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

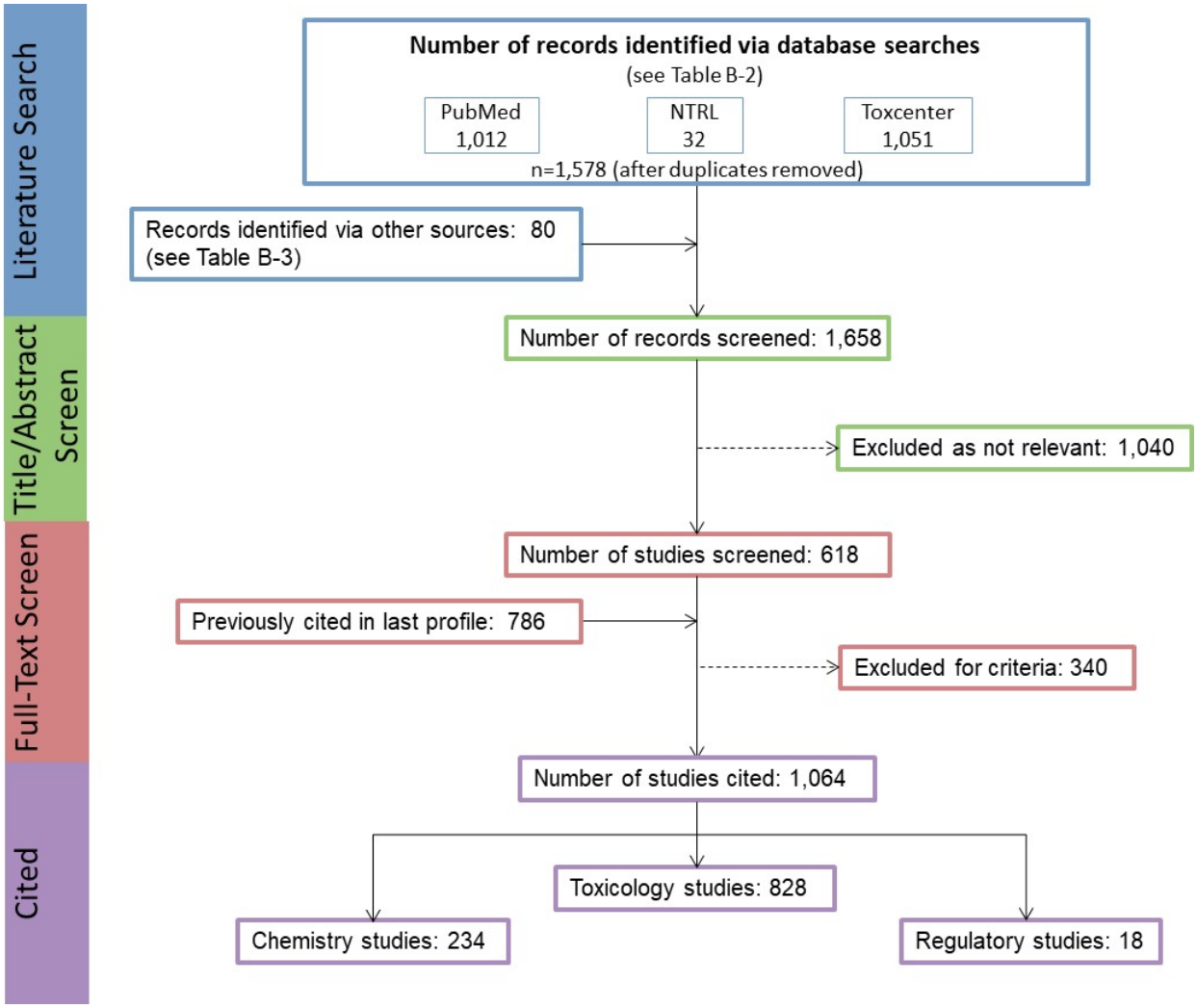
In addition, for health outcomes with robust databases that included cohort as well as case-control or cross-sectional studies, only those studies in which exposure was measured prior to outcome determination (cohort studies) were included. For endpoints with fewer studies, all study designs were considered.

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)

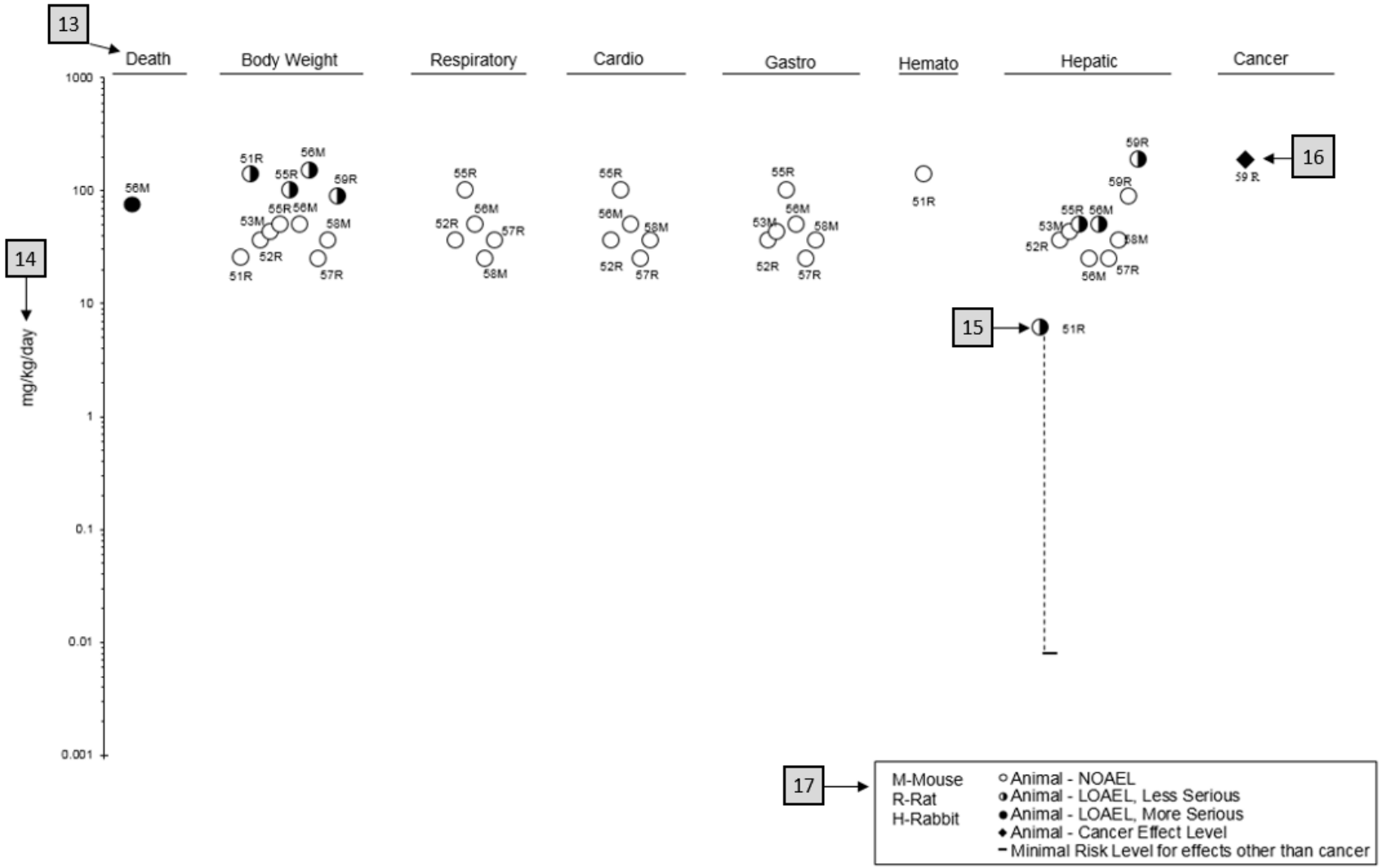
Figure key[a] (2)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 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