CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

DEHP is a widely-used chemical that enters the environment predominantly through disposal of industrial and municipal wastes in landfills. To a much lesser extent, it is volatized into air (from industrial and end uses of DEHP), carried in wastewater from industrial sources, and in effluent from municipal wastewater treatment plants (Bauer and Herrmann 1997; Clara et al. 2010; EPA 1981). It tends to sorb strongly to soils and sediments and to bioconcentrate in aquatic organisms (Staples et al. 1997; Wolfe et al. 1980a); however, potential for DEHP to biomagnify in the food chain is expected to be minimized by metabolism (EPA 1979; Johnson et al. 1977; Mackintosh et al. 2004; Staples et al. 1997; Wofford et al. 1981). Biodegradation can occur under aerobic conditions (Sugatt et al. 1984). Sorption, bioaccumulation, and biodegradation are likely to be competing processes, with the dominant fate determined by local environmental conditions. DEHP is found at low levels (<5 ng/m³) in ambient air (Eisenreich et al. 1981; Ligocki et al. 1985a). It is very difficult to determine these low levels accurately since DEHP is ubiquitously present in laboratory equipment, potentially leading to false identification of elevated phthalate concentrations due to sample contamination (Howard et al. 1985).
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The principal route of human exposure to DEHP is oral. In adults and children, ingestion of food (including food from containers that leach DEHP) accounts for approximately 95% of total oral exposure, with the remaining exposure attributed to dust ingestion (Clark et al. 2011). In toddlers and infants, ingestion of food and dust particles containing DEHP have approximately equal contributions to total oral DEHP intake (Clark et al. 2011). Occupational exposures may be significant in some settings. For all age groups, the highest exposures to DEHP result from medical procedures such as blood transfusions (upper bound limit of 8.5 mg/kg/day) or hemodialysis (upper bound limit of 0.36 mg/kg/day), during which DEHP may leach from plastic equipment directly into the blood (FDA 2001). Exposures of neonatal children to DEHP can be especially high as a result of some medical procedures (Doull et al. 1999; FDA 2001; Huber et al. 1996). For example, upper-bound doses of DEHP have been estimated to be as high as 2.5 mg/kg/day during total parenteral nutrition (TPN) administration and 14 mg/kg/day during extracorporeal membrane oxygenation (ECMO) procedures (FDA 2001). These historical values may not apply to current exposures.

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

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

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

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

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

- Altered immune responses
- Developmental effects (altered glucose homeostasis and impaired development/function of the reproductive, renal, hepatic, and nervous systems)
- Male and female reproductive effects in post-pubertal animals (altered hormones, testicular toxicity, male infertility)
- Liver and kidney toxicity
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Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to DEHP

<table>
<thead>
<tr>
<th>Concentration in Air (ppm)</th>
<th>Effects in Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>Intermediate: Histopathological changes in lung</td>
</tr>
<tr>
<td>21</td>
<td>Acute: Developmental effects (visceral retardations)</td>
</tr>
<tr>
<td>19</td>
<td>Acute: Altered respiratory function</td>
</tr>
<tr>
<td>0.8</td>
<td>Intermediate: Enhanced allergic immune responses</td>
</tr>
<tr>
<td>0.3</td>
<td>Intermediate: Developmental effects (male and female reproductive development)</td>
</tr>
<tr>
<td>0.0002 ppm</td>
<td>Provisional Intermediate MRL</td>
</tr>
</tbody>
</table>

***DRAFT FOR PUBLIC COMMENT***
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#### Figure 1-2. Health Effects Found in Animals Following Oral Exposure to DEHP

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Effects in Animals</th>
</tr>
</thead>
</table>
| 1,000-5,000      | Acute: Death; renal; neurological; reproductive (female)  
                  Intermediate: Death; respiratory  
                  Chronic: Gastrointestinal |
| 500-789          | Acute: Body weight (decrease); hepatic; developmental (respiratory system)  
                  Chronic: Body weight (decrease); endocrine; developmental (female reproductive system) |
| 140-375          | Intermediate: Body weight (decrease); hematological  
                  Chronic: Death; hepatic; cancer |
| 91-113           | Acute: Developmental (death, renal system)  
                  Intermediate: Renal; neurological; reproductive (female); developmental (death, musculoskeletal, respiratory system) |
| 6-50             | Acute: Reproductive (male); developmental (decreased body weight; hepatic, reproductive systems)  
                  Intermediate: Hepatic; altered glucose homeostasis; reproductive (male)  
                  Chronic: Renal, reproductive (male) |
| 0.03-3           | Acute: Developmental (altered glucose homeostasis)  
                  Intermediate: Body weight (increase); immunological (allergy); developmental (body weight; altered glucose homeostasis; hepatic, renal, neurological; reproductive systems); other noncancer (increased adipose tissue) |

0.003 mg/kg/day  
0.0001 mg/kg/day  
Provisional Acute MRL  
Provisional Intermediate MRL
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Immune Effects. Limited human data provide inconsistent findings regarding increased risk of asthma, wheeze, and elevated immunoglobulin E (IgE) levels in childhood (Gascon et al. 2015a; Ku et al. 2015; Wang et al. 2014). In animals, repeated exposure to DEHP had an adjuvant effect on the mouse immune system response to the allergen ovalbumin (OVA) in sensitized animals at oral doses ≥0.03 mg/kg/day (lowest dose evaluated) (Guo et al. 2012; Han et al. 2014; Yang et al. 2008) and after exposure to air concentrations of 0.81 ppm, but not concentrations up to 0.11 ppm (Larsen et al. 2007). In these studies, enhanced immune responses included increases in immune cells in bronchoalveolar lavage (BAL) fluid and lymph nodes, immunoglobulins, cell infiltration and airway remodeling in the lungs, and airway responsiveness.


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. 2008).

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

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

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

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

Epidemiological data on potential female reproductive effects following exposure to DEHP are limited. In rodents, there are some data suggesting that the female reproductive system may be susceptible to
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DEHP toxicity. Decreased fertility was reported in females in a cross-over mating study in mice at doses \( \geq 130 \text{ mg/kg/day} \) (Lamb et al. 1987; Morrissey et al. 1988; NTP 1984). However, cross-over mating trials in rats did not indicate decreased female fertility at doses up to 659 mg/kg/day (Blystone et al. 2010; NTP 2005). In pregnant animals, increased resorptions, postimplantation loss, and/or complete litter loss were observed in some studies. The lowest gestational exposure levels associated with these effects are 500 mg/kg/day in rats (Dalsenter et al. 2006) and 95 mg/kg/day in mice (Price et al. 1988b).

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

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

Additional hepatic effects (centrilobular necrosis and inflammation, hepatocyte cytoplasmic eosinophilia, bile duct lesions, altered foci) were observed in some rodent studies, but LOAEL doses generally exceeded 1,000 mg/kg/day (Berman et al. 1995; Exxon Chemical Americas 1990; Schilling et al. 2001). Increased incidences of hepatocellular eosinophilia were reported in F1 rats in one 2-generation study at doses \( \geq 340 \text{ mg/kg/day} \) (Schilling et al. 2001), but not at doses up to 1,040 mg/kg/day in another 2-generation study (Schilling et al. 1999).
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Renal Effects. Limited data are available in humans. Human studies show no differences in serum urea or creatinine levels in workers exposed to DEHP (Wang et al. 2015) or children exposed to DEHP via contaminated food (Wu et al. 2013). However, two studies suggest increases in the ratio of albumin to creatinine (ACR) in urine with increasing levels of DEHP metabolites in urine (Trasande et al. 2014; Tsai et al. 2016).

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

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

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

The carcinogenic potential of DEHP has been evaluated in several chronic-duration oral studies in rats and mice. Studies in F344 rats and B6C3F1 mice have consistently reported increased incidences of liver
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tumors following chronic oral exposure to DEHP at doses >350 mg/kg/day (Cattley et al. 1987; David et al. 1999, 2000a, 2000b; Hayashi et al. 1994; Kluwe et al. 1982a, 1982b, 1985; NTP 1982; Rao et al. 1987, 1990). Only David et al. (1999, 2000a) reported an increased incidence of hepatocellular tumors in male F344 rats at lower doses, observing a dose-related increase in tumors at dietary doses ≥147 mg/kg/day, but not ≤29 mg/kg/day (David et al. 1999, 2000a). There is limited evidence of an increased incidence of pancreatic adenomas following chronic exposure to DEHP; however, these tumors were only observed in male F344 rats at high dose levels (≥789 mg/kg/day) (David et al. 2000a; Rao et al. 1990). Additionally, one study reported a significant increase in the incidence of rats with any Leydig cell tumor (unilateral, bilateral, or multifocal) in Sprague-Dawley rats following lifetime exposure to DEHP at doses of 300 mg/kg/day (Voss et al. 2005).

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

1.3 MINIMAL RISK LEVELS (MRLs)

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

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

<table>
<thead>
<tr>
<th>Acute (ppm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>19</td>
</tr>
<tr>
<td>Developmental</td>
<td>21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate (ppm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental</td>
<td>0.3</td>
</tr>
<tr>
<td>Immunological</td>
<td>0.81</td>
</tr>
<tr>
<td>Body weight</td>
<td>1.6</td>
</tr>
</tbody>
</table>

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

The provisional MRL values are summarized in Table 1-1.
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**Figure 1-4. Summary of Sensitive Targets of DEHP – Oral**

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

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

**Acute (mg/kg/day)**

- Developmental: 1
- Reproductive: 10

**Intermediate (mg/kg/day)**

- Immunological: 0.03
- Developmental: 0.04
- Reproductive: 10

**Chronic (mg/kg/day)**

- Renal: 9.5
- Reproductive: 14
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#### Table 1-1. Minimal Risk Levels (MRLs) for DEHP\(^a\)

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

\(^a\)See Appendix A for additional information.

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