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Provisional Peer-Reviewed Toxicity Values for

Diundecyl Phthalate
(CASRN 3648-20-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
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U.S. Environmental Protection Agency
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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR DIUNDECYL PHTHALATE (CASRN 3648-20-2)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Diundecyl phthalate (DUP) (CASRN 3648-20-2) is a widely used chemical intermediate in the synthesis of various industrial chemicals. It is a primary plasticizer for polyvinyl chloride formulations and is used in car interiors, perfumes, and cosmetics. It is listed as a high production volume chemical (NLM, 2009). DUP is a clear viscous fluid and stable under room conditions. The chemical structure of DUP is depicted in Figure 1, and its molecular formula is C_6H_4 1,2 $[COO(CH_2)_{10}CH_3]_2$ or $C_{30}H_{50}O_4$. Some physicochemical properties of DUP are provided in Table 1.

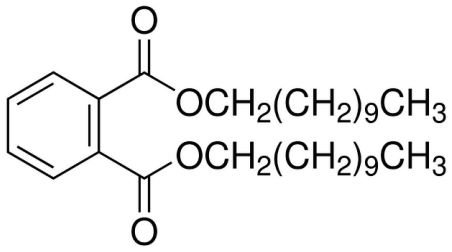

Figure 1. Chemical Structure of Diundecyl Phthalate

Table 1. Physicochemical Properties of Diundecyl Phthalate (CASRN 3648-20-2)

Property (Unit)	Value[a]
Density (g/cm^3)	0.955 at 20°C
Vapor pressure (mm Hg at 25°C)	1.22×10^{-9}
Log octanol-water partition coefficient (unitless)	11.49
Henry's law constant ($atm\text{-}m^3/mol$)	5.60×10^{-5}
Solubility in water (mg/L at 20°C)	1.11
Molecular weight (g/mol)	474.72

[a]Source: NLM (2009), unless otherwise noted.

A summary of available toxicity values for DUP from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Diundecyl Phthalate (CASRN 3648-20-2)

Source/Parameter[a]	Value (Applicability)	Notes	Reference
Noncancer			
ACGIH	NV	NA	ACGIH (2013)
ATSDR	NV	NA	ATSDR (2014)
Cal/EPA	NV	NA	(Cal/EPA); Cal/EPA (2015a); Cal/EPA (2014)
NIOSH	NV	NA	NIOSH (2010)
OSHA	NV	NA	OSHA (2011); OSHA (2006)
IRIS	NV	NA	(U.S. EPA)
DWSHA	NV	NA	U.S. EPA (2012a)
HEAST	NV	NA	U.S. EPA (1994)
CARA HEEP	NV	NA	U.S. EPA (1994)
NTP	NV	NA	NTP (2012)
WHO	NV	NA	(WHO)
Cancer			
IRIS	NV	NA	(U.S. EPA)
HEAST	NV	NA	U.S. EPA (2011a)
IARC	NV	NA	IARC (2013)
NTP	NV	NA	NTP (2014)
Cal/EPA	NV	NA	(Cal/EPA); Cal/EPA (2015a); Cal/EPA (2011)
ACGIH	NV	NA	ACGIH (2013)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA Occupational Safety and Health Administration; WHO = World Health Organization.

NA = not applicable; NV = not available.

Literature searches were conducted on sources published from 1900 through December 2014 for studies relevant to the derivation of provisional toxicity values for diundecyl phthalate, CASRN 3648-20-2. The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA's Declassified CBI database, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, IARC, NIOSH, NTP, OSHA, and WHO.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant database for DUP and includes all potentially relevant subchronic-duration studies. The principal study that is chosen to derive provisional toxicity values is identified in bold. Following the table, important aspects of all the studies listed are provided in the study summary section in the same order as in the table, and reference can be made to details provided in Tables 3A and 3B. The phrase "statistical significance," used throughout the document, indicates a p-value <0.05 unless otherwise indicated.

Table 3A. Summary of Potentially Relevant Noncancer Data for Diundecyl Phthalate (CASRN 3648-20-2)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
No Data								
2. Inhalation (mg/m^3)[a]								
No Data								
Animal								
1. Oral (mg/kg-d)[a]								
Short term[d]	**5/5, F344 rat, daily diet for 21 d**	**0, 286, 1,177, or 2,445 (M); 0, 284, 1,101, or 2,086 (F)** **(0, 0.3, 1.2, or 2.5% DUP in the diet in both sexes)**	**Increased absolute and relative liver weights in both sexes.**	**NA (M) 284 (F)**	**119.4 for increased absolute and relative liver weight in males**	**286 (M) 1,101 (F)**	**Barber et al. (1987), BIBRA (1986)**	**TR, PR, PS**
	6/0, S-D rat, daily gavage for 28 d	0 or 500	Sperm effects: Decreased sperm counts, sperm motility, sperm curvilinear velocity, sperm straightness, and sperm linearity Serum chemistry: Increased alkaline phosphatase, and glutamate oxaloacetate	NA	NDr	500	Kwack et al. (2009)	PR
Chronic[f]	ND							
Developmental toxicity	0/20−22, S-D rat, daily gavage GD 6−20	0, 250, 500, or 1,000	Maternal: NA Fetal: Increased fetal malformation (supernumerary 14th rib)	Maternal: 1,000 Fetal: 250	Maternal: NDr Fetal: NDr	Maternal: NA Fetal: 500	Saillenfait et al. (2013) (LOAEL with minimal significance)	PR
Carcinogenicity	ND							

Table 3A. Summary of Potentially Relevant Noncancer Data for Diundecyl Phthalate (CASRN 3648-20-2)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
2. Inhalation (mg/m^3)[a]								
Subchronic[e]	ND							
Chronic[f]	ND							
Reproductive/ Developmental	ND							
Carcinogenicity	ND							

[a]Dosimetry: NOAEL, BMDL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-d) for oral noncancer effects.
[b]Notes: PS = principal study, indicated by bold text; PR = peer reviewed; TR = technical report.
[c]Acute = exposure for ≤24 h (U.S. EPA, 2002).
[d]Short-term = repeated exposure for >24 h ≤ 30 d (U.S. EPA, 2002).
[e]Long-term (Subchronic) = repeated exposure for >30 d ≤ 10% lifespan for humans (more than 30 days up to approximately 90 days in typically used laboratory animal species). (U.S. EPA, 2002).
[f]Chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species). (U.S. EPA, 2002).

GD = Gestation Day; NA = not applicable; ND = no data; NDr = not determined; S-D = Sprague-Dawley.
M and F in the parentheses denote male and female, respectively.

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Table 3B. Summary of Potentially Relevant Cancer Data for Diundecyl Phthalate (CASRN 3648-20-2)								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry**	**Critical Effects**	**NOAEL**	**BMDL**	**LOAEL**	**Reference (Comments)**	**Notes**
Human								
1. Oral (mg/kg-d)								
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Carcinogenicity	ND							
Animal								
1. Oral (mg/kg-d)								
Carcinogenicity	ND							
2. Inhalation (mg/m^3)								
Carcinogenicity	ND							

ND = no data.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

No studies have been identified.

Other Exposures

Medeiros et al. (1999) evaluated the skin sensitization response to DUP in an irritation test and human repeated insult patch test (HRIPT) using the modified Draize procedure (Draize, 1959). The irritation test was conducted after a single 24 hours occluded patch exposure to DUP in 15 subjects (14 females and 1 male). Evaluations were conducted 30 minutes and 24 hours after patch removal. No significant irritation was observed in any of the subjects. The HRIPT test was conducted after repeated applications (up to nine times) of DUP to the same skin site with a contact period of 24 hours per application. Following a 10- to 17-day rest period, the challenge phase was initiated on the 6th week, and DUP was again applied for 24 hours. Dermal reactions were scored 48 and 72 hours after each application. Out of a 128 total test subjects (both males and females) enrolled in the study, only 104 test subjects (both males and females) completed the study. No evidence of dermal irritation or sensitization was observed, indicating the lack of skin sensitization potential for DUP.

ANIMAL STUDIES

Oral Exposure

Short-term-Duration Studies

The short-term database includes two studies: a 21-day study in rats (Barber et al., 1987; BIBRA, 1986) and a 28-day study in rats (Kwack et al., 2009).

Barber et al. (1987); BIBRA (1986)

DUP (purity unknown) was fed to a group of five male and five female F344 rats at dietary levels of 0 % (control), 0.3 % (low dose), 1.2 % (mid dose), or 2.5% (high dose) for 21 days (doses of 0, 286, 1,177, or 2,445 mg/kg-day, respectively, in males and 0, 284, 1,101, or 2,086 mg/kg-day, respectively, in females are calculated based on body weight and food intake measurements provided in the study) (Barber et al., 1987; BIBRA, 1986). All rats were weighed individually 3 days before the start of treatment (Day −3), on the day treatment began (Day 0), and subsequently twice weekly until the end of the treatment period. Food intakes were measured over the period of days from Day −3 to 0, and continuous intakes were then measured at twice-weekly intervals until the day preceding necropsy. The rats were sacrificed after an overnight fast and blood was collected to determine serum triglyceride and cholesterol levels. The liver, kidneys, and testes were weighed and preserved for histological examination. In addition, samples of liver were processed for electron microscopy examination of the peroxisomes; for histochemical demonstration of neutral fat; and for biochemical determination of cyanide-insensitive palmitoyl-CoA oxidation, microsomal lauric acid 11- and 12-hydroxylation, and total and microsomal protein levels.

No variations in behavior and food intake were observed that could be considered treatment related throughout the experimental period. The male rats in the high-dose group showed a statistically and biologically (>10% change) significant reduction in body weight, whereas males in the other two treatment groups did not show any statistically significant

changes compared to control. Female rats in the mid- and high-dose groups showed a statistically significant reduction (but less than 10% change) in body weight compared to control (see Table B-1).

In the mid-dose group males, three rats had pale livers, and in high-dose group males, two rats had a pale liver. In the female rats, an enlarged liver was seen in one rat each in the mid-dose and high-dose group. Both sexes showed a statistically and biologically (>10% change) significant increase in absolute and relative liver weights in the mid-dose and high-dose groups. Although no statistically significant increase of absolute and relative liver weights were observed in the low-dose groups of both sexes, DUP treated male rats showed more than 10% change in both absolute and relative liver weights compared to control. In male rats, absolute kidney weights were statistically and biologically (>10% change) significantly lower in the mid- and high-dose groups, whereas no statistically significant difference in relative kidney weights was observed in any of the treated male groups (see Table B-1). In female rats, no statistically significant difference was observed in the absolute kidney weights of any of the treated females, but relative kidney weights were statistically significantly higher in the mid- and high-dose groups. The high-dose treated group showed a more than 10% increase compared to control (see Table B-1). Since there is no change in the absolute kidney weight of females, the increase in relative kidney weights of females could be due to a decrease in mean body weights. No statistically significant difference was found in the absolute testes weights of any of the treated groups, but relative testes weights were statistically significantly higher in the mid- and high-dose groups (see Table B-1). The change in relative testes weights (and not in the absolute testes weights) could also be due to a decrease in mean body weights.

In the high-dose group of both sexes, there was a moderate increase in peroxisomes in both periportal and centrilobular areas of the liver (low- and mid-dose groups were not examined). This was accompanied by changes in peroxisome associated parameters (i.e., increased activities of palmitoyl-CoA oxidation and lauric acid hydroxylation and decreased concentrations of serum triglycerides and cholesterol). A dose-related, statistically significant increase in cyanide-insensitive palmitoyl-CoA oxidation in the mid- and high-dose group of both sexes was observed (see Table B-2). Statistically significant increases in lauric acid 11- and 12-hydroxylase activities were observed at all doses of DUP in males but only at the high dose in females (see Table B-2). Serum triglyceride and total cholesterol concentrations were statistically significantly lower in the mid- and high-dose group in males. In females, however, no statistically significant difference was observed in the treated groups (see Table B-2). Total hepatic protein concentrations were statistically significantly higher in the mid- and high-dose group female rats (biological significance is unknown), but these values in males were similar to control.

In the liver of mid- and high-dose males, an increase in individual cell necrosis and vacuolization of centrilobular hepatocytes were observed (see Table B-3). In the high-dose males, there was also a distention of both smooth and rough endoplasmic reticulum in the centrilobular area. These findings, suggest that DUP is hepatotoxic in the mid- and high-dose groups of male rats. In females, the only effect seen was a deposit of neutral lipid in the centrilobular areas at high dose.

The degree of cytoplasmic basophilia in the liver was reduced in the mid- and high-dose group of both sexes. The study authors considered this change in staining characteristics likely

due to a change in the organelle component and metabolic status of the cell and noted that alterations of this kind have been produced by other compounds that result in increases in smooth endoplasmic reticulum and associated structures. The study authors considered this change in cytoplasmic staining represents evidence of an adaptive change rather than a toxic effect. No pathological abnormalities were detected in the testes (males) or in the kidneys of either sex.

A lowest-observed-adverse-effect level (LOAEL) of 286 mg/kg-day is identified based on increased absolute and relative liver weights in male rats. A no-observed-adverse-effect level (NOAEL) was not identified.

Kwack et al. (2009)

In a 28-day study, DUP (purity unknown) was administered to six male Sprague-Dawley rats daily by gavage (corn oil was used as vehicle) at 0 (control) or 500 mg/kg-day (Kwack et al., 2009). The control group received only corn oil. The animals were observed for immediate signs of toxicity and examined once a day throughout the experimental period to record any delayed acute effects and mortality. All rats were weighed on Days 0, 3, 6, 9, 12, 15, 18, 21, 24, and 28. Food consumption was measured at the beginning of treatment and twice per week during the 28-day treatment period. The rats were sacrificed under anesthesia, and heart, lung, liver, kidneys, adrenal glands, spleen, thymus, thyroid glands, testes, and epididymis were weighed, and organ-to-body-weight ratios were calculated. During sacrifice, blood was collected for hematology analysis while serum separated from the collected blood was used for serum biochemistry analysis. Hematology analysis included red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, platelet count, and white blood cell count. Serum biochemistry parameters included calcium, potassium, sodium, albumin, blood urea nitrogen, triglyceride, creatinine, glucose, total cholesterol, total bilirubin, total protein, alkaline phosphatase (ALP), glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT), and γ-glutamyl transferase (GGT). Urinalysis included occult blood, pH, protein, urobilinogen, glucose, nitrite, bilirubin, ketone bodies, leukocytes, and urine specific gravity. The right cauda epididymis was used for sperm count analysis, and the left cauda epididymis was used to evaluate sperm motility. The sperm motion parameters included percentage of motile sperm, average path velocity (VAP), straight-line velocity (VSL), curvilinear velocity (VCL), amplitude of the lateral head displacement (ALH), beat cross frequency (BCF), straightness (STR), and linearity (LIN).

No treatment-related statistically significant reductions in body weight, relative organ weights, or food consumption were observed throughout the experiment. Also, no statistically significant changes in any of the hematological parameters and urinalysis were observed. A statistically significant increase in serum total protein (biological significance is unknown), GOT, and ALP levels (9%, 50%, and 80%, respectively) in the treatment group compared to the control group was observed. A statistically significant decrease in the mean sperm count, mean sperm motility, VCL, STR, and LIN (28%, 63%, 17%, 19%, and 20%, respectively) in the treatment group compared to the control group was observed (see Table B-4).

The dose of 500 mg/kg-day is a LOAEL for decreased sperm counts, sperm motility VCL, STR, and LIN as well as increased serum ALP, and GOT levels in rats exposed by gavage for 28-days. A NOAEL was not identified in this study.

Chronic-Duration Studies
No studies have been identified.

Reproductive/Developmental Studies
Saillenfait et al. (2013)
Reproductive and developmental toxicity were evaluated in Sprague-Dawley rats. Groups of 20−24 female rats were housed overnight with adult males. The presence of sperm in the vaginal smear was considered to be GD 0. Groups of 20−22 pregnant rats were gavaged once daily with 0, 250 (low dose), 500 (mid dose), or 1,000 (high dose) mg/kg-day of DUP (>98% purity) in olive oil between Gestation Days (GD) 6−20 (Saillenfait et al., 2013). The animals were observed daily for any obvious signs of toxicity. Food consumption was recorded every 3 days starting on GD 6. Maternal body weights were recorded on GD 0, 6, 9, 12, 15, 18, and 21. Dams were sacrificed on GD 21 and the uterine horns were removed, and weighed. The number of implantation sites, resorptions, dead and live fetuses from the uterus, and the number of corpora lutea in each ovary were recorded. All live fetuses were individually weighed, sexed, evaluated for external anomalies, and measured for anogenital distance (AGD). Half of the live fetuses from each litter were examined for internal soft tissue changes and the other half was examined for skeletal malformations.

No treatment-related clinical signs, mortalities, or statistically significant changes in mean maternal body weights, gravid uterine weights, or maternal food consumption were observed throughout the study (see Table B-5). No statistically significant differences were observed in the number of corpora lutea or incidence of preimplantation loss. The numbers of implants were statistically significantly lower than the control at the low and mid doses but not at the high dose (see Table B-6). However, no effects on postimplantation loss, resorptions, live fetuses, fetal sex ratio (percent male fetuses per litter), or fetal body weights were observed.

No statistically significant changes in AGD were observed in any of the treatment groups of either sex. However, after adjustment with the cubic root of fetal body weight, a statistically significant decrease was observed in the mid-dose group of male fetuses. Isolated cases of malformations occurred in one fetus at low dose (omphalocele), in one fetus at mid dose (club foot) and in one fetus at high dose (diaphragmatic hernia). The study authors considered these cases incidental and not treatment related (see Table B-7). A statistically significant increase in the number of fetuses with incidence of supernumerary 14^{th} ribs was observed in the mid-, and high-dose groups. The mean percentage of affected fetuses per litter in the control, low-, mid-, and high-dose group was 10.3, 20.8, 46.6, and 25.4, respectively. The study authors reported that the historical olive oil control groups have a range from 6.8 to 19.4% of affected fetuses per litter (no further details were provided in the study). A statistically significant increase in the number of litters with incidence of supernumerary 14^{th} ribs was also observed in the mid-dose group. Among the types of supernumerary 14^{th} ribs, long supernumerary ribs (more than one third of the length of the preceding rib) were observed in one fetus in the low-dose group and in one fetus in the high-dose group. The remaining supernumerary 14^{th} ribs were either pin-point ossification sites (78-88%) or short (less than one third of the length of the preceding rib) in both control and treated groups. These pin-point ossification sites and short supernumerary ribs are transient and tends to disappear in subsequent development, and therefore the incidence of supernumerary 14^{th} ribs observed in this study may not be considered as strong evidence for a developmental toxic endpoint. In addition, although no clear dose-response relationship was observed, the study authors pointed out that a relationship to treatment cannot be ruled out

(see Table B-7). No statistically significant changes in the incidences of any other skeletal variations were observed. The elevated number of ossified caudal vertebral centra in the DUP-treated groups compared to control was not considered toxicologically meaningful by the study authors. These data indicate a maternal NOAEL of 1,000 mg/kg-day; a maternal LOAEL was not identified. The developmental NOAEL is 250 mg/kg-day, with a LOAEL (with minimal biological significance) of 500 mg/kg-day, based on the increased incidence of the supernumerary 14th ribs in rats.

Reproductive Studies

No studies have been identified.

Carcinogenicity Studies

No studies have been identified.

Inhalation Exposure

No studies have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tables 4A and 4B summarize other studies conducted with DUP that are not appropriate for selection of a point of departure (POD) for derivation of a provisional RfD (p-RfD) but provide supportive data.

Table 4A. Summary of Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute/Short-term study	0 or 0.5 mL DUP (purity not reported) applied to the trunk and lateral areas of intact skin of male albino rabbits (6/group) for 24 h. Observations were made after 24 and 48 h of application	Mild to very slight erythema and no edema was observed after 24 and 48 h	DUP produced mild to no skin irritation	DuPont (1983)
Metabolism/Toxicokinetics	^{14}C-labeled Dimethyl, diethyl, di-n-butyl, di-n-octyl, di-(2-ethylhexyl), and dicyclohexyl phthalates were incubated with small intestinal mucosal cells and hepatic cells of human (no sex mentioned), male S-D rats, male albino ferrets, and male olive baboons for evaluation of esterase activities of phthalate diesters	All phthalate diesters were hydrolyzed in both small intestinal mucosal cells and hepatic cells of all four species	Phthalate diesters undergo hydrolysis in the gastrointestinal tract with subsequent absorption and further metabolism of the resultant monoester and alcohol moieties in the liver	Lake et al. (1977); Albro and Moore (1974); Albro et al. (1973)
	Both diesters and monoesters of ^{14} C-labeled Dimethyl, di-n-butyl, and di-(2-ethylhexyl) phthalates were incubated in an everted gut sac preparation of male S-D rat for evaluation of metabolism and absorption of phthalate diesters	All phthalate diesters were hydrolyzed in the small intestinal mucosa to monoesters. Monoesters were absorbed in significantly greater quantity than corresponding diesters	Phthalate diesters undergo hydrolysis to monoesters and absorbed in the rat small intestine	White et al. (1980)

Table 4B. Summary of Diundecyl Phthalate (CASRN 3648-20-2) Genotoxicity

Endpoint	Test System	Dose Concentration	Results		Comments	References
			Without Activation[a]	With Activation[a]		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation (Ames test)	*Salmonella typhimurium* strains TA 98, 100, 1535, and 1537 in the presence or absence of S9	10−10,000 µg/plate	–	–	No positive results were observed	Zeiger et al. (1985); NTP (1983)
Genotoxicity studies in mammalian eukaryotic cells—in vitro						
Forward mutation	L5178Y mouse lymphoma cells in vitro	1,000−8,000 µg/mL (with activation); 2,000−10,000 µg/mL (without activation)	–	–	No positive results were observed	Hazleton Biotechnologies Company (1986)
Cell transformation	Balb/3T3 mouse cells in vitro	4,000−40,000 µg/mL	–	Not carried out	No positive results were observed	Barber et al. (2000); Hazleton Biotechnologies Company (1986)

[a](+) = positive; (–) = negative

Acute/Short-Term Study

DuPont (1983)

Application of 0.5 mL DUP (purity unknown) for 24 hours on the intact skin of trunk and lateral areas of male albino rabbits (6/group) produced only mild to no skin irritation after 24 and 48 hours of treatment (DuPont, 1983).

Toxicokinetics

Lake et al. (1977); Albro and Moore (1974); Albro et al. (1973); White et al. (1980)

There are no data on the toxicokinetics of DUP. However, a few studies are available on the toxicokinetics of other phthalate diesters. In general, phthalate diesters undergo partial hydrolysis in the gastrointestinal tract with subsequent absorption and further metabolism of the resultant monoester and alcohol moieties. This was demonstrated in an in vitro study using hepatic and intestinal preparations from human, rat, baboon, and ferret (Lake et al., 1977; Albro and Moore, 1974; Albro et al., 1973). Esterases within the mucosal epithelium actively hydrolyse phthalate diesters to the monoesters; thus, very little intact diester is thought to reach the systemic circulation as demonstrated using an everted gut-sac preparation from the rat small intestine (White et al., 1980).

Genotoxicity

Hazleton Biotechnologies Company (1986); Barber et al. (2000)

DUP did not induce a statistically significant increase in the mutant frequency in an in vitro L5178Y cell mouse lymphoma assay when incubated with DUP concentrations between 1,000 and 8,000 µg/mL in culture media with S9 metabolic activation and between 2,000 and 10,000 µg/mL of culture media without S9 metabolic activation system (Hazleton Biotechnologies Company, 1986). DUP did not induce a statistically significant increase in the numbers of transformation foci of BALB/3T3 cells when incubated in DUP concentrations between 4,000 and 40,000 µg/mL of culture media without S9 metabolic activation (Barber et al., 2000; Hazleton Biotechnologies Company, 1986).

Zeiger et al. (1985); NTP (1983)

DUP was not mutagenic in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 both in the presence and absence of S9 metabolic activation when incubated with DUP at concentrations up to 10,000 µg/plate (Zeiger et al., 1985; NTP, 1983).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present a summary of noncancer reference and cancer values, respectively. IRIS data are indicated in the table, if available.

Table 5. Summary of Noncancer Reference Values for Diundecyl Phthalate (CASRN 3648-20-2)

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD_{HED}	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M	Increased relative liver weight in male rats	3×10^{-2}	$BMDL_{10}$	28.7	1,000	(Barber et al. (1987); BIBRA (1986))
Chronic p-RfD (mg/kg-d)	NDr						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

NDr = not determinable.

Table 6. Summary of Cancer Values for Diundecyl Phthalate (CASRN 3648-20-2)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr			
p-IUR (mg/m^3)	NDr			

NDr = not determinable.

DERIVATION OF ORAL REFERENCE DOSES

The animal studies provide sufficient information to derive a subchronic provisional reference dose (p-RfD) for DUP. The oral toxicity database consists of two short-term-duration studies in rats and one reproductive/developmental study in rats. Table 3A summarizes the noncancer exposure-response data from available oral studies.

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The short-term-duration studies (Kwack et al., 2009; Barber et al., 1987; BIBRA, 1986), and the reproductive/developmental study (Saillenfait et al., 2013) are considered as potential key studies on which to base the subchronic p-RfD for DUP.

A LOAEL of 286 mg/kg-day for increased absolute and relative liver weights in male rats was identified in the 21-day dietary study (Barber et al., 1987; BIBRA, 1986). A LOAEL of 500 mg/kg-day for decreased sperm counts, sperm motility, VCL, STR, and LIN as well as increased serum ALP, and GOT was identified in the 28-day gavage study Kwack et al. (2009). Although a LOAEL of 500 mg/kg-day for supernumerary 14th ribs was observed in the Saillenfait et al. (2013) reproductive/developmental study, the supernumerary 14th ribs tend to disappear in subsequent development. However, the study authors mentioned that a relationship to treatment cannot be ruled out. Therefore, 500 mg/kg-day is considered as a LOAEL with minimal biological significance, and 250 mg/kg-day as a NOAEL.

The BIBRA (1986) and Barber et al. (1987) studies exposed both sexes of rats to multiple doses of DUP, analyzed multiple organs, and provided adequate information for performing BMD modeling. Although, the changes in liver weights are identified as the most sensitive effect, these studies did not analyze sperm parameters, which were reported by Kwack et al. (2009). The Kwack et al. (2009) study exposed male rats to a single dose of DUP and analyzed multiple organs. Changes in liver enzymes (e.g., significant increase in serum ALP, and GOT) and sperm parameters (e.g., significant decrease in sperm count, motility, VCL, STR, and LIN) are identified as the most sensitive effects for this study. However, the Kwack et al. (2009) study utilized only one test dose (thereby precluding BMD modeling) in one sex, which is not an optimal study design for assessment purposes.

Alterations in liver (NRC, 2008; Ganning et al., 1984) and sperm parameters (Pant et al., 2011; NRC, 2008; Fredricsson et al., 1993) as sensitive endpoints have been reported for several other phthalate esters in both laboratory animals and humans. However, it should be noted that DUP is structurally related to diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP), which are reported to be primarily hepatotoxic (CPSC, 2010a, b; Lington et al., 1997; Lake et al., 1991). In addition, the BIBRA (1986), Barber et al. (1987), and Kwack et al. (2009) studies all identified liver changes as sensitive effects. Furthermore, from the available dose response information, BMD modeling could only be performed for liver effects and not for sperm parameters data. Based on the available hazard and dose response information, the liver seems to be the most consistent and sensitive target organ observed following oral exposure to DUP.

Benchmark dose (BMD) modeling using the U.S. EPA's BMDS (Version 2.2.1) software was conducted for increased absolute and relative liver weights of both sexes from the 21-day rat study (Barber et al., 1987; BIBRA, 1986). Table 7 summarizes NOAEL, LOAEL, BMD and benchmark dose lower confidence limit (BMDL) for these endpoints as well as their PODs.

Table 7. Candidate PODs for Multiple Noncancer Effects Following Subchronic Oral Exposure to Diundecyl Phthalate[a] (CASRN 3648-20-2)

Effect	Dose (mg/kg-d)					
	NOAEL	LOAEL	BMR	BMD	BMDL	POD
Increased absolute liver weight (M)	NA	286	10%	554.8[b]	356.9[b]	356.9
Increased relative liver weight (M)	NA	286	10%	223.4	119.4	119.4
Increased absolute liver weight (F)	284	1,101	10%	371.9	303.1	303.1
Increased relative liver weight (F)	284	1,101	10%	NF	NF	284

[a]Barber et al. (1987); BIBRA (1986).
[b]An adequate fit was achieved when the high dose group was removed.

M and F in the parenthesis denotes male and female respectively.
BMD input data are presented in Appendix B. The curves and BMD output text for increased relative liver weight in male rats are provided in Appendix C.
NA = not applicable, NF = no acceptable model fit.

Based on the modeling results for liver weight changes, the lowest POD is increased relative liver weight in male rats with a $BMDL_{10}$ of 119.4 mg/kg-day. **The BIBRA (1986) and Barber et al. (1987) studies are selected as the principal studies and the $BMDL_{10}$ of 119.4 mg/kg-day based on increased relative liver weight in male rats is chosen as the POD for the derivation of the subchronic p-RfD.**

In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, U.S. EPA endorses body-weight scaling to the 3/4 power ($BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects.

A validated human physiologically based pharmacokinetic (PBPK) model for DUP is not available for use in extrapolating doses from animals to humans. In addition, the selected POD of 119.4 mg/kg-day is based on liver effects, which is not a portal-of-entry or developmental effect. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Following U.S. EPA (2011b) guidance, the POD is converted to a HED through the application of a dosimetric adjustment factor (DAF[1]) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

Where:

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a BW_a of 0.25 kg for rats and a default BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the $BMDL_{10}$ identified in the 21-day rat study yields a POD_{HED} as follows:

$$\begin{aligned} POD_{HED} &= BMDL_{10}\ (mg/kg\text{-}day) \times DAF \\ &= BMDL_{10}\ (mg/kg\text{-}day) \times 0.24 \\ &= 119.4\ (mg/kg\text{-}day) \times 0.24 \\ &= 28.7\ mg/kg\text{-}day \end{aligned}$$

A subchronic p-RfD for DUP is derived by applying an uncertainty factor (UF) of 1,000 to the POD_{HED} of 28.7 mg/kg-day as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= POD_{HED} \div UF_C \\ &= 28.7\ mg/kg\text{-}day \div 1{,}000 \\ &= \mathbf{3 \times 10^{-2}\ mg/kg\text{-}day} \end{aligned}$$

Table 8 summarizes the UFs for the subchronic p-RfD for DUP.

[1]As described in detail in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose (*U.S. EPA, 2011b*)*, rate-related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{-1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

Table 8. UFs for Subchronic p-RfD for Diundecyl Phthalate (CASRN 3648-20-2)

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for remaining uncertainty such as the toxicodynamic differences between rats and humans following oral exposure to DUP. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) as described in the RfD methodology (U.S. EPA, 2011b).
UF_H	10	A UF_H of 10 is applied for intraspecies variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of DUP in humans.
UF_L	1	A UF_L of 10 is not applied because the POD is a BMDL.
UF_S	3	A UF_S of 3 is applied because the duration of the principal study is limited to 21 d.
UF_D	10	A UF_D of 10 is applied because there are only two short term-duration studies in rats and one developmental toxicity study in rats. However, no subchronic studies and two generation reproductive studies were identified.
UF_C	1,000	$UF_C = UF_A \times UF_H \times UF_L \times UF_S \times UF_D$

The confidence of the subchronic p-RfD for DUP is low as explained in Table 9.

Table 9. Confidence Descriptor for Subchronic p-RfD for Diundecyl Phthalate (CASRN 3648-20-2)

Confidence Categories	Designation[a]	Discussion
Confidence in study	L	Confidence in the principal study is low because BIBRA (1986) and Barber et al. (1987) used a medium numbers of animals, and used a short term-duration exposure.
Confidence in database	L	Confidence in the database is low because it includes only two short term-duration studies in rats that are limited in duration and one developmental toxicity study in rats. No two-generation reproductive toxicity studies were identified.
Confidence in subchronic p-RfD	L	The overall confidence in the subchronic p-RfD is low.

[a]L = Low

Derivation of a Chronic Provisional RfD (Chronic p-RfD)

Because no chronic-duration studies exist for DUP and only limited subchronic-duration studies are available, it is inappropriate to derive a chronic p-RfD.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No suitable published studies investigating the effects of subchronic or chronic inhalation toxicity of diundecyl phthalate in humans or animals have been identified.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 10 identifies the cancer WOE descriptor for diundecyl phthalate.

Table 10. Cancer WOE Descriptor for Diundecyl Phthalate (CASRN 3648-20-2)

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	NS	NA	No human carcinogenicity data were identified.
"Likely to Be Carcinogenic to Humans"	NS	NA	No animal carcinogenicity studies were identified.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No animal carcinogenicity studies were identified.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**This descriptor is selected due to the lack of any information on the carcinogenicity of DUP.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	Although the genotoxicity studies were negative, there are no data to indicate that DUP is not carcinogenic.

NA = not applicable; NS = not selected.

MODE-OF-ACTION DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define mode of action as "a sequence of key events and processes starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation" (p. 1−10). Examples of possible modes of carcinogenic action for a given chemical include "mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immunologic suppression" (p. 1−10).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of DUP precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

No screening values are presented.

APPENDIX B. DATA TABLES

Table B-1. Body Weights and Organ Weights of F344 Rats Treated with Diundecyl Phthalate (CASRN 3648-20-2) by Diet for 21 Days[a]

Parameters	Male (mg/kg-d)				Female (mg/kg-d)			
	0	286	1,177	2,445	0	284	1,101	2,086
Mean body weight (g)	222 ± 4.5	224 ± 5.6 (0.90%)[b]	211 ± 3.1 (-4.95%)	194 ± 4.5 *** (-12.6%)	144 ± 1.5	141 ± 3.4 (-2.08%)	134 ± 1.3 *** (-6.94%)	133 ± 2.4 *** (-7.64%)
Absolute liver weight (g)	7.24 ± 0.22	8.05 ± 0.41 (11.2%)	8.94 ± 0.40 ** (23.5%)	8.42 ± 0.35 * (16.3%)	4.36 ± 0.07	4.48 ± 0.11 (2.75%)	5.80 ± 0.24 *** (33.0%)	6.53 ± 0.36 *** (49.8%)
Relative liver weight (g/100 g body weight)	3.26 ± 0.10	3.59 ± 0.10 (10.1%)	4.24 ± 0.18 *** (30.1%)	4.34 ± 0.10 *** (33.1%)	3.02 ± 0.06	3.18 ± 0.06 (5.30%)	4.32 ± 0.15 *** (43.0%)	4.92 ± 0.23 *** (62.9%)
Absolute kidney weight (g)	1.50 ± 0.04	1.50 ± 0.06 (0.00%)	1.34 ± 0.03 * (-10.7%)	1.29 ± 0.03 ** (-14.0%)	1.03 ± 0.01	0.99 ± 0.02 (-3.88%)	1.03 ± 0.04 (0.00%)	1.04 ± 0.02 (0.97%)
Relative kidney weight (g/100 g body weight)	0.68 ± 0.01	0.67 ± 0.02 (-1.47%)	0.64 ± 0.01 (-5.88%)	0.67 ± 0.01 (-1.47 %)	0.71 ± 0.01	0.71 ± 0.02 (0.00%)	0.77 ± 0.02 * (8.45%)	0.79 ± 0.01 ** (11.3%)
Absolute testes weight (g)	2.60 ± 0.07	2.67 ± 0.05	2.65 ± 0.05	2.66 ± 0.05	-	-	-	-
Relative testes weight (g/100 g body weight)	1.17 ± 0.03	1.20 ± 0.02	1.26 ± 0.02 *	1.38 ± 0.03 ***	-	-	-	-

[a]Barber et al. (1987); BIBRA (1986)
[b]Percentage change compared to control. Figures are the means ± standard error for groups of five rats.
*Significantly different from the control at $p < 0.05$.
**Significantly different from the control at $p < 0.01$.
***Significantly different from the control at $p < 0.001$.

Table B-2. Selected Changes in F344 Rats Treated with Diundecyl Phthalate by (CASRN 3648-20-2) Diet for 21 Days[a]

Parameters	Male (mg/kg-d)				Female (mg/kg-d)			
	0	**286**	**1,177**	**2,445**	**0**	**284**	**1,101**	**2,086**
Serum triglycerides (mmol/L)	0.93 ± 0.11	0.77 ± 0.03	0.45 ± 0.03 ***	0.46 ± 0.04 ***	0.59 ± 0.08	0.45 ± 0.02	0.50 ± 0.05	0.50 ± 0.03
Total cholesterol (mmol/L)	2.00 ± 0.13	1.64 ± 0.05	1.34 ± 0.17 ***	1.30 ± 0.10 ***	2.06 ± 0.05	1.84 ± 0.11	1.85 ± 0.04	1.99 ± 0.08
Palmitoyl-CoA oxidation levels in liver (mol/min/mg homogenate protein)	4.0 ± 0.34	5.3 ± 0.18	8.3 ± 0.60 ***	14.5 ± 0.62 ***	5.8 ± 0.47	6.1 ± 0.31	11.3 ± 0.81 ***	19.2 ± 0.47 ***
Lauric acid 11-hydroxylase in liver (mol/min/mg microsomal protein)	0.6 ± 0.04	0.9 ± 0.03 **	1.0 ± 0.10 ***	1.2 ± 0.07 ***	0.4 ± 0.07	0.5 ± 0.03	0.7 ± 0.11	1.3 ± 0.21 ***
Lauric acid 12-hydroxylase in liver (mol/min/mg microsomal protein)	1.1 ± 0.15	2.5 ± 0.14 ***	3.6 ± 0.25 ***	4.4 ± 0.24 ***	0.8 ± 0.07	0.7 ± 0.05	1.2 ± 0.21	2.5 ± 0.20 ***
Total hepatic protein (mg/g liver)	236 ± 4.3	237 ± 3.2	247 ± 7.7	239 ± 4.5	215 ± 2.1	225 ± 3.9	233 ± 3.4 ***	240 ± 3.6 ***
Microsomal protein (mg/g liver)	25.5 ± 1.14	24.4 ± 0.63	23.3 ± 0.61	22.7 ± 1.05	21.2 ± 0.65	19.6 ± 0.77	20.1 ± 0.92	19.6 ± 0.98

[a]Barber et al. (1987); BIBRA (1986)
Figures are the means ± standard error for groups of five rats.
*Significantly different from the control at $p < 0.05$.
**Significantly different from the control at $p < 0.01$.
***Significantly different from the control at $p < 0.00$

Table B-3. Selected Incidence of Histological Liver Changes in F344 Rats Treated with Diundecyl Phthalate by (CASRN 3648-20-2) Diet for 21 Days[a]

Parameters	Male (mg/kg-d)				Female (mg/kg-d)			
	0	**286**	**1,177**	**2,445**	**0**	**284**	**1,101**	**2,086**
Slight increase individual cell necrosis	0/5[b]	0/5	4/5*	5/5*	0/5	0/5	0/5	0/5
Slight cell vacuolization	0/5	0/5	2/5	4/5*	1/5	0/5	0/5	0/5
Moderate cell vacuolization	0/5	0/5	5/5*	3/5	0/5	0/5	0/5	0/5
Reduced cytoplasmic basophilia	0/5	0/5	5/5*	5/5*	0/5	0/5	4/5*	4/5*

[a]Barber et al. (1987); BIBRA (1986)
[b]Number of animals with lesions/number of animals observed.
*Significantly different from the control at $p < 0.05$.

Table B-4. Selected Changes in Serum and Sperm of Male Sprague-Dawley Rats Following Treatment with Diundecyl Phthalate (CASRN 3648-20-2) by Gavage for 28 Days[a]

Parameters	Control[b]	DUP (500 mg/kg-d)
Serum		
Total protein (g/dL)	7.03 ± 0.28	7.67 ± 0.46*
Glutamate oxaloacetate transaminase (IU/L)	75.67 ± 7.81	113.83 ± 15.58*
Alkaline phosphatase (IU/L)	347.0 ± 49.78	626.5 ± 55.83*
Sperm		
Count (10^6/g)	2,568.0 ± 154.9	1,851.67 ± 214.49*
Motility (%)	74.67 ± 4.51	27.50 ± 6.66*
Curvilinear velocity (µm/s)	261.3 ± 17.94	217.3 ± 18.59*
Straightness (%)	71.33 ± 3.33	57.67 ± 8.39*
Linearity (%)	31.50 ± 1.76	25.17 ± 2.48*

[a]Kwack et al. (2009).
[b]Control group received only corn oil.
Figures are the means ± standard deviation for groups of six rats.
*Significantly different from the control at $p < 0.05$.

Table B-5. Selected Maternal Findings in Female Sprague-Dawley Rats Treated with Diundecyl Phthalate (CASRN 3648-20-2) by Gavage from GD 6 to 20[a]

Parameters	Exposure Group (mg/kg-d)			
	0	250	500	1,000
Number of dead/treated	0/22	0/21	0/21	0/22
Number (%) pregnant	22 (100)	21 (100)	21 (100)	20 (90.9)
Body weight (g) GD 0	230 ± 13[b]	229 ± 11	229 ± 13	231 ± 13
Body weight (g) GD 21	414 ± 25	407 ± 25	405 ± 47	408 ± 27
Food consumption (g/d) GD 0−21	22 ± 1	23 ± 2	23 ± 3	23 ± 2
Gravid uterine weight (g)	107 ± 13	98 ± 23	96 ± 29	103 ± 15

[a]Saillenfait et al. (2013).
[b]Mean ± SD.

Table B-6. Selected Reproductive Findings in Female Sprague-Dawley Rats Treated with Diundecyl Phthalate (CASRN 3648-20-2) by Gavage from GD 6 to 20[a]

Parameters	Exposure Group (mg/kg-d)			
	0	250	500	1,000
All litters[b]	22	21	21	20
No. corpora lutea	15.7 ± 1.5[c]	14.7 ± 2.0	14.9 ± 1.8	15.3 ± 1.7
% Preimplantation loss per litter	3.0 ± 4.8	10.4 ± 17.7	8.4 ± 13.7	5.9 ± 10.2
No. Implantation sites per litter	15.2 ± 1.8	13.2 ± 3.3*	13.4 ± 2.9*	14.3 ± 1.7
% Postimplantation loss per litter[d]	6.4 ± 10.8	2.5 ± 5.9	8.0 ± 21.4	5.6 ± 5.7
% Resorptions per litter	6.1 ± 10.7	2.2 ± 4.4	7.7 ± 21.5	3.7 ± 7.2
Live litters[e]	22	21	20	20
No. live fetuses per litter	14.2 ± 1.9	12.9 ± 3.3	13.2 ± 2.7	13.8 ± 3.0
Fetal body weight (g)—All fetuses	5.52 ± 0.31	5.58 ± 0.36	5.60 ± 0.21	5.53 ± 0.27
Fetal body weight (g)—Male fetuses	5.69 ± 0.31	5.75 ± 0.34	5.78 ± 0.25	5.69 ± 0.30
Fetal body weight (g)—Female fetuses	5.37 ± 0.32	5.37 ± 0.39	5.48 ± 0.19	5.39 ± 0.28
AGD—Male fetuses	2.96 ± 0.12	2.95 ± 0.15	2.85 ± 0.11	2.86 ± 0.15
AGD—Female fetuses	1.04 ± 0.06	1.06 ± 0.06	1.07 ± 0.06	1.09 ± 0.06
AGD/(body weight)$^{1/3}$—Male fetuses	1.65 ± 0.08	1.65 ± 0.08	1.59 ± 0.05*	1.60 ± 0.09
AGD/(body weight)$^{1/3}$—Female fetuses	0.59 ± 0.03	0.60 ± 0.03	0.61 ± 0.03	0.62 ± 0.04

[a]Saillenfait et al. (2013).
[b]Includes all pregnant females at euthanization.
[c]Mean ± SD.
[d][(No. of resorptions + dead fetuses) ÷ No. implantations] × 100.
[e]Includes all animals with live fetuses at euthanization.
*Significantly different from the control at $p < 0.05$.

Table B-7. Selected Fetal Malformations and Variations Following Treatment of Female Sprague-Dawley Rats with Diundecyl Phthalate (CASRN 3648-20-2) by Gavage from GD 6 to 20[a]

Parameters	Exposure Group (mg/kg-d)			
	0	250	500	1,000
Total No. of fetuses (litters) examined[b]				
External	312 (22)	270 (21)	264 (20)	275 (20)
Visceral	156 (22)	135 (21)	132 (20)	138 (0)
Skeletal	156 (22)	135 (21)	132 (20)	137 (20)
Malformations				
Omphalocele	0	1 (1)	0	0
Diaphragmatic hernia	0	0	0	1 (1)
External variations				
Club foot (unilateral)	0	0	1 (1)	0
Skeletal variations				
Supernumerary 14th ribs (any type: includes pin-point ossification sites, short, and long ribs)	17 (10)	29 (13)	60[##] (17)*	32[#] (12)
Supernumerary 14th ribs (only long ribs [c])	0	1 (1)	0	1 (1)
No. of ossification centers				
Caudal vertebral centra	6.12 ± 0.37[d]	6.59 ± 0.70[§]	6.70 ± 0.57[§§]	6.67 ± 0.65[§§]

[a]Saillenfait et al. (2013).
[b]The incidence of individual defect is presented as number of fetuses (number of litters).
[c]More than one third of the length of the preceding rib.
[d]Mean ± SD.
*Significantly different from the control at $p < 0.05$ (Fisher's test).
[#]Significantly different from the control at $p < 0.05$ (Mann-Whitney test).
[##]Significantly different from the control at $p < 0.01$ (Mann-Whitney test).
[§]Significantly different from the control at $p < 0.05$ (Dunnett's test).
[§§]Significantly different from the control at $p < 0.01$ (Dunnett's test).

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODEL-FITTING PROCEDURE FOR CONTINUOUS DATA

The benchmark dose (BMD) modeling of continuous data was conducted with U.S. EPA's BMDS (Version 2.2.1). For these data, all continuous models available within the software were fit using a benchmark response (BMR) of 1 standard deviation (SD) relative risk. For changes in liver, body, and kidney weights, a BMR of 10% for weight changes relative to control was used. An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was homogeneous. If a homogeneous variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a homogeneous variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model did not adequately fit the variance data (i.e., Test 3; *p*-value < 0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit (BMDL) was selected if the BMDLs estimated from different models varied greater than threefold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected as a potential point of departure (POD) from which to derive the RfD.

In addition, in the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses. However, such exposures can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve in some cases. Thus, if lack of fit is due to characteristics of the dose-response data for high doses, then the U.S. EPA *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose group (U.S. EPA, 2012b). Because the focus of BMD analysis is on the low dose region of the response curve, eliminating the high-dose group is deemed reasonable.

INCREASED RELATIVE LIVER WEIGHT IN MALE F344 RATS TREATED WITH DIUNDECYL PHTHALATE FOR 21 DAYS (Barber et al., 1987; BIBRA, 1986)

Following the above procedure, continuous-variable models in the U.S. EPA BMDS (Version 2.1.1) were fit to the data shown in Table B-1 for increased relative liver weight in male rats (Barber et al., 1987; BIBRA, 1986). For increased relative liver weight, a BMR of a 10% change relative to the control mean was used. The homogeneity variance (Test 2) *p*-value of greater than 0.1 indicates that constant variance is the appropriate variance model. As assessed by the goodness-of-fit test and visual inspection, the exponential model 4 provided the best fit model (see Table C-1 and Figure C-1) resulting in a BMD_{10} of 223.4 mg/kg-day and $BMDL_{10}$ of 119.4 mg/kg-day.

Table C-1. Model Predictions for Increased Relative Liver Weight in Male F344 Rats[a]

Model	BMD_{10}	$BMDL_{10}$	*p*-Value Test 2[b]	*p*-Value Test 3[b]	Goodness-of-Fit *p*-Value[b]	AIC	Scaled Residual of Interest	Conclusion
Exponential (M2)	910.0	701.8	0.373	0.373	0.006	−19.67	2.241	Goodness-of-fit *p*-value <0.1
Exponential (M3)	910.0	701.8	0.373	0.373	0.006	−19.67	2.241	Goodness-of-fit *p*-value <0.1
Exponential (M4)	**223.4**	**119.4**	**0.373**	**0.373**	**0.502**	**−27.47**	**−0.4055**	Goodness-of-fit *p*-value >0.1
Exponential (M5)	282.8	126.3	0.373	0.373	N/A	−25.92	-1.54×10^{-8}	Goodness of fit not available
Hill	283.6	115.3	0.373	0.373	NA	−25.92	1.39×10^{-8}	Goodness of fit not available
Linear	803.0	599.0	0.373	0.373	0.010	−20.74	2.14	Goodness-of-fit *p*-value <0.1
Polynomial	803.0	599.0	0.373	0.373	0.010	−20.74	2.14	Goodness-of-fit *p*-value <0.1
Power	803.0	599.0	0.373	0.373	0.010	−20.74	2.14	Goodness-of-fit *p*-value <0.1

[a](Barber et al. (1987); BIBRA (1986)).
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's information criterion.

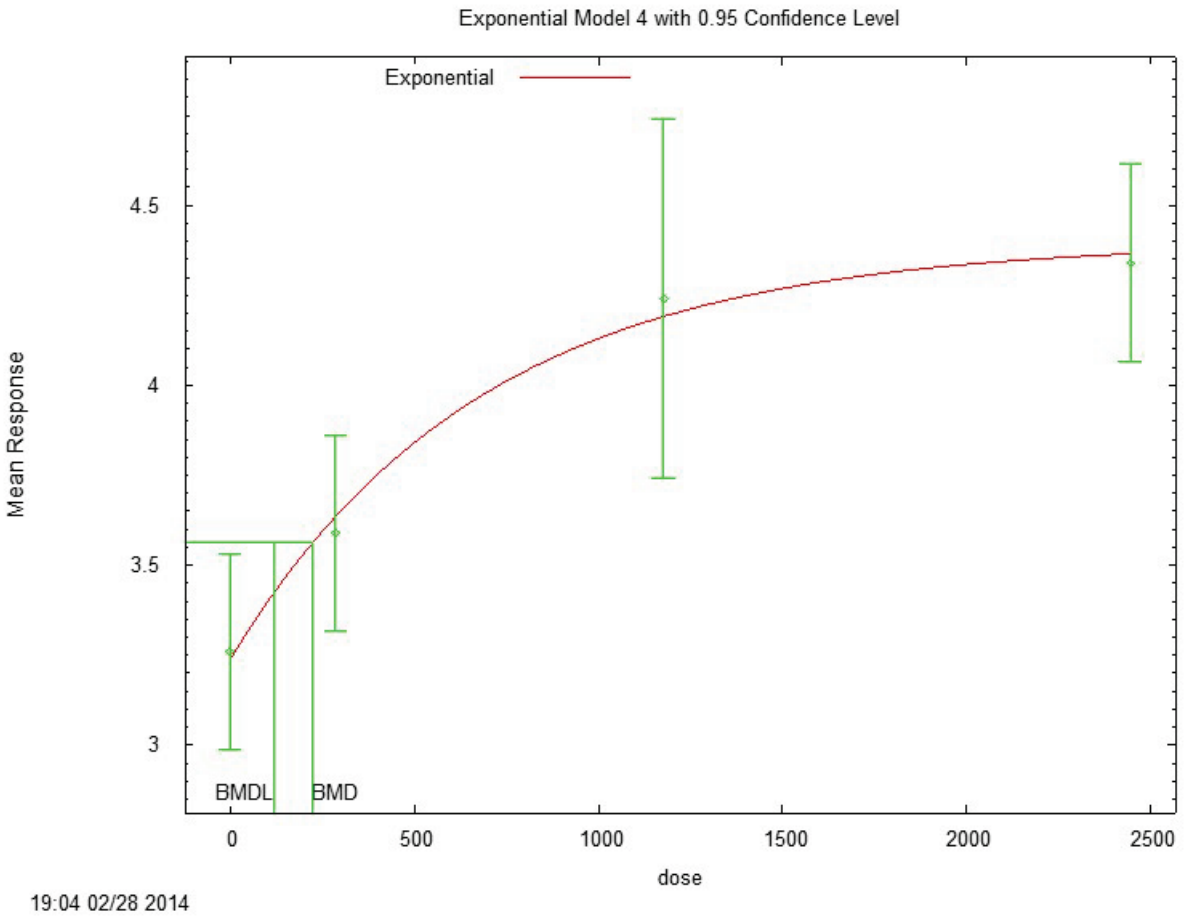

Figure C-1. Fit of Exponential Model with Homogenous Variance and Restricted Power to Data on Relative Liver Weight in Male Rats (Barber et al., 1987; BIBRA, 1986)

Text Output for Exponential BMD Model for Relative Liver Weight in Male Rats (Barber et al., 1987; BIBRA, 1986)

```
Exponential Model. (Version: 1.7;  Date: 12/10/2009)
        Input Data File: C:/US EPA/BMDS220/Data/SessionFiles/DIUP/exp_BIBRA-M-
relative liver wt-TW_PKS-ExpoConti.(d)
        Gnuplot Plotting File:
                                                Fri Feb 28 19:04:37 2014
 ================================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.
```

```
   Model 2 is nested within Models 3 and 4.
   Model 3 is nested within Model 5.
   Model 4 is nested within Model 5.


Dependent variable = Mean
Independent variable = Dose
Data are assumed to be distributed: normally
Variance Model: exp(lnalpha +rho *ln(Y[dose]))
rho is set to 0.
A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact


               Initial Parameter Values

               Variable          Model 4
               --------          --------
                 lnalpha            -2.79623
                     rho(S)                0
                       a                3.097
                       b          0.000883305
                       c              1.47142
                       d                    1

  (S) = Specified


                 Parameter Estimates

                Variable          Model 4
                --------          -------
                 lnalpha            -2.77371
                     rho                   0
                       a               3.2382
                       b          0.00146636
                       c              1.35801
                       d                    1


        Table of Stats From Input Data

  Dose      N         Obs Mean     Obs Std Dev
  -----    ---       ----------   -------------
     0      5         3.26         0.22
   286      5         3.59         0.22
  1177      5         4.24          0.4
  2445      5         4.34         0.22


             Estimated Values of Interest

  Dose      Est Mean      Est Std     Scaled Residual
------    ----------    ---------    ----------------
     0         3.238       0.2499           0.1951
```

286	3.635	0.2499	-0.4055
1177	4.191	0.2499	0.4374
2445	4.365	0.2499	-0.2269

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	17.96226	5	-25.92452
A2	19.52481	8	-23.04961
A3	17.96226	5	-25.92452
R	3.357581	2	-2.715162
4	17.73712	4	-27.47423

Additive constant for all log-likelihoods = -18.38. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	32.33	6	< 0.0001
Test 2	3.125	3	0.3727
Test 3	3.125	3	0.3727
Test 6a	0.4503	1	0.5022

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled

```
  variance appears to be appropriate here.

  The p-value for Test 6a is greater than .1.  Model 4 seems
  to adequately describe the data.


Benchmark Dose Computations:

  Specified Effect = 0.100000

         Risk Type = Relative deviation

  Confidence Level = 0.950000

               BMD =      223.389

              BMDL =      119.425
```

APPENDIX D. REFERENCES

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