-948. http://doi.org/10.1210/en.2011-1450.

Pocar P, Fiandanese N, Berrini A, et al. 2017. Maternal exposure to di(2-ethylhexyl)phthalate (DEHP) promotes the transgenerational inheritance of adult-onset reproductive dysfunctions through the female germline in mice. Toxicol Appl Pharmacol 322:113-121. http://doi.org/10.1016/j.taap.2017.03.008.

Podlecka D, Gromadzińska J, Mikołajewska K, et al. 2020. Longitudinal effect of phthalates exposure on allergic diseases in children. Ann Allergy Asthma Immunol 125(1):84-89. http://doi.org/10.1016/j.anai.2020.03.022.

Pogribny I, Tryndyak V, Boureiko A, et al. 2008. Mechanisms of peroxisome proliferator-induced DNA hypomethylation in rat liver. Mutat Res 644(1-2):17-23. http://doi.org/10.1016/j.mrfmmm.2008.06.009.

Polanska K, Ligocka D, Sobala W, et al. 2014. Phthalate exposure and child development: the Polish Mother and Child Cohort Study. Early Hum Dev 90(9):477-485. http://doi.org/10.1016/j.earlhumdev.2014.06.006.

Pollack GM, Li RCK, Ermer JC, et al. 1985a. Effects of route of administration and repetitive dosing on the disposition kinetics of di(2-ethylhexyl) phthalate and its mono-de-esterified metabolite in rats. Toxicol Appl Pharmacol 79:246-256.

Pollack GM, Buchanan JF, Slaughter RL, et al. 1985b. Circulating concentrations of di(2-ethylhexyl) phthalate and its de-esterified phthalic acid products following plasticizer exposure in patients receiving hemodialysis. Toxicol Appl Pharmacol 79(2):257-267. http://doi.org/10.1016/0041-008x(85)90347-3.

Pollack AZ, Buck Louis GM, Chen Z, et al. 2015. Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. Environ Res 137:101-107. http://doi.org/10.1016/j.envres.2014.06.028.

Poon R, Lecavalier P, Mueller R, et al. 1997. Subchronic oral toxicity of di-n-octyl phthalate and di(2-ethylhexyl) phthalate in the rat. Food Chem Toxicol 35(2):225-239. http://doi.org/10.1016/s0278-6915(96)00064-6.

Poulin P, Theil FP. 2002. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. J Pharm Sci 91(1):129-156.

Pradeep S, Josh MK, Binod P, et al. 2015. Achromobacter denitrificans strain SP1 efficiently remediates di(2-ethylhexyl)phthalate. Ecotoxicol Environ Saf 112:114-121. http://doi.org/10.1016/j.ecoenv.2014.10.035.

Preston MR, Al-Omran LA. 1989. Phthalate ester speciation in estuarine water, suspended particulates and sediments. Environ Pollut 62(2-3):183-193. http://doi.org/10.1016/0269-7491(89)90186-3.

Price SC, Ochieng W, Weaver R, et al. 1987. Studies on the mechanisms of changes produced in the liver, thyroid, pancreas, and kidney by hypolipidemic drugs and di(2-ethylhexyl)phthalate. In: Reid E, Cook GM, Luziio JP, eds. Cells membranes, and disease, including renal. New York, NY: Plenum Press, 67-78.

Price SC, Chescoe D, Grasso P, et al. 1988. Alterations in the thyroids of rats treated for long periods with di-(2-ethylhexyl) phthalate or with hypolipidaemic agents. Toxicol Lett 40(1):37-46. http://doi.org/10.1016/0378-4274(88)90181-6.

Priston RAJ, Dean BJ. 1985. Tests for the induction of chromosome aberrations, polyploidy and sister-chromatid exchanges in rat liver (RL4) cells. Prog Mutat Res 5:387-395.

Probst GS, Hill LE. 1985. Tests for the induction of DNA-repair synthesis in primary cultures of adult rat hepatocytes. Prog Mutat Res 5:381-386.

Pugh G, Isenberg J, Kamendulis L, et al. 2000. Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in cynomolgus monkeys. Toxicol Sci 56(1):181-188. http://doi.org/10.1093/toxsci/56.1.181.

Putman DL, Moore WA, Schechtman LM, et al. 1983. Cytogenic evaluation of di-(2-ethylhexyl)phthalate and its major metabolites in Fischer 344 rats. Environ Mutagen 5:227-231.

Qi W, Zhou L, Zhao T, et al. 2019. Effect of the TYK-2/STAT-3 pathway on lipid accumulation induced by mono-2-ethylhexyl phthalate. Mol Cell Endocrinol 484:52-58. http://doi.org/10.1016/j.mce.2019.01.012.

Qian X, Li J, Xu S, et al. 2019a. Prenatal exposure to phthalates and neurocognitive development in children at two years of age. Environ Int 131:105023. http://doi.org/10.1016/j.envint.2019.105023.

Qian X, Li J, Xu S, et al. 2019b. Supplementary data: Prenatal exposure to phthalates and neurocognitive development in children at two years of age. Environ Int 131. http://doi.org/10.1016/j.envint.2019.105023.

Quinnies KM, Doyle TJ, Kim KH, et al. 2015. Transgenerational effects of di-(2-ethylhexyl) phthalate (DEHP) on stress hormones and behavior. Endocrinology 156(9):3077-3083. http://doi.org/10.1210/en.2015-1326.

Quintana-Belmares RO, Krais AM, Esfahani BK, et al. 2018. Phthalate esters on urban airborne particles: Levels in PM(10) and PM(2.5) from Mexico City and theoretical assessment of lung exposure. Environ Res 161:439-445. http://doi.org/10.1016/j.envres.2017.11.039.

Rajagopal G, Bhaskaran RS, Karundevi B. 2019a. Maternal di-(2-ethylhexyl) phthalate exposure alters hepatic insulin signal transduction and glucoregulatory events in rat F(1) male offspring. J Appl Toxicol 39(5):751-763. http://doi.org/10.1002/jat.3764.

Rajagopal G, Bhaskaran RS, Karundevi B. 2019b. Developmental exposure to DEHP alters hepatic glucose uptake and transcriptional regulation of GLUT2 in rat male offspring. Toxicology 413:56-64. http://doi.org/10.1016/j.tox.2018.12.004.

Rajesh P, Balasubramanian K. 2014. Phthalate exposure in utero causes epigenetic changes and impairs insulin signalling. J Endocrinol 223(1):47-66. http://doi.org/10.1530/JOE-14-0111.

Rajesh P, Sathish S, Srinivasan C, et al. 2013. Phthalate is associated with insulin resistance in adipose tissue of male rat: Role of antioxidant vitamins (C & E). J Cell Biochem 114(3):558-569. http://doi.org/10.1002/jcb.24399.

Ran D, Luo Y, Gan Z, et al. 2019. Neural mechanisms underlying the deficit of learning and memory by exposure to di(2-ethylhexyl) phthalate in rats. Ecotoxicol Environ Saf 174:58-65. http://doi.org/10.1016/j.ecoenv.2019.02.043.

Rao MS, Usuda N, Subbarao V, et al. 1987. Absence of gamma-glutamyl transpeptidase activity in neoplastic lesions induced in the liver of male F-344 rats by di-(2-ethylhexyl)phthalate, a peroxisome proliferator. Carcinogenesis 8(9):1347-1350. http://doi.org/10.1093/carcin/8.9.1347.

Rao MS, Yeldandi AV, Subbarao V. 1990. Quantitative analysis of hepatocellular lesions induced by di(2-ethylhexyl)phthalate in F-344 rats. J Toxicol Environ Health 30(2):85-89. http://doi.org/10.1080/15287399009531413.

Rattan S, Brehm E, Gao L, et al. 2017. Prenatal exposure to di(2-ethylhexyl) phthalate disrupts ovarian function in a transgenerational manner in female mice. Biol Reprod 98(1):130-145. http://doi.org/10.1093/biolre/iox154.

Rattan S, Brehm E, Gao L, et al. 2018. Di(2-ethylhexyl) phthalate exposure during prenatal development causes adverse transgenerational effects on female fertility in mice. Toxicol Sci 163(2):420-429. http://doi.org/10.1093/toxsci/kfy042.

Rattan S, Beers HK, Kannan A, et al. 2019. Prenatal and ancestral exposure to di(2-ethylhexyl) phthalate alters gene expression and DNA methylation in mouse ovaries. Toxicol Appl Pharmacol 379:114629. http://doi.org/10.1016/j.taap.2019.114629.

Ray LE, Murray HE, Giam CS. 1983. Organic pollutants in marine samples from Portland, Maine. Chemosphere 12(7-8):7-8.

Reddy JK, Moody DE, Azarnoff DL, et al. 1976. Di-(2-ethylhexyl)phthalate: an industrial plasticizer induces hypolipidemia and enhances hepatic catalase and carnitine acetyltransferase activities in rat and mice. Life Sci 18(9):941-945. http://doi.org/10.1016/0024-3205(76)90412-4.

Reddy BS, Rozati R, Reddy BV, et al. 2006. Association of phthalate esters with endometriosis in Indian women. BJOG 113(5):515-520. http://doi.org/10.1111/j.1471-0528.2006.00925.x.

Reeves KW, Diaz Santana M, Manson JE, et al. 2019. Urinary phthalate biomarker concentrations and postmenopausal breast cancer risk. J Natl Cancer Inst 111(10):1059-1067. http://doi.org/10.1093/jnci/djz002.

RePORTER. 2021. Di(2-ethylhexyl)phthalate (DEHP). National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. March 16, 2021.

Rhodes C, Orton TC, Pratt IS, et al. 1986. Comparative pharmacokinetics and subacute toxicity of di(2-ethylhexyl) phthalate (DEHP) in rats and marmosets: extrapolation of effects in rodents to man. Environ Health Perspect 65:299-307.

Ritsema R, Cofino WP, Frintrop P CM, et al. 1989. Trace-level analysis of phthalate esters in surface water and suspended particulate matter by means of capillary gas chromatography with electron-capture and mass-selective detection. Chemosphere 18(11-12):11-12.

Ritter EJ, Scott WJ, Randall JL, et al. 1987. Teratogenicity of di(2-ethylhexyl) phthalate, 2-ethylhexanol, 2-ethylhexanoic acid, and valproic acid, and potentiation by caffeine. Teratology 35(1):41-46. http://doi.org/10.1002/tera.1420350107.

Roberts RA, Ganey PE, Ju C, et al. 2007. Role of the Kupffer cell in mediating hepatic toxicity and carcinogenesis. Toxicol Sci 96(1):2-15.

Robledo CA, Peck JD, Stoner J, et al. 2015. Urinary phthalate metabolite concentrations and blood glucose levels during pregnancy. Int J Hyg Environ Health 218(3):324-330. http://doi.org/10.1016/j.ijheh.2015.01.005.

Rock G, Secours VE, Franklin CA, et al. 1978. The accumulation of mono-2-ethylhexylphthalate (MEHP) during storage of whole blood and plasma. Transfusion 18(5):553-558.

Romani F, Tropea A, Scarinci E, et al. 2014. Endocrine disruptors and human reproductive failure: The invitro effect of phthalates on human luteal cells. Fertil Steril 102(3):831-837. http://doi.org/10.1016/j.fertnstert.2014.05.041.

Roth B, Herkenrath P, Lehmann HJ, et al. 1988. Di-(2-ethylhexyl)-phthalate as plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. Eur J Pediatr 147(1):41-46. http://doi.org/10.1007/bf00442609.

Rowland IR. 1974. Metabolism of di-(2-ethylhexyl) phthalate by the contents of the alimentary tract of the rat. Food Cosmet Toxicol 12(3):293-303. http://doi.org/10.1016/0015-6264(74)90001-7.

Rowland IR, Cottrell RC, Phillips JC. 1977. Hydrolysis of phthalate esters by the gastro-intestinal contents of the rat. Food Chem Toxicol 15(1):17-21. http://doi.org/10.1016/s0015-6264(77)80257-5.

Roy WR. 1994. Groundwater contamination from municipal landfills in the USA. In: Adriano DC, Iskandar AK, Murarka IP, eds. Contamination of groundwaters. Northwood, England: Science Reviews, 411-446.

RTECS. 2013. Phthalic acid, bis(2-ethylhexyl) ester. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc.

Ruddick JA, Villeneuve DC, Chu I, et al. 1981. An assessment of the teratogenicity in the rat and mutagenicity in Salmonella of mono-2-ethylhexyl phthalate. Bull Environ Contam Toxicol 27(2):181-186. http://doi.org/10.1007/bf01611005.

Rudel RA, Brody JG, Spengler JD, et al. 2001. Identification of selected hormonally active agents and animal mammary carcinogens in commercial and residential air and dust samples. J Air Waste Manage Assoc 51:499-513.

Rushbrook CJ, Jorgenson TA, Hodgson JR. 1982. Dominant lethal study of di(2-ethylhexyl)phthalate and its major metabolites in ICR/SIM mice. Environ Mutagen 4:387.

Russell DJ, McDuffie B. 1983. Analysis for phthalate esters in environmental samples: Separation from polychlorinated biphenyls and pesticides using dual column liquid chromatography. Int J Environ Anal Chem 15(3):165-184.

Rusyn I, Corton JC. 2012. Mechanistic considerations for human relevance of cancer hazard of di(2-ethylhexyl) phthalate. Mutat Res 750(2):141-158. http://doi.org/10.1016/j.mrrev.2011.12.004.

Rusyn I, Peters JM, Cunningham ML. 2006. Modes of action and species-specific effects of di-(2-ethylhexyl)phthalate in the liver. Crit Rev Toxicol 36(5):459-479. http://doi.org/10.1080/10408440600779065.

Sadakane K, Ichinose T, Takano H, et al. 2014. Effects of oral administration of di-(2-ethylhexyl) and diisononyl phthalates on atopic dermatitis in NC/Nga mice. Immunopharmacol Immunotoxicol 36(1):61-69. http://doi.org/10.3109/08923973.2013.866678.

Saillenfait AM, Sabaté JP, Robert A, et al. 2013. Dose-dependent alterations in gene expression and testosterone production in fetal rat testis after exposure to di-n-hexyl phthalate. J Appl Toxicol 33(9):1027-1035. http://doi.org/10.1002/jat.2896.

Sanchez JH, Abernethy DJ, Boreiko CJ. 1987. Lack of di-(2-ethyhhexyl) phthalate activity in the C3H/10T1/2 cell transformation system. Toxicol in Vitro 1(1):49-53.

Sanner T, Rivedal E. 1985. Tests with the Syrian hamster embryo (SHE) cell transformation assay. Prog Mutat Res 5:665-671.

Sarath Josh MK, Pradeep S, Vijayalekshmy Amma KS, et al. 2016. Human ketosteroid receptors interact with hazardous phthalate plasticizers and their metabolites: an in silico study. J Appl Toxicol 36(6):836-843. http://doi.org/10.1002/jat.3221.

Sasaki T, Yoshikawa K, Harada H, et al. 2003. No immunotoxic effect on T cells with di (2-ethylhexyl) phthalate in male C57BL/6 mice. Environ Health Prev Med 8(2):59-63. http://doi.org/10.1007/bf02897928.

Satake S, Nakamura C, Minamide Y, et al. 2010. Effect of a large dose of di (2-ethylhexyl) phthalate (DEHP) on hepatic peroxisome in cynomolgus monkeys (Macaca fascicularis). J Toxicol Pathol 23(2):75-83. http://doi.org/10.1293/tox.23.75.

Sathyanarayana S, Barrett E, Butts S, et al. 2014. Phthalate exposure and reproductive hormone concentrations in pregnancy. Reproduction 147(4):401-409. http://doi.org/10.1530/rep-13-0415.

Sathyanarayana S, Grady R, Barrett ES, et al. 2016a. First trimester phthalate exposure and male newborn genital anomalies. Environ Res 151:777-782. http://doi.org/10.1016/j.envres.2016.07.043.

Sathyanarayana S, Barrett E, Nguyen R, et al. 2016b. First trimester phthalate exposure and infant birth weight in the infant development and environment study. Int J Environ Res Public Health 13(10):945. http://doi.org/10.3390/ijerph13100945.

Sathyanarayana S, Butts S, Wang C, et al. 2017. Early prenatal phthalate exposure, sex steroid hormones, and birth outcomes. J Clin Endocrinol Metab 102(6):1870-1878. http://doi.org/10.1210/jc.2016-3837.

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

SCENIHR. 2016. Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update). Revision February 2016. Scientific Committee on Emerging and Newly-Identified Health Risks. European Commission. http://ec.europa.eu/health/scientific_committees/policy/index_en.htm. June 18, 2018.

Schaedlich K, Gebauer S, Hunger L, et al. 2018. DEHP deregulates adipokine levels and impairs fatty acid storage in human SGBS-adipocytes. Sci Rep 8(1):3447. http://doi.org/10.1038/s41598-018-21800-4.

Schecter A, Lorber M, Guo Y, et al. 2013. Phthalate concentrations and dietary exposure from food purchased in New York State. Environ Health Perspect 121(4):473-494. http://doi.org/10.1289/ehp.1206367.

Schilling K, Deckardt K, Gembardt C, et al. 1999. Support: Di-2-ethylhexyl phthalate -two-generation reproduction toxicity range-finding study in Wistar rats - continuous dietary administration, with cover letter dated 09/16/1999. Eastman Chemical Co. Submitted under TSCA Section 8E. OTS0530371-6. 89990000316.

Schilling K, Deckardt K, Gembardt C, et al. 2001. Support: Di-2-ethylhexyl phthalate -two-generation reproduction toxicity study in Wistar rats continuous dietary administration, with cover letter dated

04/2/2001. Eastman Chemical Co. Submitted under TSCA Section 8E. OTS0574025-1. 89010000147.

Schmezer P, Pool BL, Klein RG, et al. 1988. Various short-term assays and two long-term studies with the plasticizer di(2-ethylhexyl)phthalate in the Syrian golden hamster. Carcinogenesis 9(1):37-43. http://doi.org/10.1093/carcin/9.1.37.

Schmid P, Schlatter C. 1985. Excretion and metabolism of di(2-ethylhexyl)-phthalate in man. Xenobiotica 15(3):251-256.

Schmidt JS, Schaedlich K, Fiandanese N, et al. 2012. Effects of di(2-ethylhexyl) phthalate (DEHP) on female fertility and adipogenesis in C3H/N mice. Environ Health Perspect 120(8):1123-1129. http://doi.org/10.1289/ehp.1104016.

Schwope AD, Reid RC. 1988. Migration to dry foods. Food Addit Contam 5(Suppl 1):445-454.

Scott RC, Dugard PH, Ramsey JD, et al. 1987. In vitro absorption of some o-phthalate diesters through human and rat skin. Environ Health Perspect 74:223-227. http://doi.org/10.2307/3430452.

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

Serrano SE, Braun J, Trasande L, et al. 2014. Phthalates and diet: a review of the food monitoring and epidemiology data. Environ Health 13(1):43. http://doi.org/10.1186/1476-069X-13-43.

Shaffer CB, Carpenter CP, Smyth HF. 1945. Acute and subacute toxicity of di(2-ethylhexyl)phthalate with note upon its metabolism. J Ind Hyg Toxicol 27:130-135.

Shao P, Wang Y, Zhang M, et al. 2019. The interference of DEHP in precocious puberty of females mediated by the hypothalamic IGF-1/PI3K/Akt/mTOR signaling pathway. Ecotoxicol Environ Saf 181:362-369. http://doi.org/10.1016/j.ecoenv.2019.06.017.

Shapiro GD, Dodds L, Arbuckle TE, et al. 2015. Exposure to phthalates, bisphenol A and metals in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC study. Environ Int 83:63-71. http://doi.org/10.1016/j.envint.2015.05.016.

Sharma R, Lake BG, Gibson GG. 1988. Co-induction of microsomal cytochrome P-452 and the peroxisomal fatty acid β-oxidation pathway in the rat by clofibrate and di-(2-ethylhexyl) phthalate. Biochem Pharmacol 37(7):1203-1206. http://doi.org/10.1016/0006-2952(88)90771-x.

Sharma RK, Lake BG, Makowski R, et al. 1989. Differential induction of peroxisomal and microsomal fatty-acid-oxidising enzymes by peroxisome proliferators in rat liver and kidney. Characterisation of a renal cytochrome P-450 and implications for peroxisome proliferation. Eur J Biochem 184(1):69-78. http://doi.org/10.1111/j.1432-1033.1989.tb14991.x.

Sharma RP, Schuhmacher M, Kumar V. 2018. Development of a human physiologically based pharmacokinetic (PBPK) model for phthalate (DEHP) and its metabolites: A bottom up modeling approach. Toxicol Lett 296:152-162. http://doi.org/10.1016/j.toxlet.2018.06.1217.

She Y, Jiang L, Zheng L, et al. 2017. The role of oxidative stress in DNA damage in pancreatic β cells induced by di-(2-ethylhexyl) phthalate. Chem Biol Interact 265:8-15. http://doi.org/10.1016/j.cbi.2017.01.015.

Sheikh IA, Turki RF, Abuzenadah AM, et al. 2016. Endocrine disruption: Computational perspectives on human sex hormone-binding globulin and phthalate plasticizers. PLoS ONE 11(3):e0151444. http://doi.org/10.1371/journal.pone.0151444.

Sheldon LS, Hites RA. 1979. Sources and movement of organic chemicals in the Delaware River. Environ Sci Technol 13(5):574-579.

Shen R, Zhao LL, Yu Z, et al. 2017. Maternal di-(2-ethylhexyl) phthalate exposure during pregnancy causes fetal growth restriction in a stage-specific but gender-independent manner. Reprod Toxicol 67:117-124. http://doi.org/10.1016/j.reprotox.2016.12.003.

Shen L, Tang X, Wei Y, et al. 2018. Vitamin E and vitamin C attenuate di-(2-ethylhexyl) phthalate-induced blood-testis barrier disruption by p38 MAPK in immature SD rats. Reprod Toxicol 81:17-27. http://doi.org/10.1016/j.reprotox.2018.06.015.

Shin M, Ohnishi M, Iguchi S, et al. 1999. Peroxisome-proliferator regulates key enzymes of the tryptophan-NAD+ pathway. Toxicol Appl Pharmacol 158(1):71-80. http://doi.org/10.1006/taap.1999.8683.

Shinohara N, Uchino K. 2020. Diethylhexyl phthalate (DEHP) emission to indoor air and transfer to house dust from a PVC sheet. Sci Total Environ 711:134573. http://doi.org/10.1016/j.scitotenv.2019.134573.

Shinohara N, Mizukoshi A, Uchiyama M, et al. 2019. Emission characteristics of diethylhexyl phthalate (DEHP) from building materials determined using a passive flux sampler and micro-chamber. PLoS ONE 14(9):e0222557. http://doi.org/10.1371/journal.pone.0222557.

Shintani H. 2000. Pretreatment and chromatographic analysis of phthalate esters, and their biochemical behavior in blood products. Chromatographia 52(11/12):721-726.

Shiota K, Nishimura H. 1982. Teratogenicity of di(2-ethylhexyl) phthalate (DEHP) and di-n-butyl phthalate (DBP) in mice. Environ Health Perspect 45(0):65-70. http://doi.org/10.2307/3429385.

Shiota K, Chou MJ, Nishimura H. 1980. Embryotoxic effects of di-2-ethylhexyl phthalate (DEHP) and di-n-butyl phthalate (DBP) in mice. Environ Res 22(1):245-253. http://doi.org/10.1016/0013-9351(80)90136-x.

Shiue I. 2015a. Urinary heavy metals, phthalates, perchlorate, nitrate, thiocyanate, hydrocarbons, and polyfluorinated compounds are associated with adult hearing disturbance: USA NHANES, 2011-2012. Environ Sci Pollut Res Int 22(24):20306-20311. http://doi.org/10.1007/s11356-015-5546-8.

Shiue I. 2015b. Arsenic, heavy metals, phthalates, pesticides, hydrocarbons and polyfluorinated compounds but not parabens or phenols are associated with adult remembering condition: US NHANES, 2011-2012. Environ Sci Pollut Res Int 22(8):6381-6386. http://doi.org/10.1007/s11356-015-4261-9.

Shiue I. 2015c. Urinary heavy metals, phthalates and polyaromatic hydrocarbons independent of health events are associated with adult depression: USA NHANES, 2011-2012. Environ Sci Pollut Res Int 22(21):17095-17103. http://doi.org/10.1007/s11356-015-4944-2.

Shiue I, Hristova K. 2014. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3-19% of the population attributable risk for high blood pressure: US NHANES, 2009-2012. Hypertens Res 37(12):1075-1081. http://doi.org/10.1038/hr.2014.121.

Shneider B, Cronin J, Van Marter L, et al. 1991. A prospective analysis of cholestasis in infants supported with extracorporeal membrane oxygenation. J Pediatr Gastroenterol Nutr 13(3):285-289.

Shoaff JR, Romano ME, Yolton K, et al. 2016. Prenatal phthalate exposure and infant size at birth and gestational duration. Environ Res 150:52-58. http://doi.org/10.1016/j.envres.2016.05.033.

Shoaff J, Papandonatos GD, Calafat AM. 2017a. Early-life phthalate exposure and adiposity at 8 years of age. Environ Health Perspect 215(9) http://doi.org/28935615.

Shoaff J, Papandonatos GD, Calafat AM, et al. 2017b. Supplementary data: Early-life phthalate exposure and adiposity at 8 years of age. Environ Health Perspect 125. http://doi.org/10.1289/EHP1022.

Short RD, Robinson EC, Lington AW, et al. 1987. Metabolic and peroxisome proliferation studies with di(2-ethylhexyl)phthalate in rats and monkeys. Toxicol Ind Health 3(2):185-195. http://doi.org/10.1177/074823378700300213.

Silva MJ, Barr DB, Reidy JA, et al. 2003. Glucuronidation patterns of common urinary and serum monoester phthalate metabolites. Arch Toxicol 77(10):561-567. http://doi.org/10.1007/s00204-003-0486-3.

Silva MJ, Reidy JA, Preau JL, et al. 2006. Oxidative metabolites of diisononyl phthalate as biomarkers for human exposure assessment. Environ Health Perspect 114(8):1158-1161. http://doi.org/10.1289/ehp.8865.

Simmon VF, Kauhanen K, Tardiff RG. 1977. Mutagenic activity of chemicals identified in drinking water. In: Progress in genetic toxicology: Proceedings of the Second International Conference on Environmental Mutagens. Edinburgh, London: Elsevier/North Holland Press, 249-258.

Simmons J, Yeatts S, Zhao J, et al. 2005. Evaluation of systemic toxicity in mixtures of trichloroethylene (TCE), heptachlor (HEPT), and di(2-ethylhexyl)phthalate (DEHP) assessed in a 5x5x5 design. Toxicologist 84:395.

Singh S, Li SS. 2011. Phthalates: Toxicogenomics and inferred human diseases. Genomics 97(3):148-157. http://doi.org/10.1016/j.ygeno.2010.11.008.

Singh AR, Lawrence WH, Autian J. 1974. Mutagenic and antifertility sensitivities of mice to di-2-ethylhexyl phthalate (DEHP) and dimethoxyethyl phthalate (DMEP). Toxicol Appl Pharmacol 29:35-46.

Singh AR, Lawrence WH, Autian J. 1975. Maternal-fetal transfer of 14C-di-2-ethylhexyl phthalate and 14C-diethyl phthalate in rats. J Pharm Sci 64(8):1347-1350. http://doi.org/10.1002/jps.2600640819.

Sjoberg P, Bondesson U, Hammarlund M. 1985a. Non-linearities in the pharmacokinetics of di-(2-ethylhexyl) phthalate and metabolites in male rats. Arch Toxicol 58(2):72-77.

Sjoberg P, Bondesson U, Kjellen L, et al. 1985b. Kinetics of di-(2-ethylhexyl) phthalate in immature and mature rats and effect on testis. Acta Pharmacol Toxicol (Copenh) 56:30-37.

Sjoberg P, Bondesson U, Sedin G, et al. 1985c. Dispositions of di- and mono-(2-ethylhexyl) phthalate in newborn infants subjected to exchange transfusions. Eur J Clin Invest 15(6):430-436. http://doi.org/10.1111/j.1365-2362.1985.tb00297.x.

Sjoberg P, Lindqvist NG, Ploen L. 1986. Age-dependent response of the rat testes to di(2-ethylhexyl) phthalate. Environ Health Perspect 65:237-242.

Sjoberg P, Egestad B, Klasson-Wehler E, et al. 1991. Glucuronidation of mono(2-ethylhexyl)phthalate. Biochem Pharmacol 41(10):1493-1496.

Smith CA, Holahan MR. 2014. Reduced hippocampal dendritic spine density and BDNF expression following acute postnatal exposure to di(2-ethylhexyl) phthalate in male Long Evans rats. PLoS ONE 9(10):e109522. http://doi.org/10.1371/journal.pone.0109522.

Smith CA, MacDonald A, Holahan MR. 2011. Acute postnatal exposure to di(2-ethylhexyl) phthalate adversely impacts hippocampal development in the male rat. Neuroscience 193:100-108. http://doi.org/10.1016/j.neuroscience.2011.06.082.

Smith-Oliver T, Butterworth BE. 1987. Correlation of the carcinogenic potential of di(2-ethylhexyl)phthalate (DEHP) with induced hyperplasia rather than with genotoxic activity. Mutat Res 188(1):21-28. http://doi.org/10.1016/0165-1218(87)90110-8.

Sobol Z, Homiski ML, Dickinson DA, et al. 2012. Development and validation of an in vitro micronucleus assay platform in TK6 cells. Mutat Res 746(1):29-34. http://doi.org/10.1016/j.mrgentox.2012.02.005.

Sol CM, Santos S, Asimakopoulos AG, et al. 2020. Associations of maternal phthalate and bisphenol urine concentrations during pregnancy with childhood blood pressure in a population-based prospective cohort study. Environ Int 138:105677. http://doi.org/10.1016/j.envint.2020.105677.

Song Y, Hauser R, Hu FB, et al. 2014. Urinary concentrations of bisphenol A and phthalate metabolites and weight change: A prospective investigation in US women. Int J Obes 38(12):1532-1537. http://doi.org/10.1038/ijo.2014.63.

Souter I, Bellavia A, Williams PL, et al. 2020a. Urinary concentrations of phthalate metabolite mixtures in relation to serum biomarkers of thyroid function and autoimmunity among women from a fertility center. Environ Health Perspect 128(6):67007. http://doi.org/10.1289/ehp6740.

Souter I, Bellavia A, Williams PL, et al. 2020b. Supplemental material: Urinary concentrations of phthalate metabolite mixtures in relation to serum biomarkers of thyroid function and autoimmunity among women from a fertility center. Environ Health Perspect 128. http://doi.org/10.1289/ehp6740.

Specht IO, Bonde JP, Toft G, et al. 2015. Serum phthalate levels and time to pregnancy in couples from Greenland, Poland and Ukraine. PLoS ONE 10(3):e0120070. http://doi.org/10.1371/journal.pone.0120070.

Stahlhut RW, van Wijngaarden E, Dye TD, et al. 2007. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ Health Perspect 115(6):876-882. http://doi.org/10.1289/ehp.9882.

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

Staples CA, Werner AF, Hoogheem TJ. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. Environ Toxicol Chem 4:131-142.

Staples CA, Peterson DR, Parkerton TF, et al. 1997. The environmental fate of phthalate esters: A literature review. Chemosphere 35(4):667-749.

Stein TP, Schluter MD, Steer RA, et al. 2013. Autism and phthalate metabolite glucuronidation. J Autism Dev Disord 43(11):2677-2685. http://doi.org/10.1007/s10803-013-1822-y.

Steiner I, Scharf L, Fiala F, et al. 1998. Migration of di-(2-ethylhexyl) phthalate from PVC child articles into saliva and saliva simulant. Food Addit Contam 15(7):812-817. http://doi.org/10.1080/02652039809374715.

Stelmach I, Majak P, Jerzynska J, et al. 2015. The effect of prenatal exposure to phthalates on food allergy and early eczema in inner-city children. Allergy Asthma Proc 36(4):72-78. http://doi.org/10.2500/aap.2015.36.3867.

Stenchever MA, Allen MA, Jerominski L, et al. 1976. Effects of bis(2-ethylhexyl) phthalate on chromosomes of human leukocytes and human fetal lung cells. J Pharm Sci 65:1648-1651.

Stermer AR, Murphy CJ, Ghaffari R, et al. 2017. Mono-(2-ethylhexyl) phthalate-induced Sertoli cell injury stimulates the production of pro-inflammatory cytokines in Fischer 344 rats. Reprod Toxicol 69:150-158. http://doi.org/10.1016/j.reprotox.2017.02.013.

Strassle PD, Smit LAM, Hoppin JA. 2018. Endotoxin enhances respiratory effects of phthalates in adults: Results from NHANES 2005-6. Environ Res 162:280-286. http://doi.org/10.1016/j.envres.2018.01.017.

Stringer R, Labunska I, Santillo D, et al. 2000. Concentrations of phthalate esters and identification of other additives in PVC children's toys. Environ Sci Pollut Res Int 7(1):27-36. http://doi.org/10.1065/espr199910.00.

Stroheker T, Cabaton N, Nourdin G, et al. 2005. Evaluation of anti-androgenic activity of di-(2-ethylhexyl)phthalate. Toxicology 208(1):115-121. http://doi.org/10.1016/j.tox.2004.11.013.

Stroheker T, Regnier JF, Lassurguere J, et al. 2006. Effect of in utero exposure to di-(2-ethylhexyl)phthalate: distribution in the rat fetus and testosterone production by rat fetal testis in culture. Food Chem Toxicol 44(12):2064-2069. http://doi.org/10.1016/j.fct.2006.07.007.

Stubin AI, Brosnan TM, Porter KD, et al. 1996. Organic priority pollutants in New York City municipal wastewaters: 1989-1993. Water Environ Res 68(6):1037-1044.

Su PH, Chen JY, Lin CY, et al. 2014. Sex steroid hormone levels and reproductive development of eight-year-old children following in utero and environmental exposure to phthalates. PLoS ONE 9(9):e102788. http://doi.org/10.1371/journal.pone.0102788.

Su PH, Chang CK, Lin CY, et al. 2015. Prenatal exposure to phthalate ester and pubertal development in a birth cohort in central Taiwan: a 12-year follow-up study. Environ Res 136:324-330. http://doi.org/10.1016/j.envres.2014.10.026.

Suemizu H, Sota S, Kuronuma M, et al. 2014. Pharmacokinetics and effects on serum cholinesterase activities of organophosphorus pesticides acephate and chlorpyrifos in chimeric mice transplanted with human hepatocytes. Regul Toxicol Pharmacol 70(2):468-473. http://doi.org/10.1016/j.yrtph.2014.08.010.

Sugatt RH, O'Grady DP, Banerjee S, et al. 1984. Shake flask biodegradation of 14 commercial phthalate esters. Appl Environ Microbiol 47(4):601-606.

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

Sumner RN, Tomlinson M, Craigon J, et al. 2019. Independent and combined effects of diethylhexyl phthalate and polychlorinated biphenyl 153 on sperm quality in the human and dog. Sci Rep 9(1):3409. http://doi.org/10.1038/s41598-019-39913-9.

Sun W, Ban JB, Zhang N, et al. 2014a. Perinatal exposure to di-(2-ethylhexyl)-phthalate leads to cognitive dysfunction and phospho-tau level increase in aged rats. Environ Toxicol 29(5):596-603. http://doi.org/10.1002/tox.21785.

Sun Q, Cornelis MC, Townsend MK, et al. 2014b. Association of urinary concentrations of bisphenol A and phthalate metabolites with risk of type 2 diabetes: a prospective investigation in the Nurses' Health Study (NHS) and NHSII cohorts. Environ Health Perspect 122(6):616-623. http://doi.org/10.1289/ehp.1307201.

Sun J, Chen B, Zhang L, et al. 2016. Phthalate ester concentrations in blood serum, urine and endometrial tissues of Chinese endometriosis patients Int J Clin Exp Med 9(2):3808-3819.

Sun X, Li J, Jin S, et al. 2018. Associations between repeated measures of maternal urinary phthalate metabolites during pregnancy and cord blood glucocorticoids. Environ Int 121(Pt 1):471-479. http://doi.org/10.1016/j.envint.2018.09.037.

Sun X, Chen W, Weng S, et al. 2020. Effects of the environmental endocrine disruptors di-2-ethylhexyl phthalate and mono-2-ethylhexyl phthalate on human sperm function in vitro. Reprod Fertil Dev 32(6):629-636. http://doi.org/10.1071/rd19164.

Supornsilchai V, Soder O, Svechnikov K. 2007. Stimulation of the pituitary-adrenal axis and of adrenocortical steroidogenesis ex vivo by administration of di-2-ethylhexyl phthalate to prepubertal male rats. J Endocrinol 192(1):33-39. http://doi.org/10.1677/joe-06-0004.

Suzuki Y, Yoshinaga J, Mizumoto Y, et al. 2012. Foetal exposure to phthalate esters and anogenital distance in male newborns. Int J Androl 35(3):236-244. http://doi.org/10.1111/j.1365-2605.2011.01190.x.

Swan SH. 2008. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. Environ Res 108(2):177-184. http://doi.org/10.1016/j.envres.2008.08.007.

Swan SH, Main KM, Liu F, et al. 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect 113(8):1056-1061.

Swan SH, Liu F, Hines M, et al. 2010. Prenatal phthalate exposure and reduced masculine play in boys. Int J Androl 33(2):259-269. http://doi.org/10.1111/j.1365-2605.2009.01019.x.

Swan SH, Sathyanarayana S, Barrett ES, et al. 2015. First trimester phthalate exposure and anogenital distance in newborns. Hum Reprod 30(4):963-972. http://doi.org/10.1093/humrep/deu363.

Swartz RC, Schults DW, Ditsworth GR, et al. 1985. Sediment toxicity, contamination, and macrobenthic communities near a large sewage outfall. In: Boyle TP, ed. Validation and predictability of laboratory methods for assessing the fate and effects of contaminants in aquatic ecosystems. Philadelphia, PA: American Society for Testing and Materials, 152-175.

Szewczyńska M, Pośniak M, Dobrzyńska E. 2020. Determination of phthalates in particulate matter and gaseous phase emitted into the air of the working environment. Int J Environ Sci Technol 17(1):175-186. http://doi.org/10.1007/s13762-019-02435-y.

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

Takagi A, Sai K, Umemura T, et al. 1990. Significant increase of 8-hydroxydeoxyguanosine in liver DNA of rats following short-term exposure to the peroxisome proliferators di(2-ethylhexyl)phthalate and di(2-ethylhexyl)adipate. Jpn J Cancer Res 81(3):213-215.

Tamura H, Iida T, Watanabe T, et al. 1990. Long-term effects of hypolipidemic peroxisome proliferator administration on hepatic hydrogen peroxide metabolism in rats. Carcinogenesis 11(3):445-450. http://doi.org/10.1093/carcin/11.3.445.

Tamura H, Iida T, Watanabe T, et al. 1991. Lack of induction of hepatic DNA damage on long-term administration of peroxisome proliferators in male F-344 rats. Toxicology 69(1):55-62.

Tanaka T. 2002. Reproductive and neurobehavioural toxicity study of bis(2-ethylhexyl) phthalate (DEHP) administered to mice in the diet. Food Chem Toxicol 40(10):1499-1506. http://doi.org/10.1016/s0278-6915(02)00073-x.

Tanaka A, Adachi T, Takahashi T, et al. 1975. Biochemical studies on phthalic esters I. Elimination, distribution and metabolism of di-(2-ethylhexyl)phthalate in rats. Toxicology 4(2):253-264. http://doi.org/10.1016/0300-483x(75)90105-5.

Tanaka A, Matsumoto A, Yamaha T. 1978. Biochemical studies on phthalic esters. III. Metabolism of dibutyl phthalate (DBP) in animals. Toxicology 9(1-2):109-123.

Tang C, Luo C, Hua Y, et al. 2019. Placental P-glycoprotein inhibition enhances susceptibility to di-(2-ethylhexyl)-phthalate induced cardiac malformations in mice: A possibly promising target for congenital heart defects prevention. PLoS ONE 14(5):e0214873. http://doi.org/10.1371/journal.pone.0214873.

Tanida T, Warita K, Ishihara K, et al. 2009. Fetal and neonatal exposure to three typical environmental chemicals with different mechanisms of action: mixed exposure to phenol, phthalate, and dioxin cancels the effects of sole exposure on mouse midbrain dopaminergic nuclei. Toxicol Lett 189(1):40-47. http://doi.org/10.1016/j.toxlet.2009.04.005.

Teirlynck OA, Belpaire F. 1985. Disposition of orally administered di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate in the rat. Arch Toxicol 57:226-230.

Teirlynck O, Kaufman JM, Bogaert MG, et al. 1988. Testicular toxicity induced by single dosing of di- and mono-(2-ethylhexyl) phthalate in the rat. Toxicol Lett 40(1):85-91. http://doi.org/10.1016/0378-4274(88)90186-5.

Teitelbaum SL, Mervish N, Moshier EL, et al. 2012. Associations between phthalate metabolite urinary concentrations and body size measures in New York City children. Environ Res 112:186-193. http://doi.org/10.1016/j.envres.2011.12.006.

Téllez-Rojo MM, Cantoral A, Cantonwine DE, et al. 2013. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. Sci Total Environ 461-462:386-390. http://doi.org/10.1016/j.scitotenv.2013.05.021.

Tennant RW, Margolin BH, Shelby MD, et al. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236:933-941.

Testa C, Nuti F, Hayek J, et al. 2012. Di-(2-ethylhexyl) phthalate and autism spectrum disorders. ASN Neuro 4(4):223-229. http://doi.org/10.1042/an20120015.

Thiess A, Fleig I. 1978. [Chromosomal studies in workers exposed to di-2-ethylhexylphthalate (DOP).]. Zentralbl Arbeitsmed 28:351-355. (German)

Thomas JM, Yordy JR, Amador JA, et al. 1986. Rates of dissolution and biodegradation of water-insoluble organic compounds. Appl Environ Microbiol 52(2):290-296.

Thomsen AML, Riis AH, Olsen J, et al. 2017. Female exposure to phthalates and time to pregnancy: A first pregnancy planner study. Hum Reprod 32(1):232-238. http://doi.org/10.1093/humrep/dew291.

Thuren A, Larsson P. 1990. Phthalate esters in the Swedish atmosphere. Environ Sci Technol 24(4):554-559.

Tian M, Liu L, Zhang J, et al. 2019. Positive association of low-level environmental phthalate exposure with sperm motility was mediated by DNA methylation: A pilot study. Chemosphere 220:459-467. http://doi.org/10.1016/j.chemosphere.2018.12.155.

Tickner J, Schettler T, Guidotti T, et al. 2001. Health risks posed by use of di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: A critical review. Am J Ind Med 39(1):100-111.

Toft G, Jonsson BA, Lindh CH, et al. 2012. Association between pregnancy loss and urinary phthalate levels around the time of conception. Environ Health Perspect 120(3):458-463. http://doi.org/10.1289/ehp.1103552.

Tomaszewski KE, Montgomery CA, Melnick RL. 1988. Modulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity in F344 rats by di(2-ethylhexyl)phthalate. Chem Biol Interact 65(3):205-222. http://doi.org/10.1016/0009-2797(88)90107-x.

Tomita I, Nakamura Y, Yagi Y, et al. 1982a. Teratogenicity/fetotoxicity of DEHP in mice. Environ Health Perspect 45:71-75.

Tomita I, Nakamura Y, Aoki N, et al. 1982b. Mutagenic/carcinogenic potential of DEHP and MEHP. Environ Health Perspect 45:119-125.

Tomonari Y, Kurata Y, David RM, et al. 2006. Effect of di(2-ethylhexyl) phthalate (DEHP) on genital organs from juvenile common marmosets: I. Morphological and biochemical investigation in 65-week toxicity study. J Toxicol Environ Health 69(17):1651-1672. http://doi.org/10.1080/15287390600630054.

Tonk EC, Verhoef A, Gremmer ER, et al. 2012. Relative sensitivity of developmental and immune parameters in juvenile versus adult male rats after exposure to di(2-ethylhexyl) phthalate. Toxicol Appl Pharmacol 260(1):48-57. http://doi.org/10.1016/j.taap.2012.01.018.

Toyosawa K, Okimoto K, Kobayashi I, et al. 2001. Di(2-ethylhexyl)phthalate induces hepatocellular adenoma in transgenic mice carrying a human prototype c-Ha-ras gene in a 26-week carcinogenicity study. Toxicol Pathol 29(4):458-466.

Trasande L, Attina TM. 2015. Association of exposure to di-2-ethylhexylphthalate replacements with increased blood pressure in children and adolescents. Hypertension 66(2):301-308. http://doi.org/10.1161/hypertensionaha.115.05603.

Trasande L, Sathyanarayana S, Spanier AJ, et al. 2013a. Urinary phthalates are associated with higher blood pressure in childhood. J Pediatr 163(3):747-753. http://doi.org/10.1016/j.jpeds.2013.03.072.

Trasande L, Spanier AJ, Sathyanarayana S, et al. 2013b. Urinary phthalates and increased insulin resistance in adolescents. Pediatrics 132(3):e646-e655. http://doi.org/10.1542/peds.2012-4022.

Trasande L, Sathyanarayana S, Trachtman H. 2014. Dietary phthalates and low-grade albuminuria in US children and adolescents. Clin J Am Soc Nephrol 9(1):100-109. http://doi.org/10.2215/cjn.04570413.

TRI18. 2020. TRI explorer: Providing access to EPA's toxics release inventory data. U.S. Environmental Protection Agency. https://enviro.epa.gov/triexplorer/tri_release.chemical. May 5, 2020.

Tripathi A, Pandey V, Sahu AN, et al. 2019. Di-(2-ethylhexyl) phthalate (DEHP) inhibits steroidogenesis and induces mitochondria-ROS mediated apoptosis in rat ovarian granulosa cells. Toxicology Research 8(3):381-394. http://doi.org/10.1039/c8tx00263k.

Trosko JE. 1997. Challenge to the simple paradigm that 'carcinogens' are 'mutagens' and to the in vitro and in vivo assays used to test the paradigm. Mutat Res 373:245-249.

Trosko JE. 2001. Commentary: Is the concept of "tumor promotion" a useful paradigm? Mol Carcinog 30:131-137.

Tsai YA, Lin CL, Hou JW, et al. 2016. Effects of high di(2-ethylhexyl) phthalate (DEHP) exposure due to tainted food intake on pre-pubertal growth characteristics in a Taiwanese population. Environ Res 149:197-205. http://doi.org/10.1016/j.envres.2016.05.005.

Tsai YA, Tsai MS, Hou JW, et al. 2018a. Evidence of high di(2-ethylhexyl) phthalate (DEHP) exposure due to tainted food intake in Taiwanese pregnant women and the health effects on birth outcomes. Sci Total Environ 618:635-644. http://doi.org/10.1016/j.scitotenv.2017.07.175.

Tsai YA, Tsai MS, Hou JW, et al. 2018b. Supplemental material: Evidence of high di(2-ethylhexyl) phthalate (DEHP) exposure due to tainted food intake in Taiwanese pregnant women and the health effects on birth outcomes. Sci Total Environ 618. http://doi.org/10.1016/j.scitotenv.2017.07.175.

Tsukada A, Suemizu H, Murayama N, et al. 2013. Plasma concentrations of melengestrol acetate in humans extrapolated from the pharmacokinetics established in in vivo experiments with rats and chimeric mice with humanized liver and physiologically based pharmacokinetic modeling. Regul Toxicol Pharmacol 65(3):316-324. http://doi.org/10.1016/j.yrtph.2013.01.008.

Tsumura Y, Ishimitsu S, Kaihara A, et al. 2001. Di(2-ethylhexyl) phthalate contamination of retail packed lunches caused by PVC gloves in the preparation of foods. Food Addit Contam 18(6):569-579.

Tsutsui T, Watanabe E, Barrett JC. 1993. Ability of peroxisome proliferators to induce cell transformation, chromosome aberrations and peroxisome proliferation in cultured Syrian hamster embryo cells. Carcinogenesis 14(4):611-618.

Tully K, Kupfer D, Dopico AM, et al. 2000. A plasticizer released from IV drip chambers elevates calcium levels in neurosecretary terminals. Toxicol Appl Pharmacol 168:183-188.

TURI. 2006. Five chemicals alternatives assessment study. Toxics Use Reduction Institute. University of Massachusetts Lowell.

Turner JH, Petricciani JC, Crouch ML, et al. 1974. An evaluation of the effects of diethylhexyl phthalate (DEHP) on mitotically capable cells in blood packs. Transfusion 14(6):560-566. http://doi.org/10.1111/j.1537-2995.1974.tb04577.x.

Turunen M, Dallner G. 1998. Elevation of ubiquinone content by peroxisomal inducers in rat liver during aging. Chem Biol Interact 116:79-91.

Tyl RW, Price CJ, Marr MC, et al. 1988. Developmental toxicity evaluation of dietary di(2-ethylhexyl)phthalate in Fischer 344 rats and CD-1 mice. Fundam Appl Toxicol 10(3):395-412. http://doi.org/10.1016/0272-0590(88)90286-2.

Uhde E, Bednarek M, Fuhrmann F, et al. 2001. Phthalic esters in the indoor environment--test chamber studies on PVC-coated wallcoverings. Indoor Air 11(3):150-155.

Ungewitter E, Rotgers E, Bantukul T, et al. 2017. Teratogenic effects of in utero exposure to di-(2-ethylhexyl)-phthalate (DEHP) in B6:129S4 mice. Toxicol Sci 157(1):8-19. http://doi.org/10.1093/toxsci/kfx019.

Upson K, Sathyanarayana S, De Roos AJ, et al. 2013. Phthalates and risk of endometriosis. Environ Res 126:91-97. http://doi.org/10.1016/j.envres.2013.07.003.

USGS. 2006. Determination of semivolatile organic compounds and polycyclic aromatic hydrocarbons in solids by gas chromatography/mass spectrometry. U.S. Geological Survey. Techniques and Methods 5–B3.

Vafeiadi M, Myridakis A, Roumeliotaki T, et al. 2018a. Association of early life exposure to phthalates with obesity and cardiometabolic traits in childhood: Sex specific associations. Front Public Health 6:327. http://doi.org/10.3389/fpubh.2018.00327.

Vafeiadi M, Myridakis A, Roumeliotaki T, et al. 2018b. Supplementary data: Association of early life exposure to phthalates with obesity and cardiometabolic traits in childhood: Sex specific associations. Front Public Health 6. http://doi.org/10.3389/fpubh.2018.00327.

Valvi D, Casas M, Romaguera D, et al. 2015. Prenatal phthalate exposure and childhood growth and blood pressure: Evidence from the Spanish INMA-Sabadell birth cohort study. Environ Health Perspect 123(10):1022-1029. http://doi.org/10.1289/ehp.1408887.

Van Vliet ED, Reitano EM, Chhabra JS, et al. 2011. A review of alternatives to di (2-ethylhexyl) phthalate-containing medical devices in the neonatal intensive care unit. J Perinatol 31(8):551-560. http://doi.org/10.1038/jp.2010.208.

Velez MP, Arbuckle TE, Fraser WD. 2015. Female exposure to phenols and phthalates and time to pregnancy: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. Fertil Steril 103(4):1011-1020. http://doi.org/10.1016/j.fertnstert.2015.01.005.

Velinsky DJ, Riedel G, Ashley JTF, et al. 2011. Historical contamination of the Anacostia River, Washington, D.C. Environ Monit Assess 183:307-328.

Venturelli AC, Fischer SV, Nogueira de Morais R, et al. 2015. Effects of exposure to di-(2-ethylhexyl) phthalate (DEHP) during lactation and puberty on sexual maturation and glycemic homeostasis in males rats. Clin Nutr ESPEN 10(1):e5-e12. http://doi.org/10.1016/j.clnme.2014.10.002.

Venturelli AC, Meyer KB, Fischer SV, et al. 2019. Effects of in utero and lactational exposure to phthalates on reproductive development and glycemic homeostasis in rats. Toxicology 421:30-40. http://doi.org/10.1016/j.tox.2019.03.008.

Vessman J, Rietz G. 1974. Determination of di(ethylhexyl) phthalate in human plasma and plasma proteins by electron capture gas chromatography. J Chromatogr 100(1):153-163.

Villanger GD, Drover SSM, Nethery RC, et al. 2020a. Associations between urine phthalate metabolites and thyroid function in pregnant women and the influence of iodine status. Environ Int 137:105509. http://doi.org/10.1016/j.envint.2020.105509.

Villanger GD, Drover SSM, Nethery RC, et al. 2020b. Supplemental material: Associations between urine phthalate metabolites and thyroid function in pregnant women and the influence of iodine status. Environ Int 137. http://doi.org/10.1016/j.envint.2020.105509.

Vo T, Jung E, Dang V, et al. 2009a. Differential effects of flutamide and di-(2-ethylhexyl) phthalate on male reproductive organs in a rat model. J Reprod Dev 55(4):400-411.

Vo TT, Jung EM, Dang VH, et al. 2009b. Di-(2 ethylhexyl) phthalate and flutamide alter gene expression in the testis of immature male rats. Reprod Biol Endocrinol 7:104. http://doi.org/10.1186/1477-7827-7-104.

Vogel EW, Nivard MJ. 1993. Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8(1):57-81. http://doi.org/10.1093/mutage/8.1.57.

Von Daniken A, Lutz WK, Jackh R, et al. 1984. Investigation of the potential for binding of di(2-ethylhexyl) phthalate (DEHP) and di(2-ethylhexyl)adipate (DEHA) to liver DNA in vivo. Toxicol Appl Pharmacol 73:373-387.

Voss C, Zerban H, Bannasch P, et al. 2005. Lifelong exposure to di-(2-ethylhexyl)-phthalate induces tumors in liver and testes of Sprague-Dawley rats. Toxicology 206(3):359-371. http://doi.org/10.1016/j.tox.2004.07.016.

Voss J, Stermer AR, Ghaffari R, et al. 2018. MEHP-induced rat testicular inflammation does not exacerbate germ cell apoptosis. Reproduction 156(1):35-46. http://doi.org/10.1530/rep-18-0093.

Walker C, Ghazisaeidi S, Collet B, et al. 2020. In utero exposure to low doses of genistein and di-(2-ethylhexyl) phthalate (DEHP) alters innate immune cells in neonatal and adult rat testes. Andrology 8(4):943-964. http://doi.org/10.1111/andr.12840.

Wallin RF, Klamer B, Nicora RW, et al. 1974. Di (2-ethylhexyl) phthalate (DEHP) metabolism in animals and post-transfusion tissue levels in man. Bull Parenter Drug Assoc 28(6):278-287.

Wams TJ. 1987. Diethylhexylphthalate as an environmental contaminant - A review. Sci Total Environ 66:1-16.

Wang IJ, Karmaus WJ. 2015. The effect of phthalate exposure and filaggrin gene variants on atopic dermatitis. Environ Res 136:213-218. http://doi.org/10.1016/j.envres.2014.09.032.

Wang H, Zhou Y, Tang C, et al. 2013. Urinary phthalate metabolites are associated with body mass index and waist circumference in Chinese school children. PLoS ONE 8(2):e56800. http://doi.org/10.1371/journal.pone.0056800.

Wang IJ, Lin CC, Lin YJ, et al. 2014. Early life phthalate exposure and atopic disorders in children: a prospective birth cohort study. Environ Int 62:48-54. http://doi.org/10.1016/j.envint.2013.09.002.

Wang W, Xu X, Fan CQ. 2015. Health hazard assessment of occupationally di-(2-ethylhexyl)-phthalate-exposed workers in China. Chemosphere 120:37-44. http://doi.org/10.1016/j.chemosphere.2014.05.053.

Wang YX, Zeng Q, Sun Y, et al. 2016. Phthalate exposure in association with serum hormone levels, sperm DNA damage and spermatozoa apoptosis: A cross-sectional study in China. Environ Res 150:557-565. http://doi.org/10.1016/j.envres.2015.11.023.

Wang X, Wang Y, Song Q, et al. 2017a. In utero and lactational exposure to di(2-ethylhexyl) phthalate increased the susceptibility of prostate carcinogenesis in male offspring. Reprod Toxicol 69:60-67. http://doi.org/10.1016/j.reprotox.2017.01.008.

Wang S, Zhang P, Liu R, et al. 2017b. A DEHP plasticizer alters synaptic proteins via peroxidation. Toxicology Research 6(1):89-97. http://doi.org/10.1039/c6tx00361c.

Wang B, Liu F, Dong J, et al. 2018. Maternal exposure to environmental DEHP exacerbated OVA-induced asthmatic responses in rat offspring. Sci Total Environ 615:253-261. http://doi.org/10.1016/j.scitotenv.2017.09.276.

Wang G, Chen Q, Tian P, et al. 2020. Gut microbiota dysbiosis might be responsible to different toxicity caused by di-(2-ethylhexyl) phthalate exposure in murine rodents. Environ Pollut 261:114164. http://doi.org/10.1016/j.envpol.2020.114164.

Ward JM, Hagiwara A, Anderson LM, et al. 1988. The chronic hepatic or renal toxicity of di(2-ethylhexyl) phthalate, acetaminophen, sodium barbital, and phenobarbital in male B6C3F1 mice: Autoradiographic, immunohistochemical, and biochemical evidence for levels of DNA synthesis not

associated with carcinogenesis or tumor promotion. Toxicol Appl Pharmacol 96(3):494-506. http://doi.org/10.1016/0041-008x(88)90009-9.

Watkins DJ, Tellez-Rojo MM, Ferguson KK, et al. 2014. In utero and peripubertal exposure to phthalates and BPA in relation to female sexual maturation. Environ Res 134:233-241. http://doi.org/10.1016/j.envres.2014.08.010.

Watkins DJ, Peterson KE, Ferguson KK, et al. 2016. Relating phthalate and BPA exposure to metabolism in peripubescence: The role of exposure timing, sex, and puberty. J Clin Endocrinol Metab 101(1):79-88. http://doi.org/10.1210/jc.2015-2706.

Wei Z, Song L, Wei J, et al. 2012. Maternal exposure to di-(2-ethylhexyl)phthalate alters kidney development through the renin-angiotensin system in offspring. Toxicol Lett 212(2):212-221. http://doi.org/10.1016/j.toxlet.2012.05.023.

Wei N, Feng X, Xie Z, et al. 2017. Long-term di (2-ethylhexyl)-phthalate exposure promotes proliferation and survival of HepG2 cells via activation of NFκB. Toxicol in Vitro 42:86-92. http://doi.org/10.1016/j.tiv.2017.04.015.

Wen HJ, Chen CC, Wu MT, et al. 2017. Phthalate exposure and reproductive hormones and sex-hormone binding globulin before puberty - Phthalate contaminated-foodstuff episode in Taiwan. PLoS ONE 12(4):e0175536. http://doi.org/10.1371/journal.pone.0175536.

Weng TI, Chen MH, Lien GW, et al. 2017. Effects of gender on the association of urinary phthalate metabolites with thyroid hormones in children: A prospective cohort study in Taiwan. Int J Environ Res Public Health 14(2):123. http://doi.org/10.3390/ijerph14020123.

Wenzel AG, Bloom MS, Butts CD, et al. 2018. Influence of race on prenatal phthalate exposure and anogenital measurements among boys and girls. Environ Int 110:61-70.

Werner EF, Braun JM, Yolton K, et al. 2015. The association between maternal urinary phthalate concentrations and blood pressure in pregnancy: The HOME Study. Environ Health 14:75. http://doi.org/10.1186/s12940-015-0062-3.

Wester RC, Melendres J, Sedik L, et al. 1998. Percutaneous absorption of salicylic acid, theophylline, 2,4-dimethylamine, diethyl hexyl phthalic acid, and p-aminobenzoic acid in the isolated perfused porcine skin flap compared to man in vivo. Toxicol Appl Pharmacol 151:159-165.

Weuve J, Hauser R, Calafat AM, et al. 2010. Association of exposure to phthalates with endometriosis and uterine leiomyomata: findings from NHANES, 1999-2004. Environ Health Perspect 118(6):825-832. http://doi.org/10.1289/ehp.0901543.

White PD, Carter DE, Earnest D, et al. 1980. Absorption and metabolism of 3 phthalate diesters by the rat small intestine. Food Cosmet Toxicol 18(4):383-386.

WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 25, 2012.

WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

Whyatt RM, Adibi JJ, Calafat AM, et al. 2009. Prenatal di(2-ethylhexyl)phthalate exposure and length of gestation among an inner-city cohort. Pediatrics 124(6):e1213-e1220. http://doi.org/10.1542/peds.2009-0325.

Whyatt RM, Liu X, Rauh VA, et al. 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environ Health Perspect 120(2):290-295. http://doi.org/10.1289/ehp.1103705.

Whyatt RM, Perzanowski MS, Just AC, et al. 2014. Asthma in inner-city children at 5-11 years of age and prenatal exposure to phthalates: the Columbia Center for Children's Environmental Health Cohort. Environ Health Perspect 122(10):1141-1146. http://doi.org/10.1289/ehp.1307670.

Wilkinson CF, Lamb JC. 1999. The potential health effects of phthalate esters in children's toys: a review and risk assessment. Regul Toxicol Pharmacol 30(2 Pt 1):140-155. http://doi.org/10.1006/rtph.1999.133.

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

Williams D, Blanchfield B. 1974. Retention, excretion and metabolism of phthalic acid administered orally to the rat. Bull Environ Contam Toxicol 12(1):109-112.

Wirth J, Rossano M, Potter R, et al. 2008. A pilot study associating urinary concentrations of phthalate metabolites and semen quality. Syst Biol Reprod Med 54(3):143-154. http://doi.org/10.1080/19396360802055921.

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

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

Wolff MS, Engel SM, Berkowitz GS, et al. 2008. Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect 116(8):1092-1097. http://doi.org/10.1289/ehp.11007.

Wolff MS, Teitelbaum SL, McGovern K, et al. 2014. Phthalate exposure and pubertal development in a longitudinal study of US girls. Hum Reprod 29(7):1558-1566. http://doi.org/10.1093/humrep/deu081.

Woodward MJ, Obsekov V, Jacobson MH, et al. 2020. Phthalates and sex steroid hormones among men from NHANES, 2013-2016. J Clin Endocrinol Metab 105(4):e1225-1234. http://doi.org/10.1210/clinem/dgaa039.

Wormuth M, Scheringer M, Vollenweider M, et al. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Anal 26(3):803-824. http://doi.org/10.1111/j.1539-6924.2006.00770.

Wu MT, Wu CF, Chen BH, et al. 2013. Intake of phthalate-tainted foods alters thyroid functions in Taiwanese children. PLoS ONE 8(1):e55005. http://doi.org/10.1371/journal.pone.0055005.

Wu H, Olmsted A, Cantonwine DE, et al. 2017. Urinary phthalate and phthalate alternative metabolites and isoprostane among couples undergoing fertility treatment. Environ Res 153:1-7. http://doi.org/10.1016/j.envres.2016.11.003.

Wu CF, Hsiung CA, Tsai HJ, et al. 2018. Interaction of melamine and di-(2-ethylhexyl) phthalate exposure on markers of early renal damage in children: The 2011 Taiwan food scandal. Environ Pollut 235:453-461. http://doi.org/10.1016/j.envpol.2017.12.107.

Wu M, Xu L, Teng C, et al. 2019. Involvement of oxidative stress in di-2-ethylhexyl phthalate (DEHP)-induced apoptosis of mouse NE-4C neural stem cells. Neurotoxicology 70:41-47. http://doi.org/10.1016/j.neuro.2018.10.013.

Xie C, Jin R, Zhao Y, et al. 2015. Paraoxonase 2 gene polymorphisms and prenatal phthalates' exposure in Chinese newborns. Environ Res 140:354-359. http://doi.org/10.1016/j.envres.2015.03.028.

Xie X, Deng T, Duan J, et al. 2019. Comparing the effects of diethylhexyl phthalate and dibutyl phthalate exposure on hypertension in mice. Ecotoxicol Environ Saf 174:75-82. http://doi.org/10.1016/j.ecoenv.2019.02.067.

Xu Y, Agrawal S, Cook TJ, et al. 2007. Di-(2-ethylhexyl)-phthalate affects lipid profiling in fetal rat brain upon maternal exposure. Arch Toxicol 81(1):57-62. http://doi.org/10.1007/s00204-006-0143-8.

Xu Y, Agrawal S, Cook T, et al. 2008. Maternal di-(2-ethylhexyl)-phthalate exposure influences essential fatty acid homeostasis in rat placenta. Placenta 29(11):962-969. http://doi.org/10.1016/j.placenta.2008.08.011.

Xu C, Chen J, Qiu Z, et al. 2010. Ovotoxicity and PPAR-mediated aromatase downregulation in female Sprague-Dawley rats following combined oral exposure to benzo[a]pyrene and di-(2-ethylhexyl) phthalate. Toxicol Lett 199(3):323-332. http://doi.org/10.1016/j.toxlet.2010.09.015.

Xu X, Yang Y, Wang R, et al. 2015. Perinatal exposure to di-(2-ethylhexyl) phthalate affects anxiety- and depression-like behaviors in mice. Chemosphere 124:22-31. http://doi.org/10.1016/j.chemosphere.2014.10.056.

Xu J, Zhou L, Wang S, et al. 2018. Di-(2-ethylhexyl)-phthalate induces glucose metabolic disorder in adolescent rats. Environ Sci Pollut Res Int 25(4):3596-3607. http://doi.org/10.1007/s11356-017-0738-z.

Xu Y, Park SH, Yoon KN, et al. 2019. Effects of citrate ester plasticizers and bis (2-ethylhexyl) phthalate in the OECD 28-day repeated-dose toxicity test (OECD TG 407). Environ Res 172:675-683. http://doi.org/10.1016/j.envres.2019.03.004.

Yaghjyan L, Sites S, Ruan Y, et al. 2015a. Associations of urinary phthalates with body mass index, waist circumference and serum lipids among females: National Health and Nutrition Examination Survey 1999-2004. Int J Obes 39(2):994-1000. http://doi.org/10.1038/ijo.2015.8.

Yaghjyan L, Sites S, Ruan Y, et al. 2015b. Supplemental data: Associations of urinary phthalates with body mass index, waist circumference and serum lipids among females: National Health and Nutrition Examination Survey 1999-2004. Int J Obes 39.

Yaghjyan L, Ghita GL, Dumont-Driscoll M, et al. 2016. Maternal exposure to di-2-ethylhexylphthalate and adverse delivery outcomes: A systematic review. Reprod Toxicol 65:76-86. http://doi.org/10.1016/j.reprotox.2016.07.002.

Yagi Y, Nakamura Y, Tomita I, et al. 1980. Teratogenic potential of di- and mono-(2-ethylhexyl)phthalate in mice. J Environ Pathol Toxicol 4(2-3):533-544.

Yamashita M, Suemizu H, Murayama N, et al. 2014. Human plasma concentrations of herbicidal carbamate molinate extrapolated from the pharmacokinetics established in in vivo experiments with chimeric mice with humanized liver and physiologically based pharmacokinetic modeling. Regul Toxicol Pharmacol 70(1):214-221. http://doi.org/10.1016/j.yrtph.2014.06.028.

Yang G, Qiao Y, Li B, et al. 2008. Adjuvant effect of di-(2-ethylhexyl) phthalate on asthma-like pathological changes in ovalbumin-immunised rats. Food Agric Immunol 19(4):351-362. http://doi.org/10.1080/09540100802545869.

Yang G, Zhou X, Wang J, et al. 2012. MEHP-induced oxidative DNA damage and apoptosis in HepG2 cells correlates with p53-mediated mitochondria-dependent signaling pathway. Food Chem Toxicol 50(7):2424-2431. http://doi.org/10.1016/j.fct.2012.04.023.

Yao HY, Han Y, Gao H, et al. 2016. Maternal phthalate exposure during the first trimester and serum thyroid hormones in pregnant women and their newborns. Chemosphere 157:42-48. http://doi.org/10.1016/j.chemosphere.2016.05.023.

Ye H, Ha M, Yang M, et al. 2017. Di2-ethylhexyl phthalate disrupts thyroid hormone homeostasis through activating the Ras/Akt/TRHr pathway and inducing hepatic enzymes. Sci Rep 7:40153. http://doi.org/10.1038/srep40153.

Yolton K, Xu Y, Strauss D, et al. 2011. Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol 33(5):558-566. http://doi.org/10.1016/j.ntt.2011.08.003.

Yoon JS, Mason JM, Nalencia R, et al. 1985. Chemical mutagenesis testing in drosophila. IV. Results of 45 coded compounds tested for the National Toxicology Program. Environ Mutagen 7:349-367.

Yoshikawa K, Tanaka A, Yamaha T, et al. 1983. Mutagenicity study of nine monoalkyl phthalates and a dialkyl phthalate using Salmonella typhimurium and Escherichia coli. Food Chem Toxicol 21(2):221-223.

You M, Dong J, Fu Y, et al. 2018. Exposure to di-(2-ethylhexyl) phthalate during perinatal period gender-specifically impairs the dendritic growth of pyramidal neurons in rat offspring. Front Neurosci 12:444. http://doi.org/10.3389/fnins.2018.00444.

Yu C, Chu K. 2009. Occurrence of pharmaceuticals and personal care products along the West Prong Little Pigeon River in east Tennessee, USA. Chemosphere 75(10):1281-1286. http://doi.org/10.1016/j.chemosphere.2009.03.043.

Yu Z, Han Y, Shen R, et al. 2018. Gestational di-(2-ethylhexyl) phthalate exposure causes fetal intrauterine growth restriction through disturbing placental thyroid hormone receptor signaling. Toxicol Lett 294:1-10. http://doi.org/10.1016/j.toxlet.2018.05.013.

Yu Q, Xiong X, He J, et al. 2019. Photolysis of bis(2-ethylhexyl) phthalate in aqueous solutions at the presence of natural water photoreactive constituents under simulated sunlight irradiation. Environ Sci Pollut Res Int 26(26):26797-26806. http://doi.org/10.1007/s11356-019-05913-5.

Yu Z, Wang F, Han J, et al. 2020. Opposite effects of high- and low-dose di-(2-ethylhexyl) phthalate (DEHP) exposure on puberty onset, oestrous cycle regularity and hypothalamic kisspeptin expression in female rats. Reprod Fertil Dev 32(6):610-618. http://doi.org/10.1071/rd19024.

Yuwatini E, Hata N, Kuramitz H, et al. 2013. Effect of salting-out on distribution behavior of di(2-ethylhexyl) phthalate and its analogues between water and sediment. SpringerPlus 2:422. http://doi.org/10.1186/2193-1801-2-422.

Zacharewski TR, Meek MD, Clemons JH, et al. 1998. Examination of the in vitro and in vivo estrogenic activities of eight commercial phthalate esters. Toxicol Sci 46(2):282-293. http://doi.org/10.1093/toxsci/46.2.282.

Zeiger E, Haworth S, Mortelmans K, et al. 1985. Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in Salmonella. Environ Mol Mutagen 7(2):213-232. http://doi.org/10.1002/em.2860070209.

Zhang YH, Zheng LX, Chen BH. 2006. Phthalate exposure and human semen quality in Shanghai: a cross-sectional study. Biomed Environ Sci 19(3):205-209.

Zhang Y, Lin L, Liu Z, et al. 2008. Disruption effects of monophthalate exposures on inter-Sertoli tight junction in a two-compartment culture model. Environ Toxicol 23(3):302-308. http://doi.org/10.1002/tox.20343.

Zhang X-F, Zhang T, Wang L, et al. 2013. Effects of diethylhexyl phthalate (DEHP) given neonatally on spermatogenesis of mice. Mol Biol Rep 40(11):6509-6517. http://doi.org/10.1007/s11033-013-2769-y.

Zhang Y, Meng X, Chen L, et al. 2014. Age and sex-specific relationships between phthalate exposures and obesity in Chinese children at puberty. PLoS ONE 9(8):e104852. http://doi.org/10.1371/journal.pone.0104852.

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.

Zhang J, Liu L, Wang X, et al. 2016. Low-level environmental phthalate exposure associates with urine metabolome alteration in a Chinese male cohort. Environ Sci Technol 50(11):5953-5960. http://doi.org/10.1021/acs.est.6b00034.

Zhang W, Shen XY, Zhang WW, et al. 2017. Di-(2-ethylhexyl) phthalate could disrupt the insulin signaling pathway in liver of SD rats and L02 cells via PPARγ. Toxicol Appl Pharmacol 316:17-26. http://doi.org/10.1016/j.taap.2016.12.010.

Zhang L, Li H, Gao M, et al. 2018a. Genistein attenuates di-(2-ethylhexyl) phthalate-induced testicular injuries via activation of Nrf2/HO-1 following prepubertal exposure. Int J Mol Med 41(3):1437-1446. http://doi.org/10.3892/ijmm.2018.3371.

Zhang P, Guan X, Yang M, et al. 2018b. Roles and potential mechanisms of selenium in countering thyrotoxicity of DEHP. Sci Total Environ 619-620:732-739. http://doi.org/10.1016/j.scitotenv.2017.11.169.

Zhang Y, Mu X, Gao R, et al. 2018c. Foetal-neonatal exposure of di (2-ethylhexyl) phthalate disrupts ovarian development in mice by inducing autophagy. J Hazard Mater 358:101-112. http://doi.org/10.1016/j.jhazmat.2018.06.042.

Zhang Y, Gao H, Mao L, et al. 2018d. Effects of the phthalate exposure during three gestation periods on birth weight and their gender differences: A birth cohort study in China. Sci Total Environ 613-614:1573-1578. http://doi.org/10.1016/j.scitotenv.2017.08.319.

Zhang YZ, Zhang ZM, Zhou LT, et al. 2019. Di (2-ethylhexyl) phthalate disorders lipid metabolism via TYK2/STAT1 and autophagy in rats. Biomed Environ Sci 32(6):406-418. http://doi.org/10.3967/bes2019.055.

Zhang Y, Mustieles V, Yland J, et al. 2020a. Association of parental preconception exposure to phthalates and phthalate substitutes with preterm birth. JAMA Netw Open 3(4):e202159. http://doi.org/10.1001/jamanetworkopen.2020.2159.

Zhang S, Sun C, Zhao S, et al. 2020b. Exposure to DEHP or its metabolite MEHP promotes progesterone secretion and inhibits proliferation in mouse placenta or JEG-3 cells. Environ Pollut 257:113593. http://doi.org/10.1016/j.envpol.2019.113593.

Zhang Y, Zhou L, Zhang Z, et al. 2020c. Effects of di (2-ethylhexyl) phthalate and high-fat diet on lipid metabolism in rats by JAK2/STAT5. Environ Sci Pollut Res Int 27(4):3837-3848. http://doi.org/10.1007/s11356-019-06599-5.

Zhang Y, Mustieles V, Yland J, et al. 2020d. Supplementary material: Association of parental preconception exposure to phthalates and phthalate substitutes with preterm birth. JAMA Netw Open 3. http://doi.org/10.1001/jamanetworkopen.2020.2159.

Zhang TD, Ma YB, Li HC, et al. 2020e. Low dose of genistein alleviates mono-(2-ethylhexyl) phthalate-induced fetal testis disorder based on organ culture model. Oxid Med Cell Longev 2020:4569268. http://doi.org/10.1155/2020/4569268.

Zhao Y, Chen L, Li LX, et al. 2014. Gender-specific relationship between prenatal exposure to phthalates and intrauterine growth restriction. Pediatr Res 76(4):401-408. http://doi.org/10.1038/pr.2014.103.

Zhao H, Li J, Zhou Y, et al. 2018. Investigation on metabolism of di(2-ethylhexyl) phthalate in different trimesters of pregnant women. Environ Sci Technol 52(21):12851-12858. http://doi.org/10.1021/acs.est.8b04519.

Zhou JL, Liu YP. 2000. Kinetics and equilibria of the interactions between diethylhexyl phthalate and sediment particles in simulated estuarine systems. Mar Chem 71:165-176.

Zhou L, Chen H, Xu Q, et al. 2019. The effect of di-2-ethylhexyl phthalate on inflammation and lipid metabolic disorder in rats. Ecotoxicol Environ Saf 170:391-398. http://doi.org/10.1016/j.ecoenv.2018.12.009.

Zhu Y, Wan Y, Zhang B, et al. 2018. Relationship between maternal phthalate exposure and offspring size at birth. Sci Total Environ 612:1072-1078. http://doi.org/10.1016/j.scitotenv.2017.08.207.

Zolfaghari M, Drogui P, Seyhi B, et al. 2014. Occurrence, fate and effects of di (2-ethylhexyl) phthalate in wastewater treatment plants: A review. Environ Pollut 194C:281-293. http://doi.org/10.1016/j.envpol.2014.07.014.

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 Office of Innovation and Analytics, Toxicology Section, 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 Office of Innovation and Analytics, Toxicology Section, 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: January 2022
Profile Status: Final
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 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: January 2022
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL: 0.0002 ppm
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: An 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 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 (0, 0.3, or 1.6 ppm). 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- to 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 (0, 0.3, or 1.6 ppm). 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 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 LOAEL of 0.3 ppm was adjusted from intermittent exposure to account for a continuous exposure scenario:

$LOAEL_{ADJ}$ = LOAEL of 0.3 ppm x (6 hours/24 hours) x (5 days/7 days) = 0.05 ppm

Human Equivalent Concentration: A PBPK modeling approach was initially considered to calculate a human equivalent to the rat $BMCL_{ADJ}$. However, a PBPK modeling approach was rejected due to a lack of experimental data regarding the proper dose metric (proximate toxicant) for DEHP-induced developmental toxicity. A human equivalent concentration (HEC) was calculated by multiplying the duration-adjusted LOAEL by the regional gas dose ratio (RGDR). The RGDR for extrarespiratory tract effects is the ratio of animal to human blood:gas partition coefficients.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RGDR_{ER}$$
$$LOAEL_{HEC} = LOAEL_{ADJ} \times ([H_{b/g}]_A/[H_{b/g}]_H)$$

$[H_{b/g}]_A$ = animal blood/air partition coefficient
$[H_{b/g}]_H$ = human blood/air partition coefficient

A default value of 1 is used for the ratio of blood/air partition coefficients because the DEHP values are unknown.

$LOAEL_{HEC}$ = 0.05 ppm x 1 = 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

MRL = $LOAEL_{HEC}$ ÷ UFs
MRL = 0.05 ppm ÷ (3 x 10 x 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 LOAEL was associated with 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 quality and fertilization rate of mouse oocytes following pre-mating exposure to ≥0.2 mg/kg/day (Parra-Forero et al. 2019).

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. 2016b; 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. 2009b; 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: January 2022
Profile Status: Final
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

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: January 2022
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.003 mg/kg/day
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: 38
Species: Rat

MRL Summary: An 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 2014). These effects were observed at all tested doses (≥1 mg/kg/day). The 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 neurodevelopmental effects and altered glucose homeostasis in offspring following developmental exposure (Table A-2). Other effects, including alterations in the developing and adult male reproductive system, were not observed until much higher doses (Table A-2). Although neurodevelopmental effects were observed at the lowest identified LOAEL (0.2 mg/kg/day), support for neurodevelopmental effects following acute oral exposure is inconsistent. In particular, findings regarding anxiety following oral exposure to DEHP in rodents are mixed, with some studies reporting increased anxiety (Barakat et al. 2018; Carbone et al. 2013; Liu et al. 2018b) and others reporting decreased anxiety (Feng et al. 2020). Additionally, Barakat et al. (2018) reported increased anxiety in an open field test at ≥0.2 mg/kg/day (based on decreased time spent in the center of the open field), but they did not observe elevated anxiety in the elevated plus maze until maternal doses of 750 mg/kg/day. Due to the discrepancies in the anxiety endpoint, ATSDR did not further consider this as a critical effect. Therefore, the next most sensitive effect (altered glucose homeostasis in offspring at 1 mg/kg/day) was selected as the critical effect.

Table A-2. Summary of Candidate Lowest LOAELs for Acute-Duration Oral Exposure to DEHP

		NOAEL/LOAEL (mg/kg/day)			
Species	Duration (route)	NOAEL	LOAEL	System: effect	Reference
CD-1 mouse	10 days [GD 11–PND 0] (IN)	ND	0.2	***Developmental:*** increased anxiety in adult offspring	Barakat et al. 2018

Table A-2. Summary of Candidate Lowest LOAELs for Acute-Duration Oral Exposure to DEHP

Species	Duration (route)	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	System: effect	Reference
Wistar rat	13 days [GDs 9–21] (GO)	ND	1[a]	***Developmental:*** altered glucose homeostasis in adult offspring	Rajesh and Balasubramanian 2014
Long-Evans rat	14 days [PNDs 35–48] (GO)	1	10	***Developmental:*** reduced testosterone production in Leydig cells	Akingbemi et al. 2001
Sprague-Dawley rat	7 days [GDs 13–19] (GO)	ND	10	***Developmental:*** Leydig cell clustering in fetal testes	Klinefelter et al. 2012
Sprague-Dawley rat	11 days [GDs 11–21] (GO)	ND	10	***Developmental:*** sperm effects at PND 63	Vo et al. 2009a
Long-Evans rat	14 days (GO)	ND	10	***Reproductive:*** increased Leydig cell number and proliferation	Li et al. 2012a
Long-Evans rat	7–11 days (GO)	ND	10	***Reproductive:*** increased Leydig cell proliferation	Guo et al. 2013

[a]Selected POD.

DEHP = di(2-ethylhexyl)phthalate; GD = gestation day; (GO) = gavage in oil vehicle; (IN) = ingestion; LOAEL = lowest-observed-adverse-effect 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 for the critical effect of altered glucose homeostasis in offspring (Rajesh and Balasubramanian 2014) was selected as the principal study for the acute oral MRL.

Summary of the Principal Study:

Rajesh P, Balasubramanian K. 2014. 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: In order to identify the most sensitive POD, BMD modeling was attempted for the 11 measures of glucose homeostasis that were altered in offspring following exposure to ≥1 mg/kg/day (Rajesh and Balasubramanian 2014). 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 (2014) study; 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) resulted in questionable or unusable models. Because the data were not amenable to modeling, the LOAEL of 1 mg/kg/day for altered glucose homeostasis in adult rat offspring was selected as the basis of the 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

MRL = LOAEL ÷ UFs
MRL = 1 mg/kg/day ÷ (10 x 3 x 10) = 0.003 mg/kg/day

Other Additional Studies or Pertinent Information: Altered glucose homeostasis was observed in several developmental rat studies following gestation plus lactation, lactation-only, or early post-weaning exposure to DEHP (Lin et al. 2011; Mangala Priya et al. 2014; Parsanathan et al. 2019; Rajagopal et al. 2019a; Venturelli et al. 2015, 2019). Consistent with the gestation-only study by Rajesh and Balasubramanian (2014), the lowest identified LOAEL for these other studies was also 1 mg/kg/day (Mangala Priya et al. 2014; Venturelli et al. 2015). In the gestation plus lactation study, no changes in maternal rat 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 intermediate-duration mouse studies, metabolic syndrome (including abnormal glucose metabolism) was observed in offspring following maternal exposure to ≥0.2 mg/kg/day from 7 days premating through PND 0 (Fan et al. 2020) or ≥0.05 mg/kg/day from GD 1 to 19 (Gu et al. 2016).

In adult rats, altered glucose homeostasis was also observed following intermediate-duration exposure to doses ≥5 mg/kg/day (Aydemir et al. 2018; Rajesh et al. 2013; Xu et al. 2018; Zhang et al. 2017). In adult mice, altered glucose homeostasis was only observed at much higher doses of 2,000 mg/kg/day for acute

exposure and ≥180 mg/kg/day for intermediate-duration exposure (Ding et al. 2019; Lee et al. 2019a; Li et al. 2018).

Epidemiological studies suggest a potential association between impaired glucose homeostasis and DEHP exposure in adult humans, with reported associations between increased fasting serum glucose and/or insulin resistance and higher levels of DEHP metabolites in urine in eleven of thirteen studies (see Section 2.18 for references). In children and adolescents, findings are inconsistent, with reported associations between increased fasting serum glucose and/or insulin resistance and higher levels of DEHP metabolites in urine in some studies (Han et al. 2019; Kim et al. 2018a), but not others (Chen et al. 2017; Watkins et al. 2016).

Agency Contacts (Chemical Managers): Rae T. Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: January 2022
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL: 0.0001 mg/kg/day
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: 181
Species: Mouse

MRL Summary: An 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 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 were observed at 0.03–0.05 mg/kg/day (Table A-3). Observed effects included immune adjuvant effects, developmental effects (ovarian developmental deficiency, alterations in offspring body weight, metabolic syndrome, male reproductive effects), hepatic effects, and increased body weight and adiposity. While the immune alterations in sensitized animals were observed at the lowest dose, the human health relevance of findings from sensitized animals is uncertain in the absence of clear evidence that the immune system is a target of DEHP toxicity in humans or unsensitized animals. Therefore, immune effects reported by Guo et al. (2012) and Han et al. (2014a) were not further considered as the basis for the intermediate-duration oral MRL. The next most sensitive effect was altered female reproductive development at 0.04 mg/kg/day (Zhang et al. 2015). Several additional developmental effects were observed at 0.05 mg/kg/day (Gu et al. 2016; Pocar et al. 2012; Schmidt et al. 2012). Therefore, developmental effects were selected as the critical effect for the derivation of the intermediate-duration oral MRL.

Table A-3. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to DEHP

Species	Duration (route)	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	System: effect	Reference
BALB/c mouse	28 days (GO)	ND	0.03	***Immunological:*** enhanced immune response to OVA challenge in sensitized animals	Han et al. 2014a

Table A-3. Summary of Lowest LOAELs for Intermediate-Duration Oral Exposure to DEHP

Species	Duration (route)	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	System: effect	Reference
BALB/c mouse	52 days (GS)	ND	0.03	***Immunological:*** enhanced immune response to OVA challenge in sensitized animals	Guo et al. 2012
CD-1 mouse	20 days [GDs 0.5–18.5] (NS)	ND	0.04[a]	***Developmental:*** delayed meiotic progression of germ cells in ovaries of GD 17.5 F1 fetuses; accelerated folliculogenesis in F1 and F2 PND 21 offspring ***Reproductive:*** 25% decrease in maternal serum estradiol	Zhang et al. 2015
C57bbl/6AJ mice	19 days [GDs 1–19] (GO)	ND	0.05	***Developmental:*** metabolic syndrome in PNW 9 offspring	Gu et al. 2016
Sprague-Dawley rat	15 weeks (GO)	ND	0.05	***Hepatic:*** vacuolar degeneration and inflammatory infiltration	Zhang et al. 2017
C3H/N mouse	8 weeks [1 week premating–PND 21] (F)	ND	0.05	***Body weight:*** ~18% increase in maternal body weight ***Other noncancer:*** increased visceral adipose tissue and adipocyte hypertrophy	Schmidt et al. 2012
CD-1 mouse	42 days [GD 0–PND 21] (F)	ND	0.05 (serious LOAEL)	***Developmental:*** >20% decrease in offspring body weight at PNDs 21 and 42; decrease in sperm count and viability; decrease in offspring seminal vesicle weight	Pocar et al. 2012
C3H/N mouse	8 weeks [1 week premating–PND 21] (F)	ND	0.05 (serious LOAEL)	***Developmental:*** >20% increase in offspring body weight at PND 21, increased visceral adipose tissue	Schmidt et al. 2012

[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; 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

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 intermediate oral MRL (Table A-3).

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 MRL. BMD modeling was not attempted for this dataset due to use of a single dose group.

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

MRL = LOAEL÷ UFs
MRL = 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, studies reported various developmental effects following exposure to oral doses of 0.04-0.05 mg/kg/day in intermediate-duration gestational and/or early postnatal studies, with some studies reporting serious effects at 0.05 mg/kg/day. None of these studies identified a NOAEL 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 ≥70 mg/kg/day (Blystone et al. 2010; Grande et al. 2006, 2007; Nardelli et al. 2017; NTP 2005; Schilling et al. 1999, 2001; Venturelli et al. 2019). Other studies have reported delayed vaginal opening following developmental exposure to 5 mg/kg/day (Shao et al. 2019) or 250 mg/kg/day (lowest dose tested; Liu et al. 2018a). 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 lowest identified LOAELs of 0.1 and 0.2 mg/kg/day, respectively (Hsu et al. 2016; Parra-Forero et al. 2019).

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 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. 2014a). An MRL based on these studies would be identical to the 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 an MRL of 0.0001 mg/kg/day.

Agency Contacts (Chemical Managers): Rae T. Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** DEHP
CAS Numbers: 117-81-7
Date: January 2022
Profile Status: Final
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 (Table A-4), but the lowest identified candidate POD values were several orders of magnitude greater than the POD used to derive the intermediate-duration MRL. Therefore, any MRL derived based on available chronic data would be higher than the derived intermediate MRL and may not be protective of developmental effects.

Table A-4. Summary of Lowest LOAELs for Chronic-Duration Oral Exposure to DEHP

Species	Duration (route)	NOAEL/LOAEL (mg/kg/day) NOAEL	LOAEL	System: effect	Reference
SV/129 mouse	22 months (F)	ND	9.5	***Renal:*** mild glomerulonephritis, cell proliferation, proteinuria	Kamijo et al. 2007
Sprague-Dawley rat	104 weeks (F)	ND	14	***Reproductive:*** inhibition of spermatogenesis and general tubule atrophy (magnitude not reported)	Ganning et al. 1991
F344 rat	104 weeks (F)	5.8	29	***Reproductive:*** testicular toxicity (aspermatogenesis)	David et al. 2000a

DEHP = di(2-ethylhexyl)phthalate; (F) = feed; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ND = not determined

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. 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
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

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 draft toxicological profile for DEHP released for public comment in DEHP; thus, the literature search was restricted to studies published between September 2015 and June 2020. The following main databases were searched in June 2020:

- 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, Medical Subject Headings (MeSH) headings, and keywords for DEHP. The query strings used for the literature search are presented in Table B-2.

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.

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, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

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

Table B-2. Database Query Strings

Database search date	Query string
	"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 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?)

Table B-2. Database Query Strings

Database search date	Query string
	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?)
	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

Table B-2. Database Query Strings

Database search date	Query string
	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 SAVE TEMP L48 DEHP/A D SCAN L48

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 "Sansocizer R 8000" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects, 2017, 2016, 2015, 2014, 2013, 2012

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
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.

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 1,578
- Number of records identified from other strategies: 80
- Total number of records to undergo literature screening: 1,658

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.

- Number of titles and abstracts screened: 1,648
- Number of studies considered relevant and moved to the next step: 618

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.

- Number of studies undergoing full text review: 618
- Number of studies cited in the pre-public draft of the toxicological profile: 786
- Total number of studies cited in the profile: 1,064

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).

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 2020.
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

[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
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	Thyroid: criteria applied
	Endpoints other than thyroid: all studies included
Immunological	Allergy and asthma endpoints: criteria applied
	Nonspecific inflammatory markers: not included
Neurological	All studies included
Reproductive	Criteria applied
Developmental	Criteria applied
Other noncancer	Criteria applied (diabetes/altered glucose homeostasis)
Cancer	All studies included

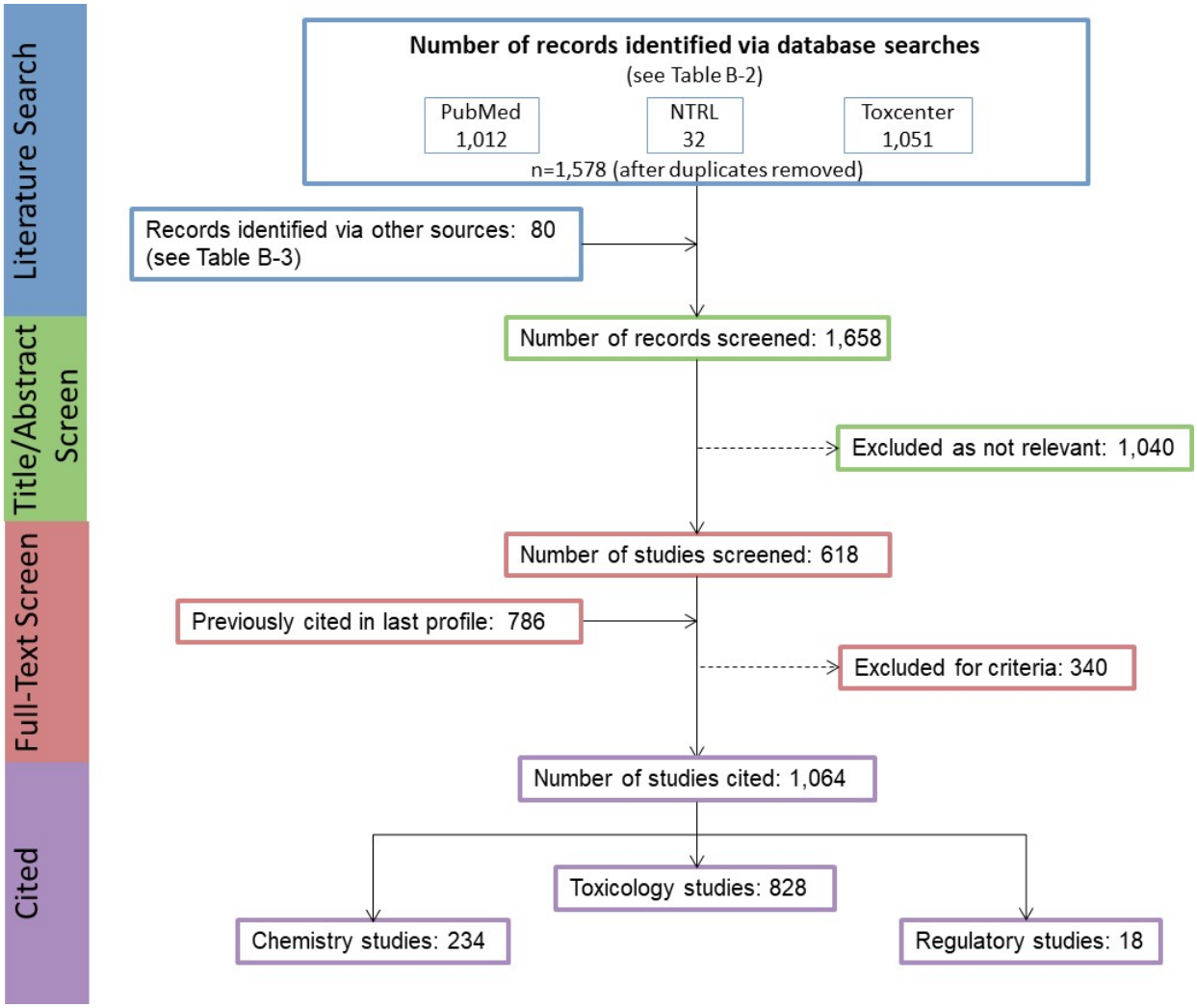
In addition, for health outcomes with robust databases that included cohort as well as case-control or cross-sectional studies, only those studies in which exposure was measured prior to outcome determination (cohort studies) were included. For endpoints with fewer studies, all study designs were considered.

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. June 2020 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), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), 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.

(12) 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.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) 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.

(15) 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).

(16) 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.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

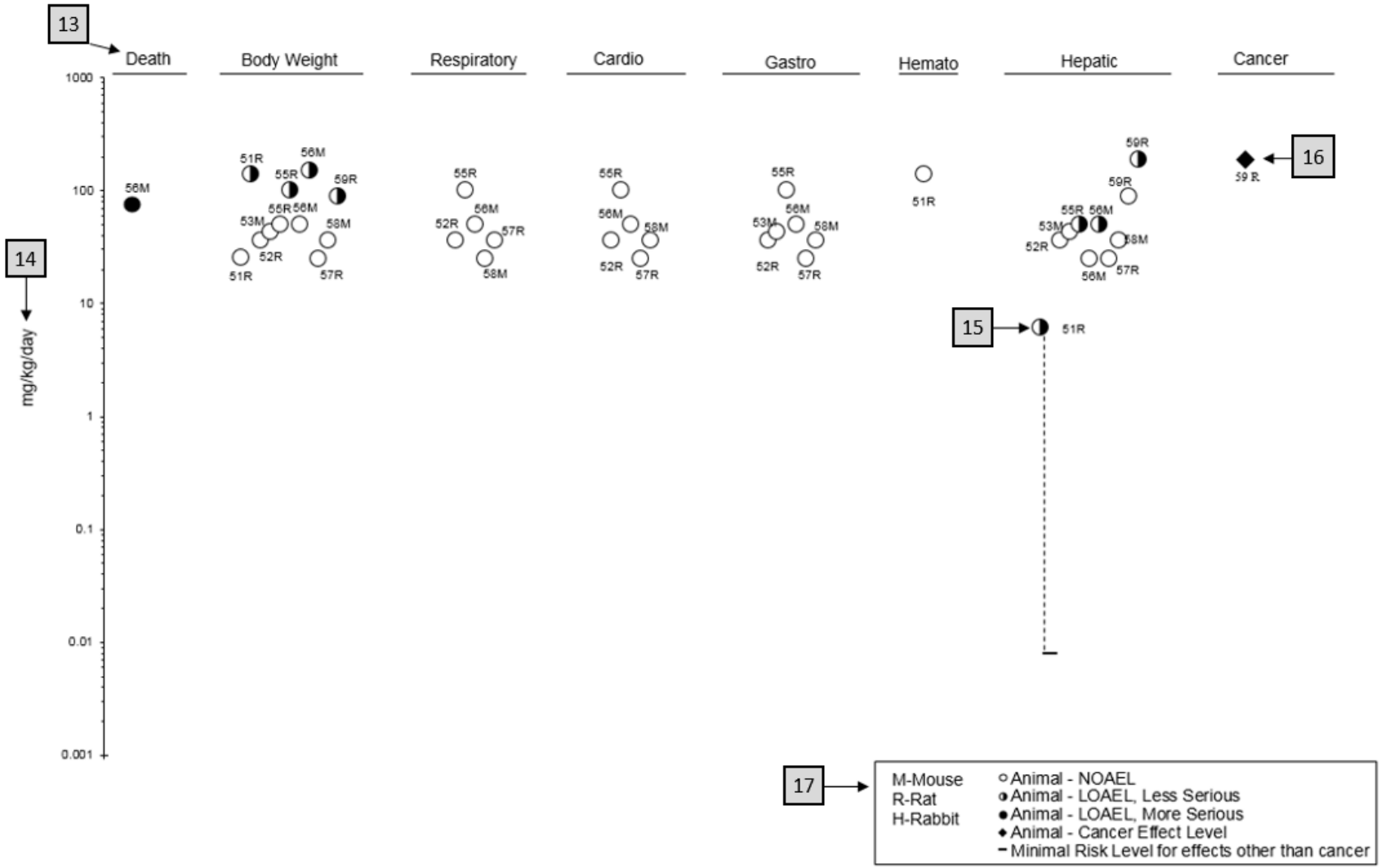
Figure key[a] (2)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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 (10)									
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.

(11) [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

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

https://www.atsdr.cdc.gov/emes/health_professionals/index.html for more information on resources for clinicians.

Managing Hazardous Materials Incidents is a 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.html).

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
SLOAEL	serious lowest-observed-adverse-effect level
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