PEER REVIEW DRAFT

Draft Report to the

U.S. Consumer Product Safety Commission

by the

CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES

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ABBREVIATIONS

AA	anti-androgenicity; anti-androgenic
ADHD	attention deficit hyperactivity disorder
AGD	anogenital distance
AGI	anogenital index
ATBC	acetyltributyl citrate
BASC	Behavior Assessment System for Children-Parent Rating Scales
BBP	butylbenzyl phthalate
BRIEF	Behavior Rating Inventory of Executive Function
CDC	Centers for Disease Control and Prevention, U.S.
CERHR	Center for the Evaluation of Risks to Human Reproduction
CHAP	Chronic Hazard Advisory Panel
CPSC	Consumer Product Safety Commission, U.S.
CPSIA	Consumer Product Safety Improvement Act of 2008
CRA	cumulative risk assessment
CSL	cranial suspensory ligament
cx-MIDP	mono(carboxy-isononyl) phthalate (also, CNP, MCNP)
cx MINP	mono(carboxy-isooctyl) phthalate (also COP, MCOP)
DBP	dibutyl phthalate
DCHP	dicyclohexyl phthalate
DEHA	di(2-ethylhexyl) adipate
DEHP	di(2-ethylhexyl) phthalate
DEHT	di(2-ethylhexyl) terephthalate
DEP	diethyl phthalate
DHEPP	di-*n*-heptyl phthalate
DHEXP	di-*n*-hexyl phthalate
DHT	dihydrotestosterone
DI	daily intake
DIBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DIHEPP	diisoheptyl phthalate
DIHEXP	diisohexyl phthalate
DINP	diisononyl phthalate
DINCH®	1,2-cyclohexanedicarboxylic acid, diisononyl ester
DINX	1,2-cyclohexanedicarboxylic acid, diisononyl ester
DIOP	diisooctyl phthalate
DMP	dimethyl phthalate
DNOP	di-*n*-octyl phthalate
DPENP	di-*n*-pentyl phthalate
DPHP	di(2-propylheptyl) phthalate
DPS	delayed preputial separation
DVO	delayed vaginal opening
EPA	Environmental Protection Agency, U.S.
EPW	epididymal weight
FDA	Food and Drug Administration, U.S.

f_{ue}	urinary excretion factor
GD	gestational day
GLP	good laboratory practices
HBM	human biomonitoring
hCG	human chorionic gonadotrophin
HI	hazard index
HQ	hazard quotient
ICH	International Conference on Harmonisation
insl3	insulin-like factor 3
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
MBP	monobutyl phthalate
MBZP	monobenzyl phthalate
MCPP	mono(3-carboxypropyl) phthalate
MDI	mental development index
MECPP	mono(2-ethyl-5-carboxypentyl) phthalate
MEHP	mono(2-ethylhexyl) phthalate
MEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono(2-ethyl-5-oxohexyl) phthalate
MEP	monoethyl phthalate
MINP	mono(isononyl) phthalate
MIS	Mullerian inhibiting substance
MMP	monomethyl phthalate
MNOP	mono-*n*-octyl phthalate
MoE	margin of exposure
NAE	no anti-androgenic effects observed
NHANES	National Health and Nutritional Examination Survey
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NR	nipple retention
NRC	National Research Council, U.S.
NTP	National Toxicology Program, U.S.
OECD	Organisation for Economic Cooperation and Development
OH-MIDP	mono(hydroxy-isodecyl) phthalate
OH-MINP	mono(hydroxy-isononyl) phthalate
oxo-MIDP	mono(oxo-isodecyl) phthalate
oxo-MINP	mono(oxo-isononyl) phthalate
PBR	peripheral benzodiazepine receptor
PDI	psychomotor developmental index
PE	phthalate ester
PND	postnatal day
POD	point of departure
PODI	point of departure index
PPARα	peroxisome proliferator-activated receptor alpha
PVC	polyvinyl chloride
RfD	reference dose

SFF	Study for Future Families
SRS	social responsiveness scale
StAR	steroidogenic acute regulatory protein
SVW	seminal vesicle weight
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TDI	tolerable daily intake
TDS	testicular dysgenesis syndrome
TEF	toxicity equivalency factors
TOTM	tris(2-ethylhexyl) trimellitate
TPIB	2,2,4-trimethyl-1,3 pentanediol diisobutyrate
T PROD	testosterone production
TXIB®	2,2,4-trimethyl-1,3 pentanediol diisobutyrate
UF	uncertainty factor

1 Executive Summary

To be added.

2 Background and Strategy

2.1 Introduction and Strategy Definition

The Consumer Product Safety Improvement Act of 2008 (CPSIA) directs the U.S. Consumer Product Safety Commission (CPSC) to convene a Chronic Hazard Advisory Panel (CHAP) "to study the effects of all phthalates and phthalate alternatives as used in children's toys and child care articles." The CHAP will recommend to the Commission whether any phthalates or phthalate alternatives other than those permanently banned should be declared banned hazardous substances. Specifically, section 108(b)(2) of the CPSIA requires the CHAP to:

> "*complete an examination of the full range of phthalates that are used in products for children and shall—*
>
> > *(i) examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates;*
> > *(ii) consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates;*
> > *(iii) examine the likely levels of children's, pregnant women's, and others' exposure to phthalates, based on a reasonable estimation of normal and foreseeable use and abuse of such products;*
> > *(iv) consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, such as personal care products;*
> > *(v) review all relevant data, including the most recent, best-available, peer-reviewed, scientific studies of these phthalates and phthalate alternatives that employ objective data collection practices or employ other objective methods;*
> > *(vi) consider the health effects of phthalates not only from ingestion but also as a result of dermal, hand-to-mouth, or other exposure;*
> > *(vii) consider the level at which there is a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals and their offspring, considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of children, pregnant women, and other potentially susceptible individuals; and*
> > *(viii) consider possible similar health effects of phthalate alternatives used in children's toys and child care articles.*
>
> *The panel's examinations pursuant to this paragraph shall be conducted de novo. The findings and conclusions of any previous Chronic Hazard Advisory Panel on this issue and other studies conducted by the Commission shall be reviewed by the panel but shall not be considered determinative.* "

In addition, the CHAP will recommend to the Commission whether any "*phthalates (or combinations of phthalates)*" other than those permanently banned, including the phthalates covered by the interim ban, or phthalate alternatives should be prohibited.[*] Based on the CHAP's recommendations, the Commission must determine whether to continue the interim

[*] CPSIA §108(b)(2)(C).

prohibition of DINP, diisodecyl phthalate (DIDP), and di-*n*-octyl phthalate (DNOP) "*in order to ensure a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals with an adequate margin of safety.*" Section 108 (b)(3)(A) of the CPSIA. The Commission also must determine whether to prohibit the use of children's products containing any other phthalates or phthalate substitutes, "*as the Commission determines necessary to protect the health of children*." Section 108 (b)(3)(B) of the CPSIA.

In an effort to complete its assignment within a reasonable time frame, the CHAP drew some boundaries around the task regarding the number of chemicals to be reviewed, identification of the most sensitive sub-populations, and the endpoint of toxicity of greatest concern. Based on toxicity and exposure data, the phthalate esters (PEs) of primary concern in this report are listed in Table 2.1 (p. 15) and Appendix A. The sub-populations of greatest concern are neonates and children as well as pregnant females. Phthalates cause a wide range of toxicities but the one considered of greatest concern for purposes of this report is a syndrome indicative of androgen insufficiency in fetal life, what is referred to in rats as the Phthalate Syndrome caused by exposure of pregnant dams to certain phthalates. Exposure results in abnormalities of the developing male reproductive tract structures (the Phthalate Syndrome).

In an effort to determine whether specific phthalates or phthalate substitutes were associated with the induction of the phthalate syndrome, members of the CHAP reviewed the toxicology literature to identify the toxicologic findings and toxic dose levels from relevant studies. Dose response relationships were reviewed and no observed adverse effect levels (NOAELs) were determined. In evaluating toxicological studies, the CHAP was guided by criteria for quality assessments, such as those developed by Klimisch *et al.,* (e.g., 1997) in which studies are assigned reliability criteria based on adherence to Good Laboratory Practice (GLP). However, the focus on GLP eliminates most scientific studies emanating from academic research. The CHAP felt that exclusion of scientific studies not compliant with GLP would have unduly skewed the outcome of the assessment, and for that reason, all studies available in the public domain were analyzed. To assess their quality, CHAP was guided by the criteria of reliability, relevance and adequacy as laid down by the Organisation for Economic Cooperation and Development (OECD, 2007). "Reliability" refers to evaluating the inherent quality of a test report or publication relating to preferably standardized methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings. "Relevance" covers the extent to which data and tests are appropriate for a particular hazard identification or risk characterization. "Adequacy" means the usefulness of data for hazard/risk assessment purposes.

Similarly, studies in humans were reviewed to assess endpoints of toxicity and parameters of exposure, where known, as well as the identities of phthalates and their and their metabolites and levels of exposure. Human and environmental exposure data were evaluated. Human biomonitoring data were analyzed to correlate no observed adverse effect levels (NOAELs) with exposure data. Sources of exposure were reviewed to determine if source information might allow targeted recommendations about efforts to minimize human exposure.

Recommendations to CPSC for regulatory actions were then derived from a combination of input on the basis of toxicity findings in animals and humans together with Hazard Index[*] calculations to help address concerns about vulnerable sub-populations and specific sources of exposure to individual chemicals or combinations of chemicals.

2.2 Selection of Toxicity Endpoints and Life Cycle Stages

The initial charge to the CHAP is to “examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates.” After lengthy discussion, the CHAP decided that although phthalates can induce a number of types of toxicities in animals (Babich and Osterhout, 2010; Carlson, 2010b; Carlson, 2010a; Osterhout, 2010; Patton, 2010; Williams, 2010b; Williams, 2010a), the most sensitive and most extensively studied is male developmental toxicity in the rat and therefore the CHAP would focus on this toxicity endpoint.

As discussed in more detail subsequently, exposure to phthalates during the latter stages of gestation in the rat has been shown to disrupt testicular development leading to subsequent reproductive tract dysgenesis. In addition, phthalates produce this developmental toxicity in male rodents with an age-dependent sensitivity, i.e., fetal animals being more sensitive than neonates which are in turn more sensitive than pubertal and adult animals (Foster *et al.*, 2006). Cognizant of this age-dependent sensitivity of phthalate-induced male developmental toxicity, the CHAP decided to focus its analysis on adverse developmental effects as the phthalate toxicity endpoints and the fetus and neonate as the life cycle stages of major interest in its efforts to complete its assigned task. To complete its charge, CHAP systematically reviewed the phthalate developmental and reproductive toxicology literature, focusing on dose levels that induced phthalate toxicity endpoints related to the “rat phthalate syndrome,” defined subsequently. Because much is known about the mechanisms by which phthalates induce the phthalate syndrome, CHAP also focused on a variety of molecular endpoints in the pathway leading to reproductive tract dysgenesis. Together, morphological, histopathological, and molecular toxicity endpoints were used to select NOAELs from specific studies and these NOAELs, in turn, were used in one of the three case studies in the Hazard Index-based cumulative assessment described in Section 2.7.

Because the developmental toxicity studies reviewed in Appendix A relate to various aspects of male sexual differentiation, a brief introduction to this subject, taken directly from the 2008 NRC publication: *Phthalates and Cumulative Risk Assessment: The Tasks Ahead,* is provided below (NRC, 2008). This is followed by a discussion of the Rat Phthalate Syndrome, the Phthalate Syndrome in Other Species (excluding humans), and concludes with a section on Mechanisms of Phthalate Action, all of which are from NRC 2008.

[*] The hazard index (HI) is the ratio of the daily intake to the reference dose.

Male Sexual Differentiation in Mammals

"Sexual differentiation in males follows complex interconnected pathways during embryo and fetal development that has been reviewed extensively elsewhere (Capel, 2000; Hughes, 2000a; 2000b; 2001; Tilmann and Capel, 2002; Brennan and Capel, 2004) Critical to the development of male mammals is the development of the testis in embryonic life from a bipotential gonad (a tissue that could develop into a testis or an ovary). The "selection" is genetically controlled in most mammals by a gene on the Y chromosome. The sex-determining gene (sry in mice and SRY in humans) acts as a switch to control multiple downstream pathways that lead to the male phenotype. Male differentiation after gonad determination is exclusively hormone-dependent and requires the presence at the correct time and tissue location of specific concentrations of fetal testis hormones-Mullerian inhibiting substance (MIS), insulin-like factors, and androgens. Although a female phenotype is produced independently of the presence of an ovary, the male phenotype depends greatly on development of the testis. Under the influence of hormones and cell products from the early testis, the Mullerian duct regresses and the mesonephric duct (or Wolffian duct) gives rise to the epididymis and vas deferens. In the absence of MIS and testosterone, the Mullerian ductal system develops further into the oviduct, uterus, and upper vagina, and the Wolffian duct system regresses. Those early events occur before establishment of a hypothalamic-pituitary-gonadal axis and depend on local control and production of hormones (that is, the process is gonadotropin-independent). Normal development and differentiation of the prostate from the urogenital sinus and of the external genitalia from the genital tubercle are also under androgen control. More recent studies of conditional knockout mice that have alterations of the luteinizing-hormone receptor have shown normal differentiation of the genitalia, although they are significantly smaller."

"Testis descent appears to require androgens and the hormone insulin-like factor 3 (insl3) (Adham et al., 2000) to proceed normally. The testis in early fetal life is near the kidney and attached to the abdominal wall by the cranial suspensory ligament (CSL) and gubernaculum. The gubernaculum contracts, thickens, and develops a bulbous outgrowth; this results in the location of the testis in the lower abdomen (transabdominal descent). The CSL regresses through an androgen-dependent process. In the female, the CSL is retained with a thin gubernaculum to maintain ovarian position. Descent of the testes through the inguinal ring into the scrotum (inguinoscrotal descent) is under androgen control."

"Because the majority of studies discussed below were conducted in rats, it is helpful to compare the rat and human developmental periods for male sexual differentiation. Production of fetal testosterone occurs over a broader window in humans (gestation weeks 8-37) than in rats (gestation days [GD] 15-21). The critical period for sexual differentiation in humans is late in the first trimester of pregnancy, and differentiation is essentially complete by 16 weeks after conception (Hiort and Holterhus, 2000). The critical period in rats occurs in later gestation, as indicated by the production of testosterone in the latter part of the gestational period, and some sexual development occurs postnatally in rats. For example, descent of the testes into the scrotum occurs in

> *gestation weeks 27-35 in humans and in the third postnatal week in rats. Generally, the early postnatal period in rats corresponds to the third trimester in humans."*

As the authors of the 2008 NRC report conclude:

> *"…it is clear that normal differentiation of the male phenotype has specific requirements for fetal testicular hormones, including androgens, and therefore can be particularly sensitive to the action of environmental agents that can alter the endocrine milieu of the fetal testis during the critical periods of development."*

2.2.1 The Rat Phthalate Syndrome

Studies conducted over the past 20 plus years have shown that phthalates produce a syndrome of reproductive abnormalities in male offspring when administered to pregnant rats during the later stages of pregnancy, e.g., GD 15-20. This group of interrelated abnormalities, known as the rat phthalate syndrome, is characterized by malformations of the epididymis, vas deferens, seminal vesicles, prostate, external genitalia (hypospadias), cryptorchidism (undescended testes) as well as retention of nipples/areolae (sexually dimorphic structures in rodents) and demasculinization of the perineum resulting in reduced anogenital distance (AGD). The highest incidence of reproductive tract malformations is observed at higher phthalate dose levels whereas changes in AGD and nipple/areolae retention are frequently observed at lower phthalate dose levels. It is important to note that not all phthalates produce all of the abnormalities of the rat phthalate syndrome under any one exposure scenario. The endocrine disrupting potency of the phthalates (producing the rat phthalate syndrome, and based on the reduction of fetal testicular testosterone) seems to be restricted to phthalates with three to seven (or eight) carbon atoms in the backbone of the alkyl sidechain with the highest potency centering around five carbon atoms in the backbone (di-*n*-pentyl phthalate, DPENP). "Active" phthalates start with diisobutyl phthalate (DIBP; three carbon atoms in the alkyl backbone) and end with DINP (~seven or eight carbons in the alky chain backbone).

DPENP > BBP ~ DBP ~ DIBP ~ DIHEXP ~ DEHP ~ DCHP > DINP[*]

Mechanistically, phthalate exposure can be linked to the observed phthalate syndrome abnormalities by an early phthalate-related disturbance of normal fetal testicular Leydig function and/or development (Foster, 2006). This disturbance is characterized by Leydig cell hyperplasia or the formation of large aggregates of Leydig cells at GD 21 in the developing testis. These morphological changes are preceded by a significant reduction in fetal testosterone production, which likely results in the failure of the Wolffian duct system to develop normally, thereby contributing to the abnormalities observed in the vas deferens, epididymis, and seminal vesicles. Reduced testosterone levels also disturb the dihydrotestosterone (DHT)-induced development of the prostate and external genitalia by reducing the amount of DHT that can be produced from testosterone by 5α-reductase. Because DHT is required for the normal apoptosis of nipple anlage[†] in males and also for growth of the perineum to produce the normal male AGD, changes in AGD and nipple retention are consistent with phthalate-induced reduction in testosterone levels. Although testicular descent also requires normal testosterone levels, another Leydig cell

[*] BBP, butyl benzyl phthalate; DBP, di-*n*-butyl phthalate; DIHEXP, diisohexyl phthalate; DEHP, di(2-ethylhexyl phthalate; DCHP, dicyclohexyl phthalate. A complete list of abbreviations begins on page ii.
[†] Precursor tissue.

product, insl3 (insulin-like factor 3), also plays a role. Phthalate exposure has been shown to decrease insl3 gene expression and mice in which the insl3 gene has been deleted show complete cryptorchidism.

2.2.2 The Phthalate Syndrome in Other Species (excluding humans)

Although the literature is replete with information about the phthalate syndrome in rats, there is, interestingly, a relative dearth of information about the phthalate syndrome in other species. In an early study, Gray *et al.*, (1982) found that di-*n*-butyl phthalate (DBP) produced uniformly severe seminiferous tubular atrophy in rats and guinea pigs, only focal atrophy in mice, and no changes in hamsters. Hamsters were insensitive to other phthalates [di(2-ethylhexyl) phthalate, DEHP and di-*n*-pentyl phthalate, DPENP] as well. A study by Higuchi *et al.*, (2003), using rabbits exposed orally to DBP, reported that the most pronounced effects observed were decreased testes and accessory gland weights as well as abnormal semen characteristics, e.g., decreased sperm concentration/total sperm/normal sperm and an increase in acrosome-nuclear defects. In a study by Gaido *et al.*, (2007), mice exposed to DBP showed significantly increased seminiferous cord diameter, the number of multinucleated gonocytes per cord, and the number of nuclei per multinucleated gonocyte. In a separate set of experiments, dosing with high levels of DBP did not significantly affect fetal testicular testosterone concentration even though the plasma concentrations of the DBP metabolite monobutyl phthalate (MBP) in mice were equal to or greater than the concentration in maternal and fetal rats. In a third set of experiments, *in utero* exposure to DBP led to the rapid induction of immediate early genes, similar to the rat; however, unlike the rat, expression of genes involved in cholesterol homeostasis and steroidogenesis were not decreased. In another study, reported only in abstract form, Marsman (1995) observed no treatment-related gross lesions at necropsy, and no histopathological lesions associated with treatment in male or female mice.

Two studies have been published on the toxicity of phthalates (specifically DBP/MBP) in non-human primates. In one study by Hallmark *et al.*, (2007), 4 day old marmosets were administered 500 mg/kg/day MBP for 14 days. In a second acute study, nine males 2-7 days of age were administered a single oral dose of 500 mg/kg-day. Results showed that MBP did suppress testosterone production after an acute exposure; however, this suppression of testosterone production was not observed when measurements were taken 14 days after the beginning of exposure to MBP. The authors speculate that the initial MBP-induced inhibition of steroidogenesis in the neonatal marmoset leads to a “reduced negative feedback and hence a compensatory increase in LH secretion to restore steroid production to normal levels.” In a follow up study, McKinnell *et al.*, (2009) exposed pregnant marmosets from ~7-15 weeks gestation with 500 mg/kg/day MBP, and male offspring were studied at birth (1-5 days; n= 6). Fetal exposure did not affect gross testicular morphology, reproductive tract development, testosterone levels, germ cell number and proliferation, Sertoli cell number, or germ:Sertoli cell ratio.

Although limited in number, and in the timing of exposure is often outside the know window of susceptibility, the studies cited above clearly show that most animals tested are more resistant to phthalates than rats. This has led some to question whether the rat is a suitable model for assessing phthalate effects in humans and stimulated the studies with non-human primates (marmosets). Unfortunately, the number of animals exposed is small, only one phthalate has been tested and at only one dose, and a limited number of time points have been assessed. In addition, the available data, although largely negative, is equivocal in that DBP did appear to suppress testosterone production when administered in the early neonatal period (Hallmark *et al.*, 2007). In presentations at CHAP meetings, the CHAP was also aware of unpublished studies that appear to show that human testes, which were implanted into nude rats that are then exposed to phthalates, did not respond to DBP. Since those presentations, the studies from Dr. Sharpe's laboratory have been published (Mitchell *et al.*, 2012). Results of these studies showed that the weight and the testosterone production of 14-20 week human fetal testis grafted under the skin of nude mice were not statistically significantly affected by DBP or MBP, although an approximately 50% reduction of testosterone levels was observed. Due to high experimental variation and the small number of repetitions, this reduction did not reach statistical significance. In contrast, exposure of rat fetal xenografts to DBP significantly reduced seminal vesicle weight and testosterone production. While these results were of interest to the CHAP, these studies do have limitations. The major limitation is the fact that most of the human testes that were transplanted into the rat were >14 weeks of gestation, which would put them beyond the critical window for the development of the reproductive tract normally under androgen control (For further discussion of this issue, see section 4.2).

The CHAP agreed that additional non-human primate studies as well as *ex vivo* studies are needed to determine whether the rat is a good model for the human; however, the CHAP also agreed that studies in rats currently offer the best available data for assessing human risk.

2.2.3 **Mechanism of Phthalate Action**

Although the majority of animal studies have focused on the morphological and histopathological effects of exposure to phthalates relative to the male reproductive system, considerable effort has also been focused on the mechanisms by which phthalates produce their adverse effects. Initial mechanistic studies centered on phthalates acting as environmental estrogens or antiandrogens; however, data from various estrogenic and antiandrogenic screening assays clearly showed that while the parent phthalate could bind to steroid receptors, the developmentally toxic monoesters exhibited little or no affinity for the estrogen or androgen receptors (David, 2006). Another potential mechanism of phthalate developmental toxicity is through peroxisome proliferator-activated receptor alpha (PPARα). Support for this hypothesis comes from data showing that circulating testosterone levels in PPARα-null mice were increased following treatment with DEHP compared with a decrease in wild-type mice, suggesting that PPARα has a role in postnatal testicular toxicity (Ward *et al.*, 1998). PPARα activation may play some role in the developmental toxicity of nonreproductive organs (Lampen *et al.*, 2003); however, data linking PPARα activation to the developmental toxicity of reproductive organs is lacking.

Because other studies had shown that normal male rat sexual differentiation is dependent upon three hormones produced by the fetal testis, i.e., anti-mullerian hormone produced by the Sertoli cells, testosterone produced by the fetal Leydig cells, and insulin-like hormone 3 (insl3), several laboratories conducted studies to determine whether the administration of specific phthalates to pregnant dams during fetal sexual differentiation that caused demasculinization of the male rat offspring would also affect testicular testosterone production and insl3 expression. Studies by (Wilson *et al.*, 2004; Borch *et al.*, 2006b; Howdeshell *et al.*, 2007) reported significant decreases in testosterone production and insl3 expression after DEHP, DBP, BBP, and by DEHP + DBP (each at one half of its effective dose). The study by Wilson *et al.,* (2004) also showed that exposure to DEHP (and similarly DBP and BBP) altered Leydig cell maturation resulting in reduced production of testosterone and insl3, from which they further proposed that the reduced testosterone levels result in malformations such as hypospadias, whereas reduced insl3 mRNA levels lead to lower levels of this peptide hormone and abnormalities of the gubernacular ligament (agenesis or elongated and filamentous) or freely moving testes (no cranial suspensory or gubernacular ligaments). Together, these studies identify a plausible link between inhibition of steroidogenesis in the fetal rat testes and alterations in male reproductive development. Other phthalates that do not alter testicular testosterone synthesis (diethyl phthalate, DEP; Gazouli *et al.*, 2002) and gene expression for steroidogenesis (DEP and dimethyl phthalate, DMP; Liu *et al.*, 2005) also do not produce the "phthalate syndrome" malformations produced by phthalates that do alter testicular testosterone synthesis and gene expression for steroidogenesis (Gray *et al.*, 2000; Liu *et al.*, 2005).

Complementary studies have also shown that exposure to DBP *in utero* leads to a coordinated decrease in expression of genes involved in cholesterol transport (peripheral benzodiazepine receptor [PBR], steroidogenic acute regulatory protein [StAR], scavenger receptor class B1 [SR-B1]) and steroidogenesis (cytochrome P450 side chain cleavage [P450scc], cytochrome P450c17 [P450c17], 3β-hydroxysteroid dehydrogenase [3β-HSD]) leading to a reduction in testosterone production in the fetal testis (Shultz *et al.*, 2001; Barlow and Foster, 2003; Lehmann *et al.*, 2004; Hannas *et al.*, 2011b). Interestingly, Lehmann *et al.*,, 2004 further showed that DBP induced significant reductions in SR-B1, 3β-HSD, and c-Kit (a stem cell factor produced by Sertoli cells that is essential for normal gonocyte proliferation and survival) mRNA levels at doses (0.1 or 1.0 mg/kg/day) that approach maximal human exposure levels. The biological significance of these data is not known given that no statistically significant observable adverse effects on male reproductive tract development have been identified at DBP dose <100 mg/kg/day and given that fetal testicular testosterone is reduced only at dose levels equal to or greater than 50 mg/kg/day.

Thus, current evidence suggests that once the phthalate monoester crosses the placenta and reaches the fetus, it alters gene expression for cholesterol transport and steroidogenesis in Leydig cells. This in turn leads to decreased cholesterol transport and decreased testosterone synthesis. As a consequence, androgen-dependent tissue differentiation is adversely affected, culminating in hypospadias and other features of the phthalate syndrome. In addition, phthalates (DEHP, DBP) also alter the expression of insl3 leading to decreased expression. Decreased levels of insl 3 result in malformations of the gubernacular ligament, which is necessary for testicular descent into the scrotal sac.

2.3 Toxicology Data

2.3.1 Use of Animal Data to Assess Hazard and Risk

The published literature on the toxicity of phthalates is extensive and varies widely in its usefulness for assessment of risks to humans. This chapter introduces the approach taken by the CHAP to evaluate such a broad and varied literature and draw conclusions about potential risks to humans from individual chemicals or mixtures of chemicals.

What is the basis for selecting key studies and studies that provide a basis for assessment of risk for humans? What is the threshold for determining that studies in humans or animals are either helpful for assessment of risk or not? For example, the results of a pilot study in a small number of lab animals are usually not suitable for risk assessment. The study was designed to select the appropriate dose levels for a more definitive study. Similarly, case histories on individual persons are not a sufficient basis for a risk assessment because the individual case may not be representative of the population. For the same reason, reports of cluster effects of small numbers of humans are often difficult to extrapolate beyond the cluster. The most desired data are from appropriately designed studies in humans or animals that account for confounders, have reasonable power to detect an effect (e.g., 80% at 0.95 probability), with results replicated in another study of similar design and purpose.

As an example of another threshold for acceptance of data, the CHAP's goal was to use data from studies that were published in peer reviewed journals. There were times when the only available information was from a source other than published literature. For example, it may have been the results of a study submitted to a public docket of a regulatory agency as part of a data call-in, or, the results may be from a recently completed study that has not yet been submitted for review by a journal. In such cases, the CHAP has considered the data but has noted in its review that the results from the study on this particular chemical have not been published.

In its assessment of risks of human exposure to phthalates and phthalate substitutes, the CHAP focused on the charge as specified in section 108 of the Consumer Product Safety Improvement Act of 2008. The hazard of greatest concern was considered to be the potential for some of the members of these chemical groups to cause structural and functional alterations to the developing reproductive organs and tissues of male offspring exposed during late gestation and the early postnatal period. These findings are most prominent in rats although inconclusive studies in humans suggest that similar effects may be seen in humans.

As the CHAP reviewed the available literature in humans and animals, the following factors were considered as conclusions were reached. In the absence of good human data, it is prudent to rely on the results of animal studies. The distinction between hazard and risk is important to understand to predict risk to humans based on animal data. The first step in risk assessment is determination of hazard (NRC, 1983). What are the effects seen in animal tests—cancer, genotoxicity, liver, kidney, or other organ toxicity, reproductive or developmental toxicity, etc.? This step is independent of dose response. What are the targets of effect and what effect is seen at what dose level in animals?

The second step is to assess risk for humans. This involves several considerations. What is the dose response? The response should become more severe with increasing dose and a larger percent of the exposed population should show the response if it is really related to exposure to the test article. Knowing the dose response in animals allows one to define a level of exposure that is not associated with an observed response (no observed adverse effect level, NOAEL) in animal studies.

Risk is a function of hazard and exposure (the probability of harm to humans). Comparison of the NOAEL in animal studies to the known or anticipated level of human exposure is the basis for calculating a margin of safety as an estimate of risk for humans. What is an acceptable margin of exposure (MoE) depends on the substance and the toxic response. It may be around ten for a life-saving drug but for a chemical in the environment or in food, the acceptable MoE may be one hundred to a thousand (EPA, 1993). Generally, the level of concern is considered low when the MoE is greater than the net uncertainty factor for a given chemical.

Animal data, then, can be a useful basis for determining risks to human subjects of research. As with human data, animal data exist over a wide range of usefulness, depending on experimental design, power, confounders, appropriateness of the animal model for the question being asked, consistency of data between studies, replication of results, etc. National and international guidelines (e.g., U.S., Food and Drug Administration, FDA; U.S. Environmental Protection Agency, EPA; International Conference on Harmonisaton, ICH; Organisation for Economic Cooperation and Development, OECD) define standards for protocols for animal studies. Protocols designed according to these guidelines are most useful for risk assessment.

What should be done when confronted with conflicting results of animal studies? Consider the quality and relevance of the studies, experimental design in the context of standard protocols, route of exposure, power, and confounders. The conservative approach is to rely on the study reporting adverse effects unless there are compelling reasons to exclude the study, i.e., considerations such as quality, design, execution or interpretation.

How should one use *in vitro* test results and data from mechanistic studies and pharmacokinetic studies? *In vitro* studies usually don’t have dose response data that allow results to be used directly in risk assessment in the same sense that *in-vivo* test results are used for that purpose. However, the results of *in vitro* and mechanistic studies can help to reinforce or modulate the level of concern upwards or downwards. The results of metabolic and pharmacokinetic or pharmacodynamic studies can help to determine the relevance of animal data for humans and may allow selection of lab animal species that are most relevant for assessment of risk for humans.

It is often difficult to determine that animal data definitely predict risk for humans. However, the results of *in vitro*, mechanistic, and metabolic/pharmacokinetic studies can help to decide if the results of animal tests should be assumed to be relevant for human risk or whether the results of animal tests should be considered not relevant for prediction of human risk. An example of the latter situation is when the ultimate toxicant is determined by animal tests to be a metabolite of a chemical that is not formed in humans. Thus, adverse effects seen in that species of animal are not considered relevant for prediction of risk to humans who do not form that particular metabolite. It must also be remembered that some chemicals have been found to be toxic to humans when the animal studies did not predict such an effect in humans. For example the sedative, thalidomide, was found to be teratogenic in humans but did not cause effects in a majority of animal species tested by conventional methodology at the time (the 1950s). Likewise, adverse effects are sometimes discovered in humans that were not seen in a previous study with fewer human subjects.

There are also other considerations for interpretation of animal data and integrating animal findings with data from humans. Data from human studies of reasonable quality generally are a stronger signal of risk to humans than findings in animal studies. However, in the absence of other data, findings in animals should be assumed to be relevant for prediction of risk to humans.

Observations in multiple animal species are a stronger signal than a finding in a single species. Studies in certain species, e.g., nonhuman primates, are often stronger signals of risk to humans than study results from other species.

The dose levels at which effects are seen in animal studies must be considered along with the presence or absence of confounding toxicity to non-reproductive organs.

Animal or human studies that are negative must be examined closely for adequacy of experimental design, sufficient power, and presence of confounders that may have masked a possible effect of the test article.

Animal or human studies that are positive must be examined closely for appropriateness of experimental design and presence of confounders that may have contributed to the effects reported.

In summary, this section has presented the approach used by the CHAP to evaluate the available toxicity literature on the phthalates and phthalate substitutes under the purview of the CHAP. The reviews of studies on individual chemicals are found in Appendix A (Developmental Toxicity) and Appendix B (Reproductive and Other Toxicity) of this report.

2.3.2 **Developmental Toxicity of Phthalates in Rats**

As directed by the Consumer Product Safety Improvement Act of 2008 (CPSIA, 2008), the CHAP was also charged to "*i*) examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates, *ii*) consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates and *iv*) consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, such as personal care products."(Section 108(b)(2)(B) of 15 U.S.C. § 2077)

To complete the charge of examining the full range of phthalates, the CHAP decided after careful consideration to limit its review to 14 phthalates, including the three permanently banned phthalates (DBP, BBP, and DEHP), the three phthalates currently on an interim ban (DNOP, DINP, and DIDP), and eight other phthalates (DMP; DEP; di-*n*-pentyl phthalate, DPENP; diisobutyl phthalate, DIBP; dicyclohexyl phthalate, DCHP, di-*n*-hexyl phthalate, DNHEXP; diisooctyl phthalate, DIOP; and di(2-propylheptyl) phthalate, DPHP). Because the first six of these phthalates were extensively reviewed by a phthalates expert panel in a series of reports from the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in 2002, our review of these phthalates begins with a brief summary of these NTP reports, which is then followed by a review of the literature since those reports (see Appendix A). For the eight other phthalates that were not reviewed by the NTP panel, the CHAP review covers all the relevant studies available to the committee. From the available literature for each of these 14 phthalates, we then identified the most sensitive developmentally toxic endpoint in a particular study as well as the lowest dose that elicited that endpoint (NOAEL). Finally, we evaluated the "adequacy" of particular studies to derive a NOAEL. Our criteria for an adequate study from which a NOAEL could be derived are: 1) at least three dose levels and a concurrent control should be used, 2) the highest dose should induce some developmental and/or maternal toxicity and the lowest dose level should not produce either maternal or developmental toxicity, 3) each test and control group should have a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy, and 4) pregnant animals need to be exposed during the appropriate period of gestation. In addition, studies should follow the EPA guideline OPPTS 870.3700 and the OECD Guideline for the Testing of Chemicals (OECD 414, adopted 22 January 2001).

We also evaluated the potential developmental toxicity of phthalate substitutes. The phthalate substitutes include acetyl tributyl citrate (ATBC), di(2-ethylhexyl) adipate (DEHA), diisononyl 1,2-dicarboxycyclohexane (DINCH®, DINX[*]), di(2-ethylhexyl) terephthalate (DEHT), trioctyl trimellitate (TOTM), and 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TXIB®, TPIB[†]). These compounds were selected from the many possible phthalate substitutes because they are already in use (ATBC, DEHT, DINX, TPIB; Dreyfus, 2010) or are considered likely to be used (DEHA, TOTM; Versar/SRC, 2010) in toys and child care articles. The same criteria were used to evaluate the "adequacy" of studies describing the developmental toxicity of phthalate substitutes as were used for phthalates. However, because of the paucity of data for many of the phthalate substitutes, studies that did not meet the listed criteria were cited. In these instances, we indicated the limitations associated with these studies.

The systematic evaluation of the developmental toxicity literature for the 14 phthalates and six phthalate substitutes and the rationale for selecting a specific NOAEL for each chemical are provided in Appendix A. A list of NOAELs is provided in the following table.

To fulfill the charges to consider the health effects of phthalates in isolation and in combination with other phthalates and to consider the cumulative effect of total exposure to phthalates, the CHAP relied upon its review of the toxicology literature of phthalates and phthalate substitutes, exposure data (sources and levels) and data obtained from the Hazard Index (HI) approach for cumulative risk assessment (see Section 2.7.1. for details). The HI is essentially the sum of the ratios of the daily intake (DI) of each individual phthalate divided by its reference dose (RfD). This approach uses NOAELs from animal studies as points of departure (PODs), which are then adjusted with uncertainty factors to yield reference doses (RfDs), and biomonitoring data for DI input. Because of limitations in the biomonitoring datasets (National Health and Nutrition Evaluation Surveys, NHANES (CDC, 2012b); and Study for Future Families, SFF (Sathyanarayana *et al.*, 2008a; 2008b)), only five phthalates were analyzed by the HI approach. These include DBP, DIBP, BBP, DEHP, and DINP. Case 3[‡] in the HI analysis uses NOAELs generated from the available literature on the developmental toxicity of these five phthalates. To

[*] DINCH® is a registered trademark of BASF. Although DINCH® is the commonly used abbreviation, the alternate abbreviation DINX is used here to represent the generic chemical.

[†] TXIB® is a registered trademark of Eastman Chemical Co. Although TXIB® is the commonly used abbreviation, the alternate abbreviation TPIB is used here to represent the generic chemical.

[‡] As discussed in Section 2.7.2.2., the CHAP considered three sets of references doses (three Cases) to calculate the hazard index.

provide NOAELs, where possible, for these five phthalates, the CHAP systematically reviewed the published, peer-reviewed literature that reported information concerning the effects of *in utero* exposure of phthalates in pregnant rats.

Table 2.1 Summary of NOAELs (mg/kg-d) for developmental endpoints affecting male reproductive development.

CHEMICAL	NOAEL	ENDPOINT	REFERENCE
Permanently Banned			
Dibutyl phthalate (DBP)	50	↑NR;↓AGD	Mylchreest *et al.*, (2000); Zhang *et al.*, (2004)
Butyl benzyll phthalate (BBP)	50	↑NR;↓AGD	Tyl *et al.*, (2004)
Di(2-ethylhexyl phthalate (DEHP)	5	DVO;DPS	Andrade *et al.*, (2006b); Grande *et al.*, (2006)
Interim Banned			
Di-n-octyl phthalate (DNOP)	NA	NA	
Di-isononyl phthalate (DINP)	50	↑NR	Boberg *et al.*, (2011)
Di-isodecyl phthalate (DIDP)	≥600	NAE	Hushka *et al.*, (2001)
Phthalates Not Banned			
Dimethyl phthalate (DMP)	≥750	NAE	Gray *et al.*, (2000)
Diethyl phthalate (DEP)	≥750	NAE	Gray *et al.*, (2000)
Di-isobutyl phthalate (DIBP)	125	↓AGD	Saillenfait *et al., (2008)*
Dipentyl phthalate (DPENP)	11	↓T PROD	Hannas *et al.*, (2011a)
Di-n-hexyl phthalate (DHEXP)	≤250	↓AGD	Saillenfait *et al.*, (2009)
Di-cyclohexyl phthalate (DCHP)	16	↓AGD	Hoshino *et al.*, (2005)
Di-isooctyl phthalate (DIOP)	NA	NA	
Di(2-propylheptyl) phthalate (DPHP)	NA	NA	
Phthalate Substitutes			
2,2,4-trimethyl-1,3-pentanediol- diisobutyrate (TPIB)	≥1125	NAE	Eastman (2007b)
Di(2-ethylhexyl) adipate (DEHA)	≥800	NAE	Dalgaard *et al.*, (2003)
Di (2-ethylhexyl)terephthalate (DEHT)	≥750	NAE	Gray *et al.*, (2000); Faber *et al.*, (2007b)
Acetyl tri-n-butyl citrate (ATBC)	≥1000	NAE	Robins (1994); Chase & Willoughby (2002)
Cyclohexanedicarboxylic acid, dinonyl ester (DINX)	≥1000	NAE	SCENIHR (2007)
Trioctyltrimellitate (TOTM)	100	↓SP	JMHW (1998)

AGD = Anogenital Distance; NR = Nipple Retention; DVO = Delayed Vaginal Opening; DPS = Delayed Preputial Separation; NA, not available; NAE = No Anti-androgenic Effects Observed; SP; Decreased Spermatocytes and Spermatids; SVW = Seminal Vesical Weight; EPW = Epididymal Weight; T PROD = Testosterone Production

2.3.3 Reproductive and Other Toxicity Data

2.3.3.1 Interpretation of Reproductive Toxicity Data

2.3.3.1.1 General Toxicity Studies

These studies range in duration from acute to chronic and may be conducted in mice, rats, dogs, or sometimes in nonhuman primates. Their purpose does not include collection of reproductive performance data but other data may be relevant to reproductive toxicity.

- Histopathology of organs. Effects of dose, duration of treatment, sex, and recovery from exposure can all be examined.
- Organ weights. Weight of organs at time of necropsy can be very useful, especially organs from males. Weights of seminal vesicles, prostate, testis, and
- Epididymis, are often biologically significant if greater than 10% increases or decreases are seen compared to control weights. Weight changes of ovaries and uterus of females are harder to interpret because of cyclicity.
- Hormone levels may be helpful but are often not available.
- Synchronicity of organs, particularly uterus, ovary and vaginal epithelium, is helpful to assess appropriate integration of reproductive functionality.

Pharmacokinetic and pharmacodynamic studies may identify sex-related differences in absorption, metabolism, distribution, and elimination as well as differences in pathophysiology that are important in their relationship to reproductive toxicities.

2.3.3.1.2 Reproductive Studies

These studies may be non-generational (fertility only) or single or multiple generation in design. They may involve treated males or females or both and are usually conducted in rats.

- Fertility studies.
    - In females, vaginal smears are made during the dosage period. Mating is confirmed by examination for vaginal plugs. At a predetermined day of gestation, the females are sacrificed, the number of live and dead implants is counted as are the number of corpora lutea in the ovary.
    - In male fertility studies, animals are dosed for 4-10 weeks before mating with untreated females. Females are examined daily for evidence of mating (vaginal plugs). After a predetermined number of days of cohabitation, the females are sacrificed and the same data are collected as in the female fertility trial. Males are necropsied and sperm counts are conducted (low sperm counts in rodents may not be accompanied by low fertility). Organs are weighed and saved for histopathology examinations.
- Single or multigeneration reproductive study. Treated males and females are mated and percent pregnancy is calculated from the number of litters. Pups are counted and weighed to assess survival and growth. In a multigeneration study, pups are saved for parenting the next generation. Remaining pups and adults are killed for necropsy

findings, organ weights, and histopathology. The reproductive measures are repeated through successive generations.

2.3.4 **Cumulative Exposure Considerations**

Human subjects come into contact not with one individual phthalate, but with large numbers of these substances. In addition, there is exposure to other chemicals that may affect humans in ways similar to phthalates.

The combined effects of phthalates have been studied in experimental models with endpoints relevant to the disruption of male sexual differentiation. Combination effects of phthalates on other toxicological endpoints have not been evaluated.

Several experimental studies have shown that multi-component mixtures of phthalates can suppress fetal androgen synthesis in male rats after administration during critical windows of susceptibility. In these studies, the effects of all individual phthalates in the mixtures were assessed by dose-response analyses. This information was then utilized to anticipate the joint effects of the combinations, by assuming that each phthalate would exert its effects without interfering with the action of the other phthalates in the mixture (the additivity assumption). In all studies published thus far, the experimentally observed effects were in good agreement with those anticipated on the basis of the dose-response relationships of the individual phthalates in the mixture (see the review in NRC, 2008 and Howdeshell *et al.*, 2007; 2008). Of note is a very recent paper where the effects of mixtures of nine phthalates (DEHP; diisoheptyl phthalate, DIHEPP; DBP; DCHP; BBP; DPENP; DIBP; di-*n*-heptyl phthalate, DHEPP; and DHEXP) were investigated and shown to act in an additive fashion in terms of suppression of fetal androgen synthesis in rats (Hannas *et al.*, 2012). The object of all these studies was not to investigate the effect of phthalate combinations at realistic exposures in the range of those experienced by humans. Rather, their merit is in demonstrating that mixture effects of these substances can be predicted quite accurately when the potency of individual phthalates in the mixture is known. This opens the possibility of dealing with the issue of cumulative exposure to phthalates by adopting modeling approaches.

Additional studies have shown convincingly that phthalates can also act in concert with other chemicals capable of disrupting male sexual differentiation through mechanisms different from those induced by phthalates. Of relevance are chemicals that diminish androgen action in fetal life by blocking the androgen receptor, or by interfering with androgen-metabolizing enzymes, such as various carboximide and azole pesticides.

The first study to examine the combined effects of a phthalate, BBP, and an antiandrogen, the pesticide linuron, showed that the combination induced decreased testosterone production and caused alterations of androgen-organized tissues and malformations of external genitalia. The two substances together always produced effects stronger than each chemical on its own (Hotchkiss *et al.*, 2004).

The results of a much larger mixture experiments involving mixtures of the three phthalates BBP, DBP, and DEHP and the antiandrogens vinclozolin, procymidone, linuron, and prochloraz in a developmental toxicity study with rats were reported by Rider *et al.*,(2008; 2009). The mixture was able to disrupt landmarks of male sexual differentiation in a way well predictable on the basis of the potency of the individual components. For other effects, such as genital malformations (hypospadias), the observed responses exceeded those expected, indicating weak synergisms. Similar results were obtained with a mixture composed of 10 anti-androgens, including the phthalates BBP, DBP, DEHP, DIBP, DPP and DIHEXP and the pesticides vinclozolin, procymidone, prochloraz, and linuron (Rider *et al.*, 2010).

Christiansen *et al.,* (2009) evaluated a mixture composed of DEHP and vinclozolin, finasteride and prochloraz. Strikingly, the effect of combined exposure to the selected chemicals on malformations of external sex organs was synergistic, and the observed responses were greater than would be predicted from the toxicities of the individual chemicals. A dose of the mixture predicted to elicit only marginal incidences of malformations produced effects in nearly all the animals. With other landmarks of male sexual differentiation, the effect of this mixture was additive.

Unexpected interactions between TCDD and DBP in terms of epididymal and testes malformations were reported by Rider *et al.,* (2010). Although TCDD on its own did not produce these effects, there was a significant exacerbation of the responses provoked by DBP.

Of particular relevance to risk assessment is to examine whether phthalates exhibit combination effects at doses that do not induce observable effects when they are administered on their own. This is important both for phthalate mixtures and for combinations of phthalates with other antiandrogenic (AA)_agents. Unfortunately, most of the combination effect studies with the phthalates and other antiandrogens were not carried out with the intention of addressing this issue directly. That gap has been bridged in the NRC report on cumulative risk assessment for phthalates (NRC, 2008) by re-analyzing published papers. The experiment by Howdeshell *et al.,* (2008) on suppression of testosterone synthesis after developmental exposure to five phthalates indicates that phthalates are able to work together at low, individually ineffective doses. The re-analysis by NRC (2008) has shown that each phthalate was not to be expected to produce statistically significant effects at the doses at which they were present in the mixture tested by Howdeshell *et al.,* (2008). Yet, the five phthalates jointly produced significant suppressions of testosterone synthesis. The study by Rider *et al.,* (2008) also provides some indications for combination effects of phthalates and androgen-receptor antagonists at low doses.

In all experimental studies conducted thus far with phthalates, and with phthalates in combination with other chemicals, the effects of the mixture were stronger than the effect of the most potent component of the combination. This highlights that the traditional approach to risk assessment with its focus on single chemicals one-by-one may inadequately address the health risks that might arise from combined exposures to multiple chemicals.

2.4 Epidemiology

There is a rapidly growing body of epidemiological studies on the potential association of exposure to phthalates with human health. Most studies primarily focus on the association of maternal phthalate exposure with male reproductive tract developmental endpoints and neurodevelopmental outcomes. Briefly summarized below is the epidemiologic literature on phthalates and these two primary health endpoints; additional details are provided in

Appendix C. All of the studies used urinary measures of phthalate metabolites as a biomarker of exposure during gestation or early childhood. It is important to note that none of these studies were designed to provide information on the specific sources of phthalate exposure or on the proportional contribution of exposure sources to body burden. In section 2.6, the contribution of children's toys to children and women's exposure is described.

2.4.1 **Phthalates and Male Reproductive Tract Developmental**

The association of gestational exposure to phthalates and reproductive tract development was explored in three study cohorts (Table 2.2) (2005; Swan, 2008; Huang *et al.*, 2009; Suzuki *et al.*, 2012). Although the results of these studies were not entirely consistent, they represent some of the first human data to assess potential risks of developmental exposure to phthalates. The Swan (2005; 2008) and Suzuki (2012) publications reported reduced AGD in male infants in relation to higher maternal urinary concentrations of DEHP metabolites, whereas the Swan study also found similar associations of MEP and MBP with reduced AGD. The Huang study (2009) did not find associations of any phthalate metabolite with reduced AGD in boys, but did in girls.

It is well known that in rodent studies some phthalates cause the 'phthalate syndrome', consisting of, among other endpoints, reduced anogenital distance (AGD), increased prevalence of reproductive tract anomalies and poor semen quality (see section 2.2 for further details). Although it is uncertain if the 'phthalate syndrome' occurs in humans, the data on AGD are suggestive (Swan *et al.*, 2005; Swan, 2008; Suzuki *et al.*, 2012) and limited human data suggest that AGD is a relevant maker for reproductive health outcomes. Hsieh *et al.*,(2008) reported that boys with hypospadias had shorter AGD than boys with normal genitals. Mendiola (2011) showed that shorter AGD was associated with poorer semen quality (i.e., lower sperm concentration, motility and poorer morphology), while Eisenberg (2011) found shorter AGD among infertile men as compared to fertile men. These human studies demonstrated that shortened AGD is associated with reproductive conditions that are similar to those observed in rats with the phthalate syndrome. This observation supports the use of human AGD as a relevant measure to assess the anti-androgenic mode of action of phthalates during fetal development.

In conclusion, these studies provide the first human data linking prenatal phthalate exposure (specifically DEP, DBP and DEHP) with anti-androgenic effects in male offspring. These results have important relevance to the hypothesized testicular dysgenesis syndrome (TDS) in humans. Skakkebaek and co-authors (2001) hypothesized that poor semen quality, testis cancer, cryptorchidism and hypospadias were symptoms of an underlying entity referred to as TDS, which had its origins during fetal life. They further hypothesized that environmental chemicals, specifically endocrine disruptors, played an important role in the etiology of TDS through disruption of embryonal programming and gonadal development during fetal life. Currently, in humans, the evidence on the potential effects of phthalates during fetal development is limited to shortened AGD.

<u>Recommendation:</u> Based on the human data on gestational exposure and reduced AGD, exposure to DEP, DBP and DEHP metabolites should be reduced. Further studies are needed to determine if fetal exposure to phthalates is associated with other endpoints (i.e., reproductive tract malformations and altered semen quality).

Table 2.2 Phthalates and reproductive tract development.

Author, yr	Design/Sample size	Exposure	Outcomes	Results	Comments
Suzuki *et al.*, (2012)	Prospective cohort (111 mother – son pairs)	Urine concentrations of phthalate metabolites	AGD and AGI (weight–normalized index of AGD)	MEHP associated with reduced AGI, suggestive association of sum of DEHP metabolites with reduced AGI. No association of MMP, MEP, MBP, MBZP, MEHHP or MEOHP with AGI.	Small study, urine sample collected late in pregnancy, multiple examiners
Huang *et al.*, (2009)	Prospective cohort (65 mother infant pairs)	Amniotic fluid and urine concentrations of phthalate metabolites	AGD, birth length and weight, gestational length	In girls, decreased AGD in relation to amniotic fluid levels of MBP and MEHP. No associations found in boys.	Small study, no associations with male AGD
Swan *et al.*, (2005)	Prospective cohort (85 mother-son pairs)	Urine concentrations of phthalate metabolites	AGD and AGI (weight–normalized index of AGD)	Decreased AGI associated with higher urinary concentrations of MBP, MIBP, MEP, MBZP	Small study, urine sample collected late in pregnancy
Swan (2008; extension of the 2005 study)	Prospective cohort (106 mother-son pairs)	Urine concentrations of phthalate metabolites	AGD (adjusted for weight percentiles)	Decreased AGD, adjusted for weight percentiles, associated with higher urinary concentrations of MEP, MBP, MEHP, MEHHP, MEOHP	Small study, urine sample collected late in pregnancy

2.4.2 Phthalates and Neurodevelopmental Outcomes

Seven prospective pregnancy cohort studies and two cross-sectional studies investigated associations of urinary phthalate metabolites with neurological measures in infants and children (Table 2.3). Synthesizing the results across studies is difficult since they used different study designs, different sets of phthalate metabolites were measured at different times during pregnancy and their concentrations differed across studies, and most importantly the studies assessed different neurological outcomes at different ages using different tests. Despite this heterogeneity, several conclusions can be offered. More weight should be given to the results from the seven prospective cohort studies, in which urinary phthalates were measured during pregnancy and related to outcomes in infancy or childhood. Cross-sectional studies in which urinary phthalate metabolite concentrations were measured concurrent with outcome assessment are difficult to interpret because the exposure measure reflects only recent exposure (past several hours) which is likely not within the etiologic relevant exposure window.

Interestingly, although each publication utilized different neurological tests at different childhood ages, poorer test scores were generally, but not always, associated with higher urinary levels of some phthalates. However, the phthalates for which associations were reported was not always consistent and differed across publications. For instance, in the Mount Sinai School of Medicine (MSSM) Study, Engel *et al.*, (2009) found a significant decline in girls in the adjusted mean Orientation score and Quality of Alertness score (assessed with the Brazelton Neonatal Behavioral Assessment Scale within 5 days of delivery) with increasing urinary concentrations of high molecular weight phthalates, largely driven by DEHP metabolites. In Engel's second publication (Engel *et al.*, 2010) on the same cohort, but examined between ages 4 to 9 years old, they found an association of higher urinary concentrations of low molecular weight (LMW) phthalates, largely driven by MEP, with poorer scores on the Behavioral Assessment System for Children Parent Rating Scales (BASC) for aggression, conduct problems, attention problems, and depression clinical scales, as well externalizing problems and behavioral symptoms index. LMW phthalates were also associated with poorer scores on the global executive composite index and the emotional control scale of the Behavior Rating Inventory of Executive Function (BRIEF). In the third MSSM publication (Miodovnik *et al.*, 2011), higher urinary concentrations of LMW phthalates were associated with higher Social responsiveness scale (SRS) scores and positively with poorer scores on Social Cognition, Social Communication, and Social Awareness.

Both the Kim *et al.,* (2011) and Whyatt *et al.,* (2011) studies explored associations of gestational urinary phthalate metabolite concentrations with the mental developmental index (MDI) and psychomotor developmental index (PDI) assessed with the Bayley Scales of Infant Development at 6 months and 3 years of age, respectively. Whyatt found associations of MBP (DBP metabolite) and monoisobutyl phthalate (MIBP, DIBP metabolite) with decreased PDI score and in girls, MBP was associated with decreased MDI. On the other hand, Kim reported a negative association of MEHHP,[*] MEOHP and MBP with PDI, whereas MEHHP was negatively associated with MDI. In boys, MEHHP, MEOHP and MBP were negatively associated with MDI and PDI. No associations were found in girls. Therefore, there was some consistency across studies in the association of MBP with decreased MDI and PDI, but not with respect to DEHP metabolites. Sex-specific associations also varied across studies.

<u>Recommendation:</u> Based on the human data on gestational phthalate exposure and associations with poorer neurodevelopmental test scores, human exposure to DEHP, DBP and DEP metabolites should be reduced.

[*] MEHHP and MEOHP are secondary metabolites of DEHP; see Section II.E.

1027 **Table 2.3 Phthalates and neurological outcomes in newborns, infants and children.**

Author, yr	Design/Sample size	Exposure	Outcome	Results	Comments
Kim *et al.*, (2009)	Cross-sectional (261 children)	Urine concentrations of MEHP, MEOHP, MBP measured when child was 8 to 11 years	Teacher assessed ADHD symptoms and neuropsychological dysfunction measured when child was 8 to 11 years	DEHP metabolites associated with ADHD scores	cross-sectional design
Cho *et al.*, (2010)	Cross-sectional (621 children)	Urine concentrations of MEHP, MEOHP, MBP measured when child was 8 to 11 years	Full Scale IQ, Verbal IQ, Vocabulary and Block design scores measured when child was 8 to 11 years	After adjusting for maternal IQ, only DEHP metabolites associated with reduced Vocabulary score	cross-sectional design
Whyatt *et al.*, (2011)	Prospective Cohort (319 mother-child pairs)	Urinary concentrations of MBP, MBZP, MIBP, and 4 DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP). Measured during the third trimester.	Mental developmental index (MDI) and psychomotor developmental index (PDI) using Bayley Scales of Infant Development II, behavioral problems assesses by maternal report on Child behavior checklist. Assessed at 3 years of age.	MBP and MIBP associated with a decreased PDI score and with increased odds of motor delay. In girls, MBP associated with decreased MDI. MBP and MBZP associated with increased odds of clinically withdrawn behavior. MBZP associated with increased odds for clinically internalizing behavior.	single spot urine sample late in pregnancy
Kim *et al.*, (2011)	Prospective Cohort (460 mother infant pairs)	Urinary concentrations of MEHHP and MEOHP and MBP measured during third trimester	Mental (MDI) and psychomotor (PDI) development indices of Bayley Scales of Infant Development. Measured at age 6 months.	After adjusting for maternal IQ, MEHHP was negatively associated with MDI, whereas MEHHP, MEOHP and MnBP were negatively associated with PDI. In males, MEHHP, MEOHP and MBP were negatively associated with MDI and PDI. No associations for females.	single spot urine sample late in pregnancy
Swan *et al.*, (2010)	Prospective Cohort (145 mother child pairs)	Urine concentrations of phthalate metabolites (measured during third trimester)	Mother assessed play behavior (pre-school activities inventory questionnaire)	Among boys, inverse association of MBP, MIBP, DEHP metabolites (MEOHP, MEHHP, and sum of DEHP metabolites) with less masculine composite scores. No associations among girls.	single spot urine sample late in pregnancy, mother reported play behavior
Engel *et al.*, (2009)	Prospective Cohort (295 mother infant pairs)	Urine concentrations of phthalate metabolites measured during	Brazelton Neonatal Behavioral Assessment (BNBA) Scale assessed within first 5 days of	Sex-specific effects. Among girls, decline in orientation score and quality of alertness score with increased high molecular weight phthalate concentrations. Boys had improved	single spot urine sample late in pregnancy

Author, yr	Design/Sample size	Exposure	Outcome	Results	Comments
		third trimester	delivery	motor performance with increased low molecular weight phthalate concentrations.	
Engel *et al.*, (2010)	Prospective Cohort (188 mother child pairs)	Urine concentrations of phthalate metabolites measured during third trimester	Behavioral rating inventory executive function (BRIEF) and Behavioral assessment system for children parent rating scale (BASC-PRS). Assessed up to three times between age 4 and 9 years.	Higher concentrations of low molecular weight phthalates were associated with poorer BASC scores for aggression, conduct problems, attention problems, and depression scales, as well as externalizing problems and behavioral symptoms index. Low molecular weight phthalates were associated with poorer scores on global executive composite index and the emotional control scale of the BRIEF. MBP associated with aggression and externalizing problems, poorer scores on working memory.	single spot urine sample late in pregnancy
Miodovnik *et al.*, (2011)	Prospective Cohort (137 mother child pairs)	Urine concentrations of phthalate metabolites measured during third trimester	Social responsiveness scale (SRS), assessed between age 7 and 9 years	Higher urinary concentrations of low molecular weight phthalates were associated with higher SRS scores, poorer scores on social cognition, social communication, and social awareness. Associations were significant for MEP and in same direction for MBP and MMP. High molecular weight phthalate concentrations were associated with non-significantly poorer SRS scores (smaller magnitudes)	single spot urine sample late in pregnancy
Yolton *et al.*, (2011)	Prospective Cohort (350 mother infant pairs)	Urine concentrations of phthalate metabolites measured at 16 and 26 weeks gestation	Infant neurobehavior, assessed with the NICU Network Neurobehavioral Scale (NNNS), measured at five weeks after delivery	Higher total DBP metabolites (MBP and MIBP) at 26 weeks (but not at 16 weeks) gestation were associated with improved behavioral organization as evidenced by lower levels of arousal, higher self-regulation, less handling required and improved movement quality, as well as a borderline association with movement quality. In males, higher total DEHP metabolites at 26 weeks were associated with more non-optimal reflexes	Two spot urine samples at 16 and 26 weeks

2.5 Human Biomonitoring (HBM)

2.5.1 Introduction

Human biomonitoring (HBM) determines internal exposures (i.e., body burdens) by measuring the respective chemicals or their metabolites in human specimens (e.g., urine or blood). Thus, HBM represents an integral measure of exposure from multiple sources and routes (Angerer *et al.*, 2006; Needham *et al.*, 2007) and permits an integrated exposure assessment even when the quantity and quality of external exposures are unknown and/or if the significance of the contribution of different routes of exposure is ambiguous.

Urine is the ideal matrix to determine internal phthalate exposure and urinary phthalate metabolites have been used in an increasing number of HBM studies. The extent of oxidative modification increases with the alkyl chain length of the phthalate monoester. Therefore, short chain phthalates (e.g., DMP, DEP DIBP or DBP) mostly metabolize only to their simple monoesters and not further. The urinary excretion of their monoesters represents approximately 70% of the oral dose. By contrast, long chain phthalates (8 or more carbons in the alkyl chain, e.g., DEHP, DINP or DIDP) are further metabolized to oxidative side chain products (alcohols, ketones and carboxylic acids). These secondary, oxidized metabolites are the main metabolites of the long chain phthalates excreted in human urine.

HBM data can be used to quantify overall phthalate exposures, to compare exposures of the general population with special subpopulations (e.g., children or pregnant women) and with toxicological animal data. For risk assessment, biomonitoring/biomarker measurements can be used to reliably extrapolate to daily doses of the respective phthalate(s) taken up, which can then be compared to health or toxicological benchmarks (e.g., NOAEL; tolerable daily intake, TDI; reference dose, RfD) normally obtained from animal studies. HBM data can also be used in epidemiological studies to correlate actual internal exposures with observed (health) effects.

2.5.2 Objectives

The objectives of this chapter are to illustrate and quantify the omnipresence of phthalate exposure in the general population (both U.S. and worldwide) and to focus on the phthalate exposure in specific U.S. subpopulations (pregnant women, National Health and Nutrition Examination Survey, NHANES, 05/06; Study for Future Families, SFF, women and infants) that are the focus of CHAP´s task. HBM derived daily intake (DI) calculations (performed *de novo* by the CHAPs task for these subpopulations) prepare the ground for the hazard index (HI) approach of Section 2.7.

We also compare daily intakes calculated from HBM data (of the above datasets) to DI estimates from the aggregate external exposure approach/scenario-based exposure estimation approach of Section 2.6. With this approach, we can reveal the presence of exposures that are possibly not reflected in the scenario based approach (HBM DI estimation higher than Scenario-based DI estimation), thus indicating that there are pathways/sources of exposure not included in the scenario based approach; or we can reveal the presence of possible external exposures that are not reflected in the HBM approach (scenario-based DI estimation higher than HBM DI estimation), thus indicating *worst case* exposure scenarios that are not present in the HBM approach of the subpopulations investigated.

2.5.3 **Methodology**

We performed a full literature review on HBM data on phthalates (and possible phthalate substitutes). We compiled and compared worldwide HBM data and paid special attention to pregnant women (NHANES 2005-06; SFF women) and infants (SFF infants) in our further deliberations.

The biomonitoring data from the National Health and Nutrition Examination Surveys (NHANES, 2005-6 data; CDC, 2012b),[*] and biomonitoring data from the Study for Future Families (SFF; Sathyanarayana *et al.*, 2008a; 2008b); pre-natal and post-natal measurements in women and measurements in infants (age: 2-36 months) are the focus of this investigation because of the CHAP's task to investigate the likely levels of children's, pregnant women's and others' exposure to phthalates and to consider the cumulative effect of total exposure to phthalates both from children's products and other sources.

Based on HBM derived daily intake estimates in conjunction with health benchmarks for individual phthalates (hazard quotient) we evaluated the presence or absence of risk associated with each individual phthalate, and we compared the risks associated with each phthalate with risks associated with other phthalates (and thus identified key phthalates in terms of risk). In the last step we evaluated the risk associated to the cumulative phthalate exposure (by adding up the individual *hazard quotients*) as expressed in the *hazard index (HI)*, see Section 2.7.

- <u>Analysis of HBM data from pregnant women (NHANES, 2005-2006 data; CDC, 2012b):</u> 15 phthalate metabolites are measured in the NHANES 2005-2006 dataset. Of these 15 metabolites we used 12 metabolites to determine the exposure to nine parent phthalates DMP, DEP, DIBP, DBP, BBP, DEHP, DINP, and DIDP/DPHP and DNOP.

- <u>Analysis of HBM data from SFF:</u> Exposure data from the SFF in young children and their mothers were provided to the CHAP by Dr. Shanna Swan and are published in part in Sathyanarayana *et al.*, (2008a; 2008b). Urinary concentrations from twelve monoesters were measured of which we used 11 to determine exposure to 8 parent phthalates: DMP, DEP, DIBP, DBP, BBP, DEHP, DINP, and DIDP/DPHP. DNOP exposure was not reported in this study, due to a low detection frequency.

- <u>Dose extrapolations/Daily Intake (DI) calculations based on HBM data</u>

  We calculated the daily intake of each parent chemical separately per adult and child from urinary concentrations (David, 2000; Kohn *et al.*, 2000; Koch *et al.*, 2003a; Wittassek *et al.*, 2011). The model for daily intake (DI) includes the creatinine-related

[*] This cycle of NHANES was the most recent version where phthalate data were available at the time of our analyses. Previous cycles were not combined with the 2005-06 data due to study design changes associated with fasting requirements.

metabolite concentrations together with reference values for the creatinine excretion in the following form:

$$DI(\mu g/kg_{bw}/day) = \frac{UE_{sum}(\mu mole/g_{crt}) \times CE(mg_{crt}/kg/day)}{F_{UE} \times (1000 mg_{crt}/g_{crt})} \times MW_{parent}(g/mole)$$

where: E_{sum} is the molar urinary excretion of the respective metabolite(s). CE is the creatinine excretion rate normalized by bodyweight which was calculated based on equations using gender, age, height and race (Mage *et al.*, 2008).* In the SFF data, height was not measured for prenatal and postnatal women; for these women, a fixed value of CE was used based on the following logic:

- A rate of 18 mg/kg/day for women and 23 mg/kg/day for men in the general population (Harper *et al.*, 1977; Kohn *et al.*, 2000).
- Wilson (2005) noted that creatinine excretion on average increases by 30% during pregnancy. Thus we set CE to 23 mg/kg/day for these SFF women, a 30% increase from 18.

The molar fraction F_{ue} describes the molar ratio between the amount of metabolite(s) excreted in urine and the amount of parent compound taken up. Values for these fractions are given in Table 2.4.

2.5.4 **Results**

Worldwide HBM data (urinary phthalate metabolites, in µg/L) is compiled in Tables 2.5 and 2.6. Specific HBM data estimated by the CHAP is highlighted in orange. The general population and the populations in focus of the CHAP´s task are exposed to all of the phthalates investigated (nearly 100% positive detects). The spectrum of exposure to the various phthalates is rather similar over all populations investigated, and dominated by some phthalates (e.g., DEHP and DEP).

Intake estimates (DI) for phthalates (in µg/kg bw/day) are compiled in Table 2.7. Specific HBM intake data generated within this CHAP (concerning the target populations within NHANES (CDC, 2012b) and SFF (Sathyanarayana *et al.*, 2008a; 2008b)) is highlighted in orange. Daily phthalate intakes in the target populations are dominated by DEP and DEHP, followed by DINP, DIDP and DBP.

In NHANES 2005-2006, comparing pregnant women to non-pregnant women in this age range, exposures were not found to be significantly different from pregnant women compared to non-pregnant women in the same age range. In the upper percentiles, as well as with weighted analyses, there are indications that exposures might be higher in pregnant women than in women in general or in the rest of the NHANES population. Daily intakes calculated in NHANES 2005-2006, 15-45yrs, are generally comparable to DI calculated from SFF women (prenatal). The SFF pre-natal estimates for DEHP is slightly lower than the other two; and the distribution for DIDP

* When height was outside the tabulated range for gender and age categories or when weight was missing, CE was considered missing.

in NHANES is slightly lower compared to the SFF data. However, these possible shifts are within the interquartile ranges of the comparison groups.

- **Infant Data (SFF):** Inspection of the SFF data reveals that the infants might have significantly higher intakes (related to their body weights) compared to their mothers (see figure 2.2).
- **Correlations:** Correlation coefficient estimates between estimated daily intakes (DI) of the nine phthalate diesters (log10 scale) for pregnant women in NHANES 2005-06 (using survey weights) reveals two clusters with significant positive correlations: (1) low molecular weight phthalates: DBP, DIBP, BBP; and (2) high molecular weight phthalates: DEHP, DINP, and DIDP (see Table 2.8). Similar clusters of correlations can be observed in the SFF dataset (see Table 2.9).

This suggests common fields of application and/or common sources of exposure within the set of low molecular weight phthalates and within the set of high molecular weight phthalates, respectively. Furthermore this means that an individual exposed to elevated amounts of one of the high molecular weight phthalates is likely exposed to elevated amounts of the other high molecular weight phthalate, too. However, the correlations are rather low to moderate (in agreement with other human biomonitoring data) which indicates that the variability of each phthalate (metabolite) in urine is influenced by more than just one exposure source and that exposures are similar. To understand peak relationships better, more than one spot or single urine sample is required to determine when the highest intakes occur over space and time and among the individuals tested. Thus, there will always be intrinsic uncertainty associated with the use of single urine samples for each subject in the cumulative risk assessment.

2.5.5 Conclusion

The following conclusions can be drawn from phthalate HBM data:

Exposure to phthalates in the U.S. (as worldwide) is omnipresent. The U.S. population is co-exposed to many phthalates simultaneously. HBM data (urinary phthalate metabolite levels) can be used to reliably extrapolate to the daily intakes (DI) of the respective parent phthalate (and compared with health benchmarks for the individual phthalates as well as on a cumulative basis – see HI approach section 2.7).

Pregnant women in the U.S. (NHANES 2005-2006; CDC, 2012b)(NHANES 2005-2006) have similar exposures compared to women of reproductive age (and other NHANES subpopulations). Distributions are highly skewed, indicating high exposures in some women. The same is true for infants and children (SFF; Sathyanarayana *et al.*, 2008a; 2008b); furthermore, exposures in infants might be higher than in their mothers.

Within the same individuals there are correlations among the high molecular weight phthalates and among the low molecular weight phthalates, and comparing mothers with children there are indications of similar correlations. This suggests that sources and routes of exposure are similar among high molecular weight phthalates and among low molecular weight phthalates. Therefore we assume it highly likely that the substitution of one phthalate will lead to increased exposure to another (similar) phthalate.

Table 2.4 Molar Urinary Excretion Fractions (f_{ue}) of phthalate metabolites related to the ingested dose of the parent phthalate determined in human metabolism studies within 24 hours after oral application.

Phthalate	Metabolite	f_{ue}		Reference
DMP	MMP	0.69*		-
DEP	MEP	0.69*		-
DBP	MBP	0.69		Anderson *et al.*, (2001)
DIBP	MIBP	0.69*		-
BBP	MBZP	0.73		Anderson *et al.*, (2001)
DEHP	MEHP	0.062	sum: 0.452	Anderson *et al.*, (2011)
	MEHHP	0.149		
	MEOHP	0.109		
	MECPP	0.132		
DINP	cx-MINP	0.099	sum: 0.305	Anderson *et al.*, (2011)
	OH-MINP	0.114		
	oxo-MINP	0.063		
	MINP	0.03		
DIDP/DPHP	cx-MIDP	0.04	sum: 0.34	Wittassek *et al.*, (2007b); Wittassek and Angerer (2008)
	OH-MIDP	n.a.		
	oxo-MIDP	n.a.		
DNOP	MNOP			

*f_{ue} taken in analogy to DBP/MBP.

Table 2.5 Median (95th percentile)[a] concentrations (in μg/L) of DEHP and DINP metabolites in various study populations.

Reference	Sampling year	n (age)	DEHP				DiNP		
			MECHP[a]	MEHHP[a]	MEOHP[a]	MEHP[a]	cx-MINP[a]	OH-MINP[a]	oxo-MINP[a]
USA									
Blount *et al.*, (2000)	1988-1994	298 (20-60)	-	-	-	2.7 (21.5)	-	-	-
Silva *et al.*, (2004)	1999/2000	2541 (>6)	-	-	-	3.2 (23.8)	-	-	-
Marsee *et al.*, (2006)	1999-2002	214 pregnant women	-	10.8 (76.4)	9.8 (65.0)	4.3 (38.6)	-	-	-
Duty *et al.*, (2005b)	1999-2003	295 men (18-54)	-	-	-	5.0 (131)	-	-	-
Adibi *et al.*, (2008)	1999-2005	246 pregnant women	37.1 (232.2)	19.9 (149.6)	17.5 (107.6)	4.8 (46.8)	-	-	-
Meeker *et al.*, (2009)	1999-2005	242 women (pre/post)	-	11.3 (44.9) 20.4 (83.1)	10.2 (42.6) 16.0 (61.7)	4.0 (21.0) 7.15 (23.6)	-	-	-
Brock *et al.*, (2002)	2000	19 (1-3)	-	-	-	4.6	-	-	-
Duty *et al.*, (2005a)	2000-2003	406 men (20-54)	-	-	-	5.2 (135)	-	-	-
Adibi *et al.*, (2009)	2000-2004	283 pregnant women	-	11.2 (99.4)	9.9 (68.4)	3.5 (40.2)	-	-	-
CDC	2001/2002	2782 (>6)	-	20.1 (192)	14.0 (120)	4.1 (38.9)	-	-	-
CDC	2003/2004	2605 (>6)	33.0 (339)	21.2 (266)	14.4 (157)	1.9 (31.0)	-	-	-
Silva *et al.*, (2006a; 2006b)	2003/2004	129 adults	15.6 (159.3)	15.3 (120.8)	7.1 (62.4)	3.1 (17.0)	8.4 (46.2)	13.2 (43.7)	1.2 (6.6)
CDC (internet)	2005/2006	2548 (>6)	35.6 (386)	23.8 (306)	15.1 (183)	2.50 (39.7)	5.10 (54.4)	-	-
CDC (internet)	2007/2008	2604 (>6)	31.3 (308)	20.7 (238)	11.4 (130)	2.20 (27.8)	6.40 (63.0)	-	-
CHAP/NHANES	2005-2006	1181 (15-45) (weighted)	37.2 (434)	25.5 (399)	16.2 (245)	3.3 (49.4)	5.1 (47.2)		
CHAP/NHANES	2005-2006	130 preg. women (weighted)	19.9 (754)	13.3 (680)	10.0 (534)	2.4 (168)	2.7 (23.8)		
CHAP/SFF	1999-2005	343 women prenatal	22.9 (129.6)	13.7 (86.5)	12.7 (79.6)	4.4 (37.1)	3.6 (14.1)		
CHAP/SFF	1999-2005	345 women postnatal	35.7 (209.5)	20.9 (149.4)	14.9 (106.4)	6.0 (42.4)			
CHAP/SFF	1999-2005	291 Infants (0-37 months)	156.2 (388.6)	65.6 (246.1)	49.9 (174.5)	10.4 (58.4)	17.0 (97.5)		

Reference	Sampling year	n (age)	DEHP				DiNP		
			MECHP[a]	MEHHP[a]	MEOHP[a]	MEHP[a]	cx-MINP[a]	OH-MiNP[a]	oxo-MiNP[a]
Germany									
Becker *et al.*, (2004)	2001/2002	254 (3-14)	-	52.1 (188)	41.4 (139)	7.2 (29.7)	-	-	-
Wittassek *et al.*, (2007a)	2001/2003	120 (20-29)	19.5 (68.6)	14.6 (58.6)	13.4 (42.3)	5.0 (28.6)	-	2.2 (13.5)	1.3 (5.7)
Koch *et al.*, (2003b)	2002	85 (7-63)	-	46.8 (224)	36.5 (156)	10.3 (37.9)	-	-	-
Koch *et al.*, (2004b)	2003	19 (2-6) 36 (20-59)	-	49.6 (107) 32.1 (64.0)	33.8 (71.0) 19.6 (36.7)	9.0 (29.0) 6.6 (14.6)	-	-	-
Becker *et al.*,(2009)	2003-2006	599 (3-14)	61.4 (209)	46.0 (164)	36.3 (123)	6.7 (25.1)	12.7 (195)	11.0 (198)	5.4 (86.7)
Fromme *et al.*, (2007)	2005	399 (14-60)	24.9	19.5	14.6	4.6	-	5.5	3.0
Göen *et al.*, (2011)	2002-2008	240 (19-29)	14.5 (49.7)	14.4 (42.2)	9.6 (36)	4.7 (16.6)	3.7 (22.4)	3.1 (16.5)	2.2 (11.2)
Koch & Calafat (2009)	2007	45 adults	13.9 (42.9)	11.5 (35.0)	8.2 (21.5)	1.8 (8.5)	5.3 (15.5)	4.7 (16.8)	1.7 (6.7)
Denmark									
Boas *et al.*, (2010)	2006/2007	845 (4–9)	m: 30 f: 27	m: 37 f: 31	m: 19 f: 16	m: 4.5 f: 3.6	m: 7.2 f: 6.5	m: 6.6 f: 4.9	m: 3.4 f: 2.7
Frederiksen *et al.*, (2011)		129 (6-21)							
Israel									
Berman *et al.*, (2009)	2006	19 pregnant women	26.7	21.5	17.5	6.8	3.0	-	-
Netherlands									
Ye *et al.*, (2008)	2004-2006	99 pregnant women	18.4 (31.5)	14.0 (30.0)	14.5 (27.4)	6.9 (82.8)	-	2.5 (38.3)	2.2 (30.0)
Japan									
Itoh *et al.*, (2007)	2004	36 (4-70)	-	-	-	5.1	-	-	-
Suzuki *et ak.* (2009)	2005-2006	50 pregnant women	-	10.6	11.0	3.96	-	-	-
China									
Guo *et al.*, (2011)	2010	183	30.0	11.3	7.0	2.1	-	-	-
Taiwan									
Huang *et al.*, (2007)	2005-2006	76 pregnant women	-	-	-	20.6 (273)	-	-	-
Sweden									
Jönsson *et al.*, (2005)	2000	234 men (18-21)	-	-	-	<LD (54)	-	-	-

Note: Specific HBM calculations performed by the CHAP for this study are highlighted in green.

[a] 95th percentile vales are in parentheses when available.

Abbreviations: LD, limit of detection; n.s., not specified.

Table 2.6 Median (95th percentile)[a] concentrations (in µg/L) of DMP, DEP, DBP, DIBP, BBP, DNOP and DIDP metabolites in various study populations.

Reference	Sampling year	N (Age)	DMP MMP	DEP MEP	DBP MBP	DIBP MIBP	BBP MBzP	DNOP MNOP	cx-MIDP	DIDP OH-MIDP	oxo-MIDP
USA											
Blount *et al.*, (2000)	1988-1994	298 (20-60)	-	305 (3750)	41.0 (294)	-	21.2 (137)	<LD (2.3)	-	-	-
Silva *et al.*, (2004)	1999/2000	2541 (>6)	-	164 (2840)	26.0 (149)	-	17.0 (103)	<LD (2.9)	-	-	-
Marsee *et al.*, (2006)	1999-2002	214 pregnant women	-	117 (3199)	16.2 (64.5)	2.5 (13.1)	9.3 (57.8)	-	-	-	-
Duty *et al.*, (2005b)	1999-2003	295 men (18-54)	4.6 (32.1)	149 (1953)	14.3 (75.4)	-	6.9 (37.1)	-	-	-	-
Adibi *et al.*, (2008)	1999-2005	246 pregnant women	-	202 (2753)	35.3 (174.9)	10.2 (36.1)	17.2 (146.8)	-	-	-	-
Meeker *et al.*, (2009)	1999-2005	242 women (pre/post)*	0.71 (5.3) 2.1 (5.9)	131 (1340) 133 (873)	17.2 (51.8) 19.4 (68.7)	2.65 (9.0) 3.6 (14.0)	9.95 (45.8) 14.8 (64.1)	-	-	-	-
Brock *et al.*, (2002)	2000	19 (1-3)	-	184.1	22.0 (203)	-	20.2 (118)	-	-	-	-
Duty *et al.*, (2005a)	2000-2003	406 men (20-54)	4.5 (31.3)	145 (1953)	14.5 (75.1)	-	6.8 (41.3)	-	-	-	-
CDC	2001/2002	2782 (>6)	1.5 (9.8)	169 (2500)	20.4 (108)	2.6 (17.9)	15.7 (122)	<LD	-	-	-
CDC	2003/2004	2605 (>6)	1.3 (16.3)	174 (2700)	23.2 (122)	4.2 (21.3)	14.3 (101)	<LD	-	-	-
Silva *et al.*, (2006a; 2006b)	2003/2004	129 adults	-	-	-	-	-	-	4.4 (104.4)	4.9 (70.6)	1.2 (15.0)
CDC (internet)	2005/2006	2548 (>6)	<LQ (12.4)	155 (2140)	20.6 (107)	5.8 (31.6)	12.4 (93.2)	<LQ	2.70 (17.5)	-	-
CDC (internet)	2007/2008	2604 (>6)	<LQ (11.3)	124 (1790)	20.0 (110)	8.0 (39.1)	11.7 (81.4)	<LQ	2.40 (16.1)	-	-
CHAP/ NHANES	2005-2006	1161 (15-45) (weighted)			22.1 (106)	6.7 (32.2)	10.3 (63.7)		2.5 (15.8)		

Reference	Sampling year	N (Age)	DMP MMP	DEP MEP	DBP MBP	DIBP MIBP	BBP MBzP	DNOP MNOP	cx-MIDP	DIDP OH-MIDP	oxo-MIDP
CHAP/ NHANES	2005-2006	130 preg women (weighted)			16.0 (91.2)	3.2 (26.2)	8.4 (38.2)		1.5 (6.6)		
CHAP/SFF	1999-2005	343 women prenatal	1.7 (9.0)	175 (2,270)	21.0 (60.1)	3.6 (13.5)	13.4 (71.3)		3.0 (8.2)		
CHAP/SFF	1999-2005	344 women postnatal	2.1 (9.6)	128.9 (1,283)	18.9 (71.0)	4.3 (20.3)	14.7 (64.1)		2.9 (23.6)		
CHAP/SFF	1999-2005	304 Infants (0-37 months)	7.3 (25.2)	272.5 (1,890)	82.0 (300.8)	15.0 (60.4)	65.8 (314.8)		13.2 (57.9)		
Germany											
Koch *et al.*, (2007)	2001/2002	254 (3-14)	-	-	166 (624)	-	18.7 (123)	-	-	-	-
Wittassek *et al.*, (2007a)	2001/2003	120 (20-29)	-	-	57.4 (338)	31.9 (132)	5.6 (25.0)	-	-	-	-
Koch *et al.*, (2003b)	2002	85 (7-63)	-	90.2 (560)	181 (248)	-	21 (146)	<LQ	-	-	-
Fromme *et al.*, (2007)	2005	399 (14-60)	-	-	49.6 (171.5)	44.9 (183)	7.2 (45.6)	-	-	-	-
Becker *et al.*, (2009)	2003-2006	599 (3-14)	-	-	93.4 (310)	88.1 (308)	18.1 (76.2)	-	-	-	-
Göen *et al.*, (2011)	2002-2008	240 (19-29)	-	-	32.8 (132.4)	28.3 (108)	5.0 (21.2)	-	-	-	-
Koch and Calafat (2009)	2007	45 adults	<LQ (17.2)	77.5 (396)	12.6 (43.5)	13.8 (62.4)	2.5 (8.4)	<LQ	0.7 (2.6)	1.0 (4.0)	0.2 (1.1)
Denmark											
Boas *et al.*, (2010)	2006/2007	845 (4–9)	-	m: 21 f: 21	m: 130 f: 121	-	m: 17 f: 12	<LQ			
Frederiksen *et al.*, (2011)		129 (6-21)									
Israel											
Berman *et al.*, (2009)	2006	19 pregnant women	-	165	30.8	15.6	5.3	-	1.5	-	-
Netherlands											
Ye *et al.*, (2008)	2004-2006	99 pregnant women	<LQ (20.1)	117 (1150)	42.7 (197)	42.1 (249)	7.5 (95.8)	<LD	-	-	-

Reference	**Sampling year**	**N (Age)**	**DMP MMP**	**DEP MEP**	**DBP MBP**	**DIBP MIBP**	**BBP MBzP**	**DNOP MNOP**	**DIDP cx-MIDP**	**OH-MIDP**	**oxo-MIDP**
Japan											
Itoh *et al.*, (2007)	2004	36 (4-70)	-	-	43	-	-	-	-	-	-
Suzuki *et al.*, (2009)	2005-2006	50 pregnant women	6.61	7.83	57.9	-	3.74	<LQ	-	-	-
China											
Guo *et al.*, (2011)	2010	183	12.0	21.5	61.2	56.7	0.6	-	-	-	-
Taiwan											
Huang *et al.*, (2007)	2005-2006	76 pregnant women	4.3 (87.7)	27.7 (2346)	81.1 (368)		0.9 (33.4)	-	-	-	-
Sweden											
Jönsson *et al.*, (2005)	2000	234 men (18-21)	-	240 (4400)	78 (330)	-	16 (74)	-	-	-	-

Note: Specific HBM calculations performed by the CHAP for this study are highlighted in green.
[a] 95^{th} percentile vales are in parentheses when available.
Abbreviations: LD: limit of detection; LQ: limit of quantification; n.s.: not specified.

Table 2.7 Daily phthalate intake (median, in µg/kg bw/day) of selected populations back-calculated from urinary metabolite levels.

Reference	Sampling year	N (age)	DEP		DBP		DIBP		BBP		DEHP		DINP	
			Median	95th P (max)	Median	95th P (max)	Median	95th P (max)	Median	95th P (max)	Median	95th P (max)	Median	95th P (max)
USA														
David (2000)	1988-1994	289 (20-60)	12.3 [a]	93.3 (243)	1.6 [a, b]	6.9 [b] (117)	-	-	0.73 [a]	3.3 (19.8)	0.60 [a, c]	3.1 [c] (38.5)	0.21 [a, m]	1.1 [m] (14.4)
Kohn *et al.*, (2000)	1988-1994	289 (20-60)	12	110 (320)	1.5 [b]	7.2 [b] (110)	-		0.88	4.0 (29)	0.71 [c]	3.6 [c] (46)	<LD	1.7 [m] (22)
Calafat & McKee (2006)	2001-2002	2772 (6- >20)	5.5 [a]	61.7	-	-	-	-	-	-	0.9 [a, c] 2.1 [a, e] 2.2 [a, f]	7.1 [c] 16.8 [e] 15.6 [f]	-	-
Marsee *et al.*, (2006)	1999-2002	214 pregnant women	6.6	112 (1263)	0.84	2.3 (5.9)	0.12	0.41 (2.9)	0.50	2.5 (15.5)	1.3 [g]	9.3 [g] (41.1)	-	-
CHAP/ NHANES	2005-2006	1161 (15-45)	3.3	37.6	0.66	2.6	0.19	0.78	0.29	1.3	3.8	45.2	1.1	9.7
CHAP/ NHANES	2005-2006	130 pregnant women (weighted)	3.4	74.8	0.64	3.5	0.17	1.0	0.30	1.3	3.5	181	1.0	11.1
CHAP SFF	1999-2005	340 women prenatal			0.88	2.5	0.15	0.57	0.51	2.8	2.9	16.6	1.1 n=18	7.6 n=18
CHAP SFF	1999-2005	335 women postnatal			0.62	2.2	0.14	0.68	0.44	1.9	2.7	21.6	0.64 n=95	3.2 n=95
CHAP SFF	1999-2005	258 Infants (0-37 months)			2.6	10.4	0.44	2.1	1.9	8.5	7.6	28.7	3.6 n=67	18.0 n=67
Germany														
Wittassek *et al.*, (2007a)	1988/1989	120 (21-29)	-	-	7.5	21.7 (70.1)	1.1	3.6 (12.9)	0.28	0.78 (6.6)	3.9 [l]	9.9 [l] (39.8)	0.21 [n]	1.4 [n] (12.9)
Koch *et al.*, (2003b)	2002	85 (7-63)	2.3	22.1 (69.3)	5.2	16.2 (22.6)	-	-	0.6	2.5 (4.5)	[13.8] [i] 4.6 [g]	[52.1 (166)] [i] 17.0 [g] (58.2)	-	-

Reference	Sampling year	N (age)	DEP		DBP		DIBP		BBP		DEHP		DINP	
			Median	95th P (max)	Median	95th P (max)	Median	95th P (max)	Median	95th P (max)	Median	95th P (max)	Median	95th P (max)
Koch *et al.*, (2007) Wittassek *et al.*, (2007b)	2001/2002	239 (2-14)	-	-	4.1[j] 7.6[k]	14.9[j] (76.4) 30.5[k] (110)	-	-	0.42[j] 0.77[k]	2.57[j] (13.9) 4.48[k] (31.3)	4.3[g, j] 7.8[g, k]	15.2[g, j] (140) 25.2[g, k] (409)	-	-
Wittassek *et al.*, (2007a)	2001/2003	119 (20-29)	-	-	2.2	7.3 (116)	1.5	4.2 (12.6)	0.22	0.75 (1.7)	2.7[l]	6.4[l] (20.1)	0.37[n]	1.5[n] (4.4)
Fromme *et al.*, (2007b)	2005	50 (14-60)			1.7	4.2	1.7	5.2	0.2	1.2	2.2[l]	7.0[l]	0.7[n]	3.5[n]
China														
Guo *et al.*, (2011)	2010	183	1.1	-	8.5	-	-	-	-	-	3.4	-	-	-
Japan														
Itoh *et al.*, (2007)	2004	35 (20-70)	-	-	1.3	(4.5)	-	-	-	-	1.8[d]	(7.3)[d]	-	-
Suzuki *et al.*, (2009)	2005-2006	50 pregnant women	0.28	(42.6)	2.18	(6.91)	-	-	0.132	(3.2)	1.73[o]	(24.6)[o]	0.06[m]	(4.38)[m]

Note: Specific HBM calculations performed by the CHAP for this study are highlighted in green.

[a] Geometric mean
[b] No differentiation between DBP and DIBP
[c] Based on UEF of MEHP determined by Anderson *et al.*, (2001)
[d] Based on UEF of MEHP determined by Koch *et al.*, (2004a; 2005)
[e] Based on UEF of OH-MEHP determined by Koch *et al.*, (2004a; 2005)
[f] Based on UEF of oxo-MEHP determined by Koch *et al.*, (2004a; 2005)
[g] Based on uefs for MEHP, OH-MEHP and oxo-MEHP determined by Koch *et al.*, (2004a; 2005)
[h] 634 persons, urine samples collected between 1988 and 2003
[i] Based on uefs for MEHP, OH-MEHP and oxo-MEHP determined by Schmid and Schlatter (1985)
[j] Creatinine based calculation model
[k] Volume based calculation model
[l] Based on uefs of five DEHP metabolites determined by Koch *et al.*, (2004a; 2005)
[m] Based on urine levels of MINP
[n] Based on urine levels of OH-MINP, oxo-MINP, and cx-MINP

Table 2.8 Pearson correlation coefficient estimates between estimated daily intakes (DI) of the eight phthalate diesters (log10 scale) for pregnant women in NHANES 2005-06 (estimated using survey weights). Highlighted values indicate clusters of low molecular weight diesters and high molecular weight diesters.

Estimate	DMP	DEP	DIBP	DBP	BBP	DEHP	DINP	DIDP
DMP	1	0.20	-0.02	-0.19	-0.05	-0.11	0.03	0.09
DEP	0.20	1	0.12	0.12	0.04	-0.17	-0.06	0.14
DIBP	-0.02	0.12	1	0.59*	0.38*	-0.13	-0.04	0.12
DBP	-0.19	0.12	0.59*	1	0.59*	-0.05	0.17	0.15
BBP	-0.05	0.04	0.38*	0.59*	1	-0.06	0.17	0.23
DEHP	-0.11	-0.17	-0.13	-0.05	-0.06	1	0.40*	0.26*
DINP	0.03	-0.06	-0.04	0.17	0.17	0.40*	1	0.52*
DIDP	0.09	0.14	0.12	0.15	0.23	0.26	0.52*	1

Table 2.9 Pearson correlation estimates (* p<0.05) for estimated daily intake (DI) values (log10 scale) for postnatal values with DI values estimated in their babies in the SFF study. N=251, except for *DINP and DIDP, where N=62.

Estimated P value	DEP	DIBP	DBP	BBP	DEHP	DINP	DIDP
DEP		-0.05	-0.003	-0.08	-0.04	-0.10	-0.15
DIBP	0.06		0.06		0.08	0.02	0.02
DBP	0.17*	0.10	0.12	-0.04	0.09	0.19	0.22
BBP		-0.03	0.01		-0.06	0.16	0.13
DEHP	0.06	0.02	0.03	0.05		0.18	
DINP	0.02	0.01	0.06	0.03	0.15		
DIDP	-0.13	0.004	0.02	-0.09	0.15		

2.6 Scenario-Based Exposure Assessment

2.6.1 Introduction

There are a multitude of home care products, toys, and other personal products and each can yield varying durations, intensities and frequencies of contact with individual and multiple phthalates over the course of a year. These contacts can lead to acute or chronic exposures among the users of individual products. Similarly, women who are pregnant or are of reproductive age will also contact products that contain phthalates. For children, the subject of the CHAP, we need to focus not only on the prenatal exposures but the exposures that occur during infancy and childhood, and most directly on toys and other products that are associated with children, e.g., teethers. The types of products will be different for a woman of reproductive age than a child, and the significance of the exposure on the unborn child can be related to when the exposures occur during a pregnancy.

The range of contacts with phthalates can be large in terms of number of products, duration and frequency of contact, and the ages during which the contacts will occur among young children and a woman of reproductive age. The nature of the contacts can be repetitive or periodic in character. For instance, cosmetics and children's personal products will be used regularly, but the use of toys can be periodic based upon level of interest, and/or the time of the year. Having such a variety of potential contacts will lead to variability in the levels detected in the urine, but there should be a baseline level that is derived from the types of products that are used routinely by an individual, and that level will be built upon the baseline that is associated with phthalates that are ingested because of their presence in foods and food packaging. In each case, however, the exposures to specific phthalates may not be the same since the phthalates used may be different in individual products, and there may be varying degrees of actual contact with each for each subgroup of concern.

2.6.1.1 Objectives

Given the complex nature of human exposures to phthalates from a multitude of sources and media, a comprehensive analysis based on sound scientific principles was conducted to assess phthalate human exposures. This assessment used the indirect method of assessing phthalate exposures to various human sub-populations that included pregnant women/women of reproductive age (age 15 to 44), infants (age 0 to <1), toddlers (age 1 to <3), and children (age 3 to 12). The specific objectives included estimating aggregate human exposures to eight phthalates (BBP, DBP, DEP, DEHP, DIBP, DIDP, DINP, and DNOP) by estimating human exposures to a variety of environmental sources, consumer products, household media, and food products. The exposure routes investigated included inhalation, direct and indirect ingestion, and dermal contact. Our goal is to determine the significance of exposure to phthalates in toys as a major part of our risk assessment and for comparison to biomonitoring data. In addition, to meet part of the charge, we estimated exposure to toddlers and infants for all soft plastic articles, except pacifiers. These compounds included the phthalates DINP and DEHP and the phthalate substitutes TPIB, DINX, ATBC, and DEHT. Although certain phthalates are currently banned in toys and child care articles, we estimated exposures that would hypothetically occur if phthalates were allowed in these products.

2.6.2 Methodology

Phthalate concentrations in various sources and media, and associated with specific human activities were used to predict the exposure distributions within each sub-population. Thus, the approach focused on the phthalate concentrations associated with sources rather than in the receptors (humans), and encompassed all the complex interactions between humans and the phthalate containing products and sources via specific routes of exposure. The example shown in Figure 2.1 show seven important routes and pathways of human exposure to phthalates. It also shows how each exposure route is associated with products and sources containing phthalates and which sub-populations are targeted by these specific exposure route and product/source combinations.

For the non-phthalate materials we only had data that could estimate exposure caused by mouthing, which would be called non-dietary ingestion.

A step-by-step approach was used to estimate scenario-based aggregate human exposures to phthalates and phthalate alternatives, and is provided in Appendices E1 to E3. This approach includes: 1) compilation of concentrations, 2) compilation of human exposure factors, 3) estimation of route-specific exposures, and 4) estimation of aggregate exposures.

2.6.3 Results

2.6.3.1 Pregnant Women/Women of Reproductive Age

The daily exposures (both mean and 95th percentile) for each of the eight phthalates for the seven separate exposure sources (including diet, prescription drugs, cosmetics, toys, child care articles, indoor environment, and outdoor environment) for all sub-populations are provided in Appendix E1 (Table E1-19) . Tables E1-3 through E1-22 in Appendix E1 tabulate the mean and 95th percentile concentrations, exposure factors, and daily exposures for pregnant women. The aggregate daily exposures (mean and 95th percentile) for each of the four sub-populations for each of the eight phthalates are reported in Table 2.11. These exposures constitute the total daily exposure from all sources and media and all exposure routes for a particular phthalate.

The information in Table 2.11 indicates that the highest estimated exposures to women were from DEP, DINP, DIDP, and DEHP. Exposures from DBP, DIBP, BBP, and DNOP were negligible (<1 µg/kg-d). The contributions for the aggregate exposures for each of the eight phthalates for women from various exposure routes are shown in Figure 2.1. The main source of phthalate exposure to pregnant women/women of reproductive age was from food, beverages and drugs via direct ingestion. In addition to ingestion, pregnant women were also exposed to DEP from cosmetics, and to DEHP, and DINP from the indoor environment. Upper bound exposures of women for different phthalates are shown in Table 2.11.

2.6.3.2 Infants

Tables E1-3 through E1-22 in Appendix E1 provide the mean and 95th percentile concentrations, exposure factors, and daily exposures for infants. The aggregate daily exposures (mean and 95th percentile) for infants for each phthalate are provided in Table 2.11. Infants were primarily exposed to DINP, DEHP, DIDP, DNOP, DEP and BBP, with DINP, DEHP, and DIDP being the highest contributors. The exposure to DINP was the highest in infants primarily from diet, but also due to the presence of DINP in teethers and toys through mouthing (Figure 2.2). DINP is currently subject to an interim ban; thus exposures are mouthing are hypothetical. It can also be seen in Figure 2.2 that similar to pregnant women, the main source of phthalate exposures to infants was from ingestion that included sources like food, and beverages. In addition to food, the other main contributors were teethers and toys (via mouthing), and cosmetics such as lotions, creams, oils, soaps, and shampoos via dermal contact. Upper bound daily exposures for infants across phthalates are shown Table 2.11.

2.6.3.3 Toddlers

Tables E1-3 through E1-22 in Appendix E1 provide the mean and 95^{th} percentile concentrations, exposure factors and daily exposures for toddlers. The aggregate daily exposures (both mean and 95^{th} percentile) of toddlers for each of the eight phthalates are tabulated in Table 2.11. Toddlers were primarily exposed to DINP, DIDP, and DEHP. The contributions to exposure from DNOP, BBP, and DEP were moderate. DBP and DIBP were less than 1 µg/kg-d. Exposure to toddlers from DIDP, DIBP, and DINP was primarily from food and beverages (Figure 2.1). It should be noted that the toddler exposures to phthalates via ingestion were the highest among all other sub-populations. This was because they consume almost all the food products that are consumed by adults and since they have much lower body weights, their daily exposures resulted in being the highest. Similar to infants, toddlers too were exposed to DINP via mouthing of teethers and toys. Toddlers were also exposed to DNOP, DEHP, and DINP by dermal contact with child care articles. However, their exposures from mouthing were much lower than that estimated for infants.

2.6.3.4 Children

Tables E1-3 through E1-22 in Appendix E1 provide the mean and 95^{th} percentile concentrations, exposure factors, and daily exposures for children. The aggregate daily exposures (mean and 95^{th} percentile) for children for each of the eight phthalates are tabulated in Table 2.11. Children were primarily exposed to DINP, BBP, and DIDP. Exposure to DNOP, DEP, and DEHP were moderate. Exposures to children from DIDP and DNOP were from food and beverages (Figure 2.1). DEP exposure was from cosmetics, drugs, and the indoor environment. The indoor environment (mainly household dust) was an important source of DEHP exposure to children.

2.6.4 Phthalate Substitutes

A summary of the major results are presented in Table 2.12. We demonstrate that all exposures in µg/kg-d for each compound are within one order of magnitude of each other for means and 95^{th} percentiles. Daily exposures range from 0.4 to 7.2 µg/kg-d. These were derived from migration rates measured during laboratory experiments, in combination with mouthing durations from a study of children's mouthing behavior. The mouthing durations are for all soft plastic articles, except pacifiers. Pacifiers are made from natural rubber or silicone. Additional details are found in Appendix E2.

2.6.5 Summary of Design

The overall goal was to obtain phthalate related data from the U.S. that were published in the last ten years and use the data to estimate inhalation, ingestion, and dermal exposures to phthalates from contacts with children's toys, and other sources/products. Given the multitude of complex human behavioral patterns and their interactions with various phthalate containing products, and the lack of major field studies it was also necessary to use data from other countries within North America and Europe and data prior to the year 2000. Finally, in cases where data were not available, professional judgment was used to estimate some of the parameters. These estimates were usually performed assuming worst case scenarios which resulted in high exposures. Thus, the results obtained from this analysis only can provide order of magnitude estimates of the potential exposure. More data are needed to refine these estimates.

The estimates apply to activities where one is in contact with a specific phthalate. Thus, results are indicative of non-homogeneous exposures to the individual phthalates from a particular sub-population. The selection of specific scenarios for the exposure assessment completed for this report is designated to replicate the meaningful components of a day or year in the life of an infant, toddler, child, or woman. For non-phthalate exposures, again, we can only address a specific scenario (mouthing soft plastic articles).

2.6.6 Conclusions

1. The highest estimated phthalate exposures to women were associated with DEP, DINP, DIDP, and DEHP. The main sources of phthalate exposure for pregnant women/women of reproductive age were from food, beverages and drugs via direct ingestion. In addition to ingestion, pregnant women were also exposed to DEP from cosmetics, and to DINP, DIDP, and DEHP via incidental ingestion of household dust and dermal contact with gloves and home furnishings.
2. Infants were primarily exposed to DINP, DEHP, DIDP, DEP, DNOP, DEP and BBP, with DINP, DEHP, and DIDP being the highest contributors. The exposure to DINP was the highest in infants primarily from diet, but also due to the presence of DINP in teethers and toys through mouthing (prior to the interim ban). The other important contributors to exposures for each phthalate besides DINP were teethers and toys (via mouthing) and cosmetics like lotions, creams, oils, soaps, and shampoos via dermal contact. Toddlers were primarily exposed to DINP, DIDP, and DEHP. The contributions from DNOP, BBP, and DEP were moderate. Exposure to toddlers from DIDP, DIBP, and DINP was food and beverages. The above notwithstanding, we determined that the toddler exposures to phthalates via ingestion were the highest among all other sub-populations (Figure 2.2). Similar to infants, toddlers were also exposed to DINP via mouthing of teethers and toys. However, their estimated exposures for mouthing behavior were much lower than those of infants.
3. Older children were primarily exposed to DINP, BBP, and DIDP. Exposure to DNOP, DEP, and DEHP were moderate. Exposure to children from DIDP and DNOP was from food and beverages (Figure 2.1). DEP exposure was from cosmetics, drugs, and the indoor environment. The indoor environment (mainly household dust) was an important source of DEHP exposure to children.
4. Phthalate substitutes. The results are limited since we have little information on all routes of exposure. However, Table 2.12 shows that, of the substitutes, ATBC yielded the highest overall average estimates of mouthing soft objects exposures, and these are equivalent to DINP exposures for the same sources. Due to the limited data available no

conclusions can be drawn other than the need to immediately complete well designed exposure studies for all routes and sources since these are being used in consumer products. Furthermore, these compounds need to be added to biomonitoring studies in the future. These data are necessary for exposure assessments associated with aggregate risk from individual compounds and cumulative risk from multiple compounds.

2.6.7 General Conclusion and Comment

Overall, food, beverages, and drugs via direct ingestion, and *not children's toys and their personal care products*, constituted the highest phthalate exposures to all sub-populations., with the highest exposure (Figure 2.1) being dependent upon the phthalate and the products that contain it. DINP had the maximum potential of exposure for infants, toddlers, and older children (Figure 2.2). DINP exposures were primarily from food, but also from mouthing teethers and toys and dermal contact with child care articles and home furnishings (Figure 2.1). The findings of this study were more or less in compliance with other phthalate exposure assessments; studies that use the direct approach (bio-monitoring studies) as well as those that utilize the indirect approach (Table 2.13) (Wormuth *et al.*, 2006; Clark *et al.*, 2011). The estimated aggregate exposures were typically higher than some of the other estimates and this could be because of some of the worst-case assumptions that were carried out for this study. Nevertheless, the results are within an order of magnitude from other findings and they provide the CPSC the ability to eliminate certain products and phthalates for further consideration in the completion of a cumulative risk assessment across products and across the populations considered at risk in this analysis because of exposures to phthalates. In addition, modeled exposure estimates are in general agreement with exposure estimates developed by the CHAP from biomonitoring data (Table 2.14).

Table 2.10 Sources of exposure to phthalate esters (PEs) included by exposure route.

Source	Target Population (age range)			
	Women (15 to 44) [a]	**Infants** (0 to <1)	**Toddlers** (2 to <3)	**Children** (3 to 12)
Children's Products				
teethers & toys	D [b]	O, D	O, D	D
changing pad	--	D	D	--
play pen	--	D	D	--
Household Products				
air freshener, aerosol	I (direct) [c]	I (indirect) [d]	I (indirect)	I (indirect)
air freshener, liquid	I (indirect)	I (indirect)	I (indirect)	I (indirect)
vinyl upholstery	D	--	D	D
gloves, vinyl	D	--	--	--
adhesive, general purpose	D	--	--	--
paint, aerosol	I, D	--	I (indirect) [d]	I (indirect) [d]
adult toys	Internal	--	--	--
Cosmetic Products				
soap/body wash	D	D	D	D
shampoo	D	D	D	D
skin lotion/cream	D	D	D	D
deodorant, aerosol	D, I (direct)	I (indirect)	I (indirect)	D, I (direct) [e]
perfume, aerosol	D, I (direct)	I (indirect)	I (indirect)	D, I (direct) [e]
hair spray, aerosol	D, I (direct)	I (indirect)	I (indirect)	D, I (direct) [e]
nail polish	D	--	--	D
Environmental Media				
outdoor air	I	I	I	I
indoor air	I	I	I	I
dust	O	O	O	O
soil	O	O	O	O
Diet				
food	O	O	O	O
water	O	O	O	O
beverages	O	O	O	O
Prescription drugs	O	--	O	O

[a] Age range, years.
[b] D, dermal; O, oral; I, inhalation.
[c] Includes direct exposure from product use.
[d] Indirect exposure from product use by others in the home.
[e] Females only.

Table 2.11 Estimated mean and 95th percentile total phthalate ester (PE) exposure (µg/kg-d) by subpopulation.

Phthalate	Women (15 to <45)		Infants (0 to <1)		Toddler (1 to <3)		Children (3 to 12)	
	Mean	*0.95*	*Mean*	*0.95*	*Mean*	*0.95*	*Mean*	*0.95*
DEP	18.1	398	3.1	14.9	2.8	2187.8	2.8	1149
DBP	0.29	5.7	0.65	1.8	0.83	2.3	0.55	7.4
DIBP	0.15	0.50	0.48	1.5	0.86	3.0	0.45	1.6
BBP	1.1	2.6	1.8	4.1	2.4	5.9	1.1	2.5
DNOP	0.17	21.0	4.5	9.8	5.5	16.1	1.5	2.8
DEHP	1.6	5.6	12.3	33.8	15.8	46.7	4.4	29.2
DINP	5.1	32.5	21.0	58.6	31.1	94.6	14.3	55.1
DIDP	3.2	12.2	10.0	26.4	16.6	47.6	9.1	28.1

Table 2.12 Estimated oral exposure (µg/kg-d) from mouthing soft plastic objects, except pacifiers.[a]

Plasticizer	Age Range								
	3 to <12 months			12 to <24 months			24 to <36 months		
	Mean [b]	*R(0.95)*	*T(0.95)*	*Mean*	*R(0.95)*	*T(0.95)*	*Mean*	*R(0.95)*	*T(0.95)*
ATBC	2.3	7.2	5.1	1.5	4.7	2.8	1.4	4.3	3.4
DINX	1.4	3.6	5.4	0.89	2.3	3.1	0.82	2.1	3.6
DEHT	0.69	1.8	2.8	0.45	1.2	1.5	0.41	1.1	1.8
TPIB	0.92	5.8	3.8	0.60	3.8	2.0	0.55	3.4	2.4

[a] Results rounded to two significant figures.
[b] Mean, calculated with the mean migration rate and mean mouthing duration; R(0.95), calculated with the 95th percentile migration rate and mean mouthing duration; T(0.95), calculated with the mean migration rate and 95th percentile mouthing duration.

Table 2.13 Comparison of modeled estimates of total phthalate ester (PE) exposure (μg/kg-d).

Phthalate	Study	Adult female		Infants		Toddlers		Children	
		Ave. [a]	*U.B.*	*Ave.*	*U.B.*	*Ave.*	*U.B.*	*Ave.*	*U.B.*
DEP	Wormuth [b]	1.4	65.7	3.5	19.4	1.5	8.1	0.7	4.6
	Clark [c]	--	--	0.3	1.2	1.2	3.8	0.9	2.8
	CHAP [d]	18.1	398	3.1	14.9	2.8	2188	2.8	1149
DBP	Wormuth	3.5	38.4	7.6	43.0	2.7	24.9	1.2	17.7
	Clark	--	--	1.5	5.7	3.4	12.0	2.4	8.1
	CHAP	0.3	5.7	0.6	1.8	0.8	2.3	0.5	7.4
DIBP	Wormuth	0.4	1.5	1.6	5.7	0.7	2.7	0.3	1.2
	Clark	--	--	1.3	5.5	2.6	6.2	2.1	4.8
	CHAP	0.1	0.5	0.5	1.5	0.9	3.0	0.5	1.6
BBP	Wormuth	0.3	1.7	0.8	7.9	0.3	3.7	0.0	1.1
	Clark	--	--	0.5	6.1	1.5	6.1	1.0	4.0
	CHAP	1.1	2.6	1.8	4.1	2.4	5.9	1.1	2.5
DEHP	Wormuth	1.4	65.7	3.5	19.4	1.5	8.1	0.7	4.6
	Clark	--	--	5.0	27.0	30.0	124	20.0	81.0
	CHAP	1.6	5.6	12.3	33.8	15.8	46.7	5.4	16.6
DINP	Wormuth	0.004	0.3	21.7	139.7	7.1	66.3	0.2	5.4
	Clark	--	--	0.8	9.9	2.1	8.7	1.3	5.5
	CHAP	5.1	32.5	21.0	58.6	31.1	94.6	14.3	55.1

[a] Ave., average; U.B., upper bound.
[b] (Wormuth *et al.*, 2006). Mean and maximum exposure estimates. Women (female adults; 18 to 80 years); infants (0 to 12 months); toddlers (1 to 3 years); children (4 to 10 years).
[c] (Clark *et al.*, 2011). Median and 95th percentile exposure estimates. Combined male and female adults (20-70 years; not shown here); infants (neonates; 0 to 6 months); toddlers (0.5 to 4 years); children (5 to 11 years).
[d] This study. Mean and 95th percentile exposure estimates. Women (women of reproductive age; 15 to 44 years); infants (0 to <1 year); toddlers (1 to <3 years); children (3 to 12 years).

Table 2.14 Comparison of modeled exposure estimates of total phthalate ester (PE) exposure (μg/kg-d) with estimates from biomonitoring studies.

Phthalate	Method [a]	Women		Infants	
		Ave. [b]	*0.95*	*Ave.*	*0.95*
DEP	*Modeled*	18.1	398.0	3.1	14.9
	SFF [c]	NR	NR	NR	NR
	NHANES	3.4	74.8	NR	NR
DBP	*Modeled*	0.3	5.7	0.6	1.8
	SFF	0.8	2.4	1.7	7.0
	NHANES	0.6	3.5	NR	NR
DIBP	*Modeled*	0.1	0.5	0.5	1.5
	SFF	0.1	0.6	0.3	1.4
	NHANES	0.2	1.0	NR	NR
BBP	*Modeled*	1.1	2.6	1.8	4.1
	SFF	0.5	2.4	1.2	6.5
	NHANES	0.3	1.3	NR	NR
DEHP	*Modeled*	1.6	5.6	12.3	33.8
	SFF	2.8	19.1	5.5	25.8
	NHANES	3.5	181	NR	NR
DINP	*Modeled*	5.1	32.5	21.0	58.6
	SFF	0.7	5.4	3.5	16.5
	NHANES	1.1	11.1	NR	NR
DIDP	*Modeled*	3.2	12.2	10.0	26.4
	SFF	1.9	21.3	6.0	25.6
	NHANES	1.7	5.7	NR	NR
r	*SFF*	0.21		0.66	
	NHANES	0.62		--	

[a] Biomonitoring results from section 2.5, based on data from NHANES (pregnant women; 2005—2006) and the Study for Future Families (SFF; Sathyanarayana *et al.*, 2008a; 2008b), Section 2.5. Modeling results from this section (2.6).

[b] Ave., average, mean (modeled) or median (NHANES and SFF); 0.95, 95th percentile; NR, not reported; r, is the correlation coefficient for this study compared to either NHANES or SFF (average exposures).

[c] Data for SFF women are the average of prenatal and postnatal values.

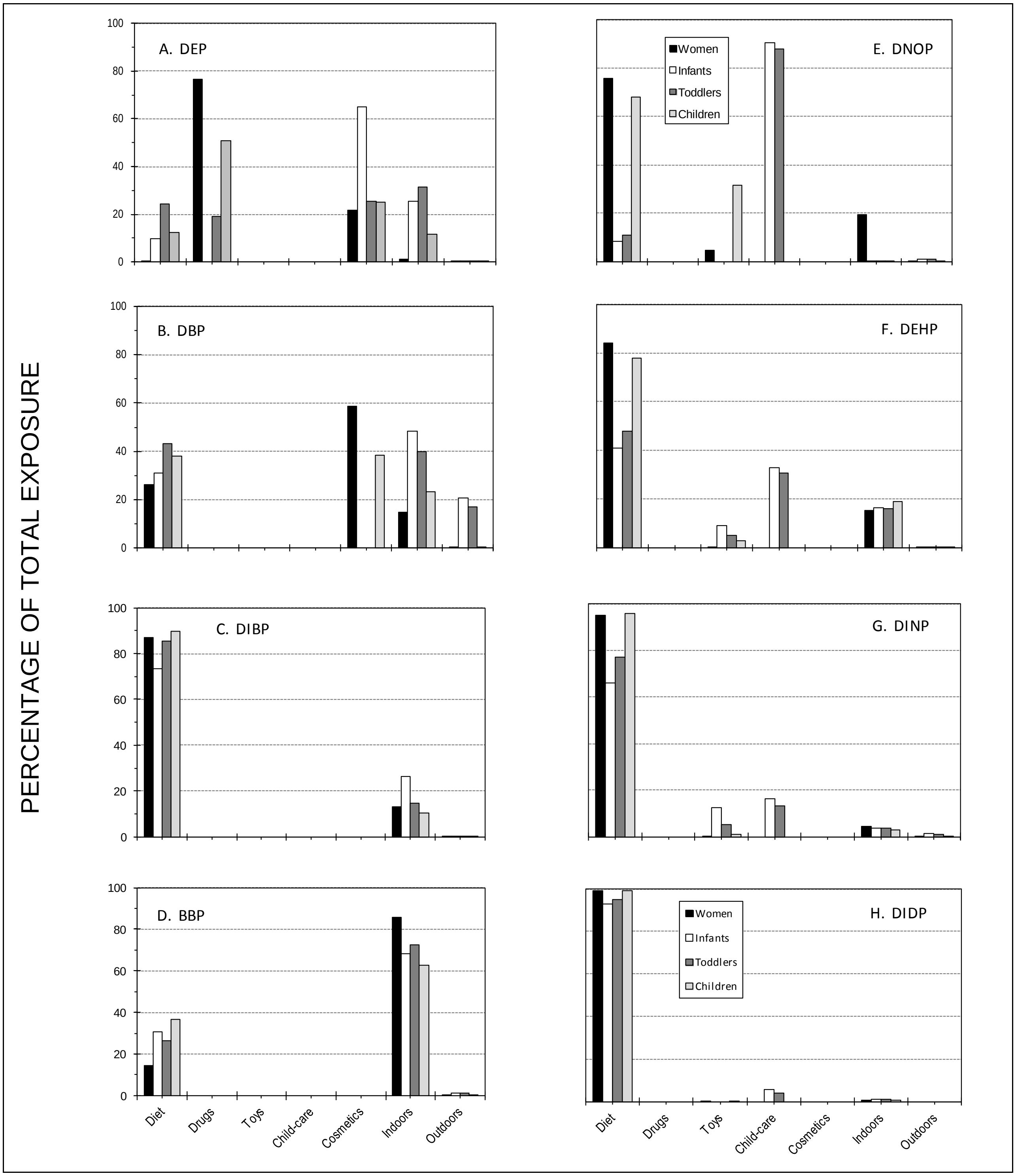

Figure 2.1 Sources of phthalate ester exposure. Percentage of total exposure for seven sources: (1) diet, (2) prescription drugs, (3) toys, (4) child care articles, (5) cosmetics, (6) indoor sources, and (7) outdoor sources. Solid black bars, women; white bars, infants; dark gray bars, toddlers; and light gray bars, children. See Appendix E1 for additional details.

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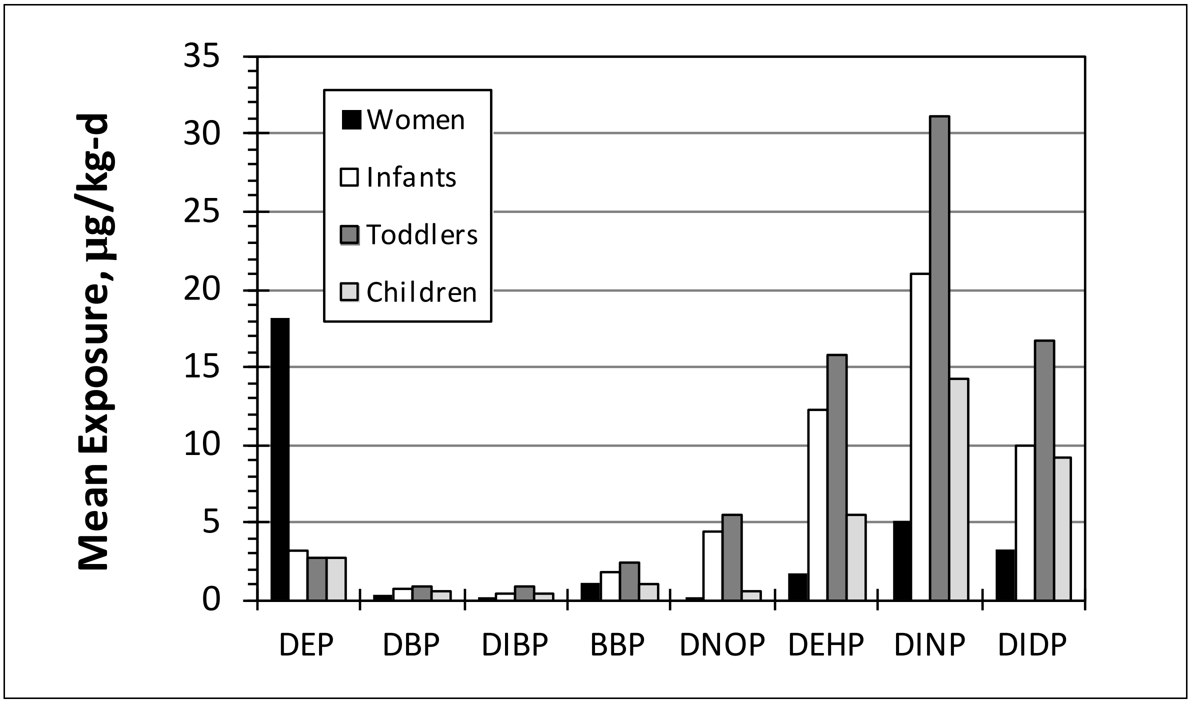

Figure 2.2 Estimated phthalate ester exposure (µg/kg-d) for eight phthalates and four subpopulations.

2.7 Hazard Index Approach

2.7.1 Choice of Approach for Quantitative Risk Assessment

As described previously (Section 2.3; NRC, 2008), some phthalates – such as DBP, DIBP, BBP, DEHP, and DINP – are able to disrupt male sexual differentiation; this culminates in what has been described as the phthalate syndrome or more generally as the androgen-insufficiency syndrome. The NRC (2008) monograph on phthalates addressed the question of whether a cumulative risk assessment for phthalates should be conducted, and if so, to identify approaches that could be used. The report concluded that the risks associated with phthalates should be evaluated by taking account of combined exposures.

Dose addition and *independent action* are two concepts that allow quantitative assessments of cumulative effects by formulating the expected (additive) effects of mixtures. Experimental data on combination effects of phthalates from multiple studies (e.g., Howdeshell *et al.*, 2008) provide strong evidence that dose addition can produce accurate predictions of mixture effects when the effects of all components are known. The NRC phthalates panel concluded that independent action often yielded similar quantitative predictions but in some cases led to substantial underestimations of combined effects (NRC, 2008). Following the work of this committee, CHAP could not identify a case in which independent action predicted combined effects that were in agreement with experimentally observed responses and at the same time were larger than the effects anticipated by using dose addition. Thus, CHAP concludes the assumption of dose addition is adequate for mixtures of phthalates and other anti-androgens for the foundation of a cumulative risk assessment.

The concept of *dose addition* has also been used as a basis for cumulative risk assessment methods. The Hazard Index (HI), the Point of Departure Index (PODI) or Toxicity Equivalency Factors (TEF) are examples of cumulative risk assessment approaches derived from *dose addition*.

The Hazard Index (HI) is widely used in cumulative risk assessment of chemical mixtures (Teuschler and Hertzberg, 1995; Kortenkamp and Faust, 2010). It is the sum of hazard quotients (HQs) defined as the ratio of exposure (e.g., estimate of daily intake, DI) to an acceptable level for a specific chemical for the same period of time (e.g., daily). Here, we define the acceptable level by the reference dose (RfD) defined by *in vivo* developmental evidence of anti-androgenic effects (AA):

$$\textbf{Hazard Quotient } (\mathrm{HQ_j}) = \frac{\mathrm{DI_j}(\mu\mathrm{g/kg/day})}{\mathrm{RfD_j}(\mathrm{AA};\ \mu\mathrm{g/kg/day})}$$

and

$$\textbf{Hazard Index (HI)} = \sum_{j=1}^{c} \mathrm{HQ_j}$$

where: *c* is the number of chemicals in the index.

The RfDs can be selected by either accessing established health benchmarks (e.g. the RfDs of the US EPA; ADIs of the CPSC) or by using NOAELs as points of departure (PODs) adjusted with uncertainty factors.

The HI offers flexibility in applying different uncertainty factors when defining RfDs for the individual substances. It is not necessary that each RfD is based on the same toxicological endpoint, but for the purposes of this analysis the requirement was made only to consider endpoints with relevance to anti-androgenicity. The Point of Departure Index (PODI) (Wilkinson *et al.*, 2000) shows similarities with the HI method, but instead of relating estimates of daily intake to RfD, their respective points of departure (PODs) (NOAELs or Benchmark doses) are used. In this way, uncertainty factors of differing numerical values that may be included in the RfD values for building the HI are removed from the calculation. An overall uncertainty factor for the mixture is used instead. However, in cumulative risk assessment for phthalates it was necessary to deal with toxicological data of differing quality. This meant that different uncertainty factors were used for deriving RfDs. The PODI method cannot provide the flexibility that is needed in dealing with differing data quality. For this reason, the HI method was given preference here.

Three different sources for RfDs were applied in the HI approach (3 cases). Case 1 includes published values used in a cumulative risk assessment (CRA) for mixtures of phthalates (Kortenkamp and Faust, 2010), case 2 includes values derived from recently published and highly reliable relative potency comparisons across chemicals from the same study (Hannas *et al.*, 2011b), and case 3 includes values from the *de novo* literature review conducted by the CHAP of reproductive and developmental endpoints focused on reliable NOAELs and PODs (Table 2.1). We considered these three cases to determine the sensitivity of the results to the assumptions for RfDs and the total impact on the HI approach.

To estimate daily intakes of mixtures of phthalates in pregnant women we used human biomonitoring data (see section 2.4). Human biomonitoring determines internal exposures (i.e., body burden) to phthalates by measuring specific phthalate metabolites in urine. Thus, biomonitoring represents an integral measure of exposure from multiple sources and routes (Angerer *et al.*, 2006; Needham *et al.*, 2007). Biomonitoring data provides evidence of exposure to mixtures of phthalates on an individual subject basis.

CHAP has used a novel approach to calculate the HI by calculating it for each individual based on their urinary concentrations of mixtures of phthalates (in our case, for each pregnant woman and infant). This is in contrast to the standard HI method of using population percentiles from exposure studies on a per chemical basis.

We applied data from two biomonitoring studies:

1. National Health and Nutrition Evaluation Surveys (2005-06)
2. Study for Future Families (SFF; Sathyanarayana *et al.*, 2008a; 2008b) with pre-natal and post-natal measurements in women. The SFF data also include concentrations from infants (age: 2-36 months).

2.7.2 **Summary Description of Methods Used**

Details of the analysis of the NHANES and SFF data are provided in Appendix D. Summary methods and results are presented here.

2.7.2.1 **Chemicals**

We initially included in our analyses six phthalates described in the Consumer Product Safety Improvement Act:

- DEHP, DBP, and BBP: banned chemicals; and
- DINP, DIDP, and DNOP: chemicals with interim prohibition on their use.

Since DIBP is also known to be anti-androgenic (comparable to DBP), we included it in the analysis. However, exposure estimates for DNOP were not available in the SFF (Sathyanarayana *et al.*, 2008a; 2008b) data and were generally not detectable in NHANES. Thus, DNOP was dropped from further consideration of cumulative risk. A discussion of exposure estimates and of these six phthalates is included in sections 2.5 and 2.6.

Although pregnant women and infants are exposed to DIDP, DEP, and DMP as evidenced from biomonitoring studies, evidence of endocrine disruption in experimental animal studies has not been found for these chemicals. However, despite human studies reporting associations of MEP with reproductive human health outcomes, these phthalates were not considered in the calculation of the hazard index.

2.7.2.2 **Reference Doses (RfDs): Three Cases**

Evaluation of risk using the HI is a comparison of human exposure estimates to points of departure (POD) estimates using toxicology data, i.e., doses associated with minimal risk that have been adjusted by uncertainty factors to account for human variability, animal to human extrapolation, and data uncertainty. These adjustments change PODs to so-called reference doses (RfDs). The selection of PODs is based on *in vivo* data with relevant endpoints. The endpoints of phthalate toxicity regarded as most relevant are characteristic of disturbance of androgen action. Here, the RfDs for pregnant women related to fetal toxicity are based on reproductive and developmental endpoints in animal studies. Our selection of RfDs for infants was based on the following logic. Rodents are most sensitive to the anti-androgenic effects of phthalates *in utero*; however, exposure at higher doses also induces testicular effects in adolescent and adult males, with adolescents being more sensitive than adults (Sjöberg *et al.*, 1986; Higuchi *et al.*, 2003). Thus, the RfDs determined for *in utero* exposures should be protective for juvenile males. We consider three cases for the calculation of HQs and the HI. These were chosen to evaluate the impact of assumptions in calculating the HI.

Case 1: Case 1 is based upon recent published values used in a CRA for anti-androgens including phthalates. The antiandrogenic RfD values for DBP, BBP, DINP, and DEHP were set as published in (Kortenkamp and Faust, 2010). We further assumed DIBP to be similar in potency to DBP. Although other authors have addressed CRAs for phthalates (Benson, 2009), we used the values from Kortenkamp and Faust due to their focus on *in vivo* anti-androgenicity.

Case 2: Case 2 is based on relative potency assumptions across phthalates. DEHP was selected as an index chemical with known *in vivo* evidence of anti-androgenicity in experimental animals and a NOAEL of 5 mg/kg/day. Three other phthalates (DIBP, DBP, and BBP) were assumed equipotent to DEHP, and DINP was assumed 2.3 times less potent (Hannas *et al.*, 2011b) An overall uncertainty factor of 100 was selected to account for inter-species extrapolation (factor of 10) and inter-individual variation (factor of 10).

Case 3: Case 3 is based on the *de novo* analysis of individual phthalates conducted by the CHAP. The RfD AA values are provided in Table 2.1 with uncertainty factors of 100.

Table 2.15 provides the PODs, uncertainty factors, and RfDs for the 5 phthalates in the three cases considered.

2.7.2.3 Calculating the Hazard Index and Margins of Exposure

Using the individual daily intake estimates for each of the phthalates, and by relating these DI values to the respective RfDs, the Hazard Quotients (HQs) and Hazard Index (HI) were calculated for each pregnant woman and infant in the NHANES and SFF (Sathyanarayana *et al.*, 2008a; 2008b) data.

Distributions of the HQs and HIs were generated for all three cases with sampling weights used from the NHANES data to accommodate the prediction for pregnant women in the U.S. population. Analogous to the HQs when the uncertainty factors are equal is the margin of exposure (MoE):

$$MoE = \frac{POD}{\text{exposure estimate}}$$

MoEs were calculated and tabulated using PODs with median and 95th percentile exposure estimates per chemical.

2.7.3 Summary Results

2.7.3.1 Calculation of Hazard Quotients and the Hazard Index from Biomonitoring Data

The Hazard Index was calculated per woman and infant using the daily intake estimates for the phthalate diesters using the three cases for RfDs. In all three cases and for both NHANES and SFF data, the distribution of the HI is highly skewed (histograms for each analysis are provided in Appendix D).

In the NHANES data, roughly 10% of pregnant women in the U.S. population (after adjustment with survey-sampling weights) have HI values that exceed 1.0.[*] The estimates are reduced in the SFF data in women from prenatal and postnatal measurements; 4-5% of infants have HI values that exceed 1.0 (Table 2.16).

[*] When the HI >1.0, there may be a concern for adverse health effects in the exposed population.

The primary contributor(s) to the HI can be identified by evaluating the hazard quotients that comprise the HI. Clearly the hazard quotient for DEHP dominates the calculation of the HI, as expected, with high exposure levels and one of the lowest RfDs. The rank contribution of the five phthalates to risk was calculated using the median 95th percentile across the cases for pregnant women in NHANES, SFF (Sathyanarayana *et al.*, 2008a; 2008b) women (prenatal and postnatal combined) and infants:

NHANES women (2005-06):	DEHP > DBP >DINP ~DIBP >BBP
SFF women:	DEHP >BBP >DBP > DIBP > DINP
SFF infants:	DEHP > DBP > BBP > DINP ~DIBP

In all cases, DEHP and DBP were associated with greatest risk; and either DIBP or DINP were associated with least risk.

MoEs were tabulated using the range of PODs across the three cases (Table 2.17). The MoEs are not exactly analogous to the HQs due to the differing uncertainty factors used in Case 1. The rank order of the MoEs is as follows, based on median and high intake estimates.

Median:	DEHP < DBP < DINP < BBP < DIBP
95th percentiles:	DEHP < DINP < DBP < BBP < DIBP

2.7.3.2 **Summary**

From biomonitoring studies there is clear evidence that both pregnant women and infants are exposed to mixtures of phthalates. Comparison of daily intake estimates to three different sets of RfDs associated with *in vivo* anti-androgenicity demonstrated a highly skewed distribution of the calculated HI in all three cases. Values of HI that exceed 1.0 are generally considered associated with unacceptable risk – particularly of concern in pregnant women and infants. Here, roughly 10% of pregnant women in the U.S. have HI values that exceed 1.0 – a similar percentage in all three cases. The percentage was reduced in the SFF data but was similar from both pre-natal and post-natal measurements – again, similar in all three cases with the exception of cases 2 and 3 in the postnatal percentages. Roughly 5% of infants in the SFF had HI values exceeding 1.0 – and were similar across the three cases.

In all three cases studied, the HI value was dominated by DEHP since it has both high exposure and a low RfD. DEHP had the highest HQs and lowest MoEs. Three phthalates (DBP, BBP, and DINP) were similar in their HQ values and MoEs. DIBP had the largest MoEs and smallest HQs.

Table 2.15 Points of Departure (PODs; mg/kg/day), uncertainty factors (UFs) and reference doses (RfDs; µg/kg-d) in the three cases for the 5 phthalates considered in the cumulative risk assessment.

Phthalate Diester	Case 1			Case 2			Case 3		
	POD	UF	RfD	POD	UF	RfD	POD	UF	RfD
DIBP	40	200	200	5	100	50	125	100	1250
DnBP	20	200	100	5	100	50	50	100	500
BBP	66	200	330	5	100	50	50	100	500
DEHP	3	100	30	5	100	50	5	100	50
DINP	750	500	1500	11.5	100	115	50	100	500

Table 2.16 Summary statistics (median, 95th, 99th percentiles) for HQs and HIs calculated from biomonitoring data from pregnant women (NHANES 2005-2006; CDC, 2012b) (SFF; Sathyanarayana *et al.*, 2008a; 2008b) and infants (SFF; Sathyanarayana *et al.*, 2008a; 2008b). NHANES values include sampling weights and thus infer to 5.3 million pregnant women in the U.S. population. SFF sample sizes range: Prenatal, N=340 (except, N=18 for DINP); Postnatal, N=335 (except, N=95 for DINP); Baby, N=258 (except, N=67 for DINP) ; HI values are the sum of nonmissing hazard quotients.

RfD Case	NHANES Pregnant Women in U.S. Population			SFF Pregnant Women (Pre- and Post-natal)						SFF Infants		
	1	2	3	1 Pre	1 Post	2 Pre	2 Post	3 Pre	3 Post	1	2	3
DIBP	0.001 0.01 0.01	0.003 0.02 0.04	<0.001 0.001 0.002	0.001 0.003 0.01	0.001 0.003 0.01	0.003 0.01 0.03	0.003 0.01 0.04	<0.001 <0.001 0.001	<0.001 0.001 0.001	0.002 0.01 0.01	0.01 0.03 0.06	<0.001 0.001 0.004
DBP	0.01 0.03 0.06	0.01 0.07 0.13	0.001 0.007 0.01	0.01 0.03 0.05	0.01 0.02 0.05	0.02 0.05 0.10	0.01 0.04 0.09	0.002 0.01 001	0.001 0.004 0.01	0.02 0.07 0.13	0.03 0.14 0.25	0.003 0.01 0.03
BBP	0.001 0.004 0.01	0.01 0.03 0.05	0.001 0.003 0.01	0.002 0.01 0.01	0.001 0.006 0.01	0.01 0.06 0.08	0.01 0.04 0.08	0.001 0.01 0.01	0.001 0.004 0.01	0.04 0.02 0.07	0.02 0.13 0.45	0.003 0.01 0.04
DEHP	0.12 6.0 12.2	0.07 3.6 7.3	0.07 3.6 7.3	0.10 0.55 2.3	0.09 0.72 1.5	0.06 0.33 1.4	0.05 0.43 0.91	0.06 0.33 1.4	0.05 0.43 0.91	0.18 0.86 3.7	0.11 0.52 2.2	0.11 0.52 2.2
DINP	0.001 0.01 0.02	0.01 0.10 0.24	0.002 0.02 0.05	0.001 0.005 0.005	<0.001 0.002 0.01	0.01 0.07 0.07	0.01 0.03 0.07	0.002 0.02 0.02	0.001 0.01 0.02	0.002 0.01 0.02	0.03 0.14 0.21	0.01 0.03 0.05
HI	0.14 6.1 12.2	0.13 3.7 7.4S	0.09 3.6 7.3	0.11 0.57 2.4	0.10 0.73 1.5	0.10 0.41 1.5	0.09 0.46 0.92	0.06 0.33 1.4	0.06 0.43 0.91	0.22 0.96 34.7	0.20 0.82 2.39	0.12 0.55 2.21
% with HI>1.0	10	9	9	4	4	3	<1	2	<1	5	5	4

Table 2.17 Margin of exposure (MoE) estimates for pregnant women using median and high (95th percentile) intake estimates using the range of PODs across the 3 cases.

Phthalate Diester	Range of PODs (3 cases) (mg/kg bw/day)	Biomonitoring Intake (NHANES) (µg/kg bw/day)	Margin of Exposure* (POD/Biom Intake in same units)	
		Median Intake	**Range**	
DIBP	5-125	0.2	25,000	625,000
DBP	5 - 50	0.6	8,000	83,000
BBP	5 - 66	0.3	17,000	220,000
DEHP	3 - 5	4	800	1,300
DINP	11.5 – 750	1	12,000	750,000
		95th Percentile	**Range**	
DIBP	5-125	1	5,000	125,000
DBP	5 - 50	4	1,300	13,000
BBP	5 - 66	1	5,000	66,000
DEHP	3 - 5	181	17	28
DINP	11.5 – 750	11	1,000	68,000

* Rounded to the nearest hundred or thousand.

3 Phthalate Risk Assessment

To arrive at transparent recommendations about restricting (or otherwise) the use of phthalates in children's toys and care products, the CHAP has employed a risk assessment approach that first analyzed the epidemiological evidence of associations between phthalate exposures and risk to human health. Such data give valuable answers to questions as to whether phthalates as a group of chemicals might be linked to human disorders. However, only in rare cases is it possible to pinpoint specific chemicals as associated with health effects, and no such case is currently available for phthalates. At present, quantitative estimates of the magnitude of risks that stem from phthalate exposures can also not be derived directly from epidemiological data. For this reason, the CHAP had to rely primarily on evidence from tests with animals to underpin phthalate risk assessment.

As discussed in Science and Decisions ("The Silverbook," NRC, 2009), quantitative statements about “safe”, “tolerable” or “acceptable” exposures, are often inappropriately taken as “bright line” estimates that clearly demarcate “harm” from “safety”, without taking account of inherent variabilities in response and the uncertainties associated with such estimates. The report advocated approaches where the level of detail of the analysis is appropriate to the issue that is to be decided in risk assessment.

Accordingly, the CHAP took an approach appropriate to the charge and the richness of the available data. The main issue to be dealt with was to make recommendations about the use of phthalates in certain children's toys and care products. The CHAP made an effort to consider phthalate exposures to the developing fetus, the most vulnerable target of toxicity for phthalates, from all sources. Practically, this meant that subpopulations of interest were women of reproductive age, neonates and toddlers.

In a hazard assessment step the CHAP examined the toxicological profile of all relevant phthalates and substitution products, with an emphasis on endpoints related to antiandrogenic effects on male reproductive development in rodents (i.e., the phthalate syndrome). The CPSIA requires the CHAP to consider the health risks from phthalates both in isolation and combination. To characterize the cumulative risks (risk in combination), the CHAP applied a hazard index approach for the antiandrogenic phthalates only: DBP, DIBP, BBP, DEHP, and DINP (section 2.7). However, the CHAP also points out, that other antiandorgens can be added to the hazard index approach, increasing the HI (Appendix D).

To characterize the risks for compounds in isolation, quantitative estimates of points of departure (NOAELs or benchmark doses) were derived from experimental studies with animals, and in a risk characterization step, these estimates were compared with exposures by calculating so-called margins of exposure (MoE). The numerical value of these MoEs was then taken into account in arriving at recommendations for specific phthalates. Typically, MoEs exceeding 100-1000 are considered adequate for protecting public health, for compounds in isolation. In taking this approach, it was possible to avoid misunderstandings that might have occurred had CHAP used points of departure and combined them with uncertainty factors to arrive at “tolerable exposures” or reference doses. These would have all too readily been taken as “bright lines” separating “risk” from “no risk”. Considering the uncertainties inherent in extrapolating animal data to the human, this would have been inappropriate. In contrast, the MoE approach offers a level of flexibility commensurate with the task at hand. It does not imply that the points of departure used in risk characterization clearly demarcate effect from absence of effects, and no absolute claims are made in terms of "safe" exposures that are not associated with harm, or are without concern.

The risks from antiandrogenic phthalates were characterized by both the MoE approach (for phthalates in isolation) and the Hazard Index approach (cumulative risk). The risks from non-antiandrogenic phthalates and phthalate alternatives were characterized by the MoE approach.

4 Discussion

4.1 Variability and Uncertainty

4.1.1 Developmental/Reproductive Toxicity Data

To fulfill the charges to consider the health effects of phthalates in isolation and in combination with other phthalates and to consider the cumulative effect of total exposure to phthalates, the CHAP relied upon its review of the toxicology literature of phthalates and phthalate substitutes, exposure data (sources and levels) and data obtained from the Hazard Index (HI) approach for cumulative risk assessment (see Section 2.7.1. for details). Because of limitations in the biomonitoring datasets (National Health and Nutrition Evaluation Surveys, NHANES; and Study for Future Families, SFF), only 5 phthalates were analyzed by the HI approach. These include DEHP, DBP, BBP, DINP, and DIBP. Case 3[*] in the HI analysis uses NOAELs generated from the available literature on the developmental toxicity of these five phthalates. To provide NOAELs, where possible, for these 5 phthalates, the CHAP systematically reviewed the published, peer-reviewed literature that reported information concerning the effects of *in utero* exposure of phthalates in pregnant rats.

The systematic evaluation of the developmental toxicity literature for the 14 phthalates and six phthalate substitutes and the rationale for selecting a specific NOAEL for each chemical are provided in Appendix 1. Our criteria for an adequate study from which a NOAEL could be derived are: 1) at least 3 dose levels and a concurrent control should be used, 2) the highest dose should induce some developmental and/or maternal toxicity and the lowest dose level should not produce either maternal or developmental toxicity, 3) each test and control group should have a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy, and 4) pregnant animals need to be exposed during the appropriate period of gestation. In addition, studies should follow the EPA Guideline OPPTS 870.3700 and the OECD Guideline for the Testing of Chemicals (OECD 414, adopted 22 January 2001). The CHAP also gave added weight to data derived from studies replicated in different laboratories.

Although the CHAP developed the above criteria to evaluate published developmental toxicity studies and thereby derive reliable NOAELs for the 9 phthalates and 6 phthalate substitutes, the final NOAELs used in the HI analysis are limited by the following. Many of the developmental toxicity studies reviewed were designed to derive mechanistic information and not NOAELs and therefore used too few dose groups, often only one, e.g., (Gray *et al.*, 2000). Many studies did use multiple dose groups; however, the number of animals per dose group was less than recommended (e.g.,Howdeshell *et al.*, 2008), or it was unclear how many dose groups were used (e.g., Kim *et al.*, 2010). In some studies in which multiple doses and sufficient animals per dose were used, the lowest dose used was also an effective dose, so that a NOAEL could not be derived (e.g., Saillenfait *et al.*, 2009). In other studies, the exposure period used, e.g., GD 7-13, did not cover the sensitive period for the disruption of male fetal sexual development (GD 15-21), which was the major endpoint of phthalate toxicity monitored. For some phthalates, only

[*] As discussed in Section 2.7.1., the CHAP considered three sets of references doses (three Cases) to calculate the hazard index.

one peer-reviewed developmental toxicity study was located, *e.g*., DIOP. The lack of replication introduces some level of uncertainty. For other phthalates, *e.g.*, DPHP, an insufficient amount of animal data or poorly described methodologies limited the usefulness of available data. Finally, for some of the phthalate substitutes, peer-reviewed data were lacking, *e.g.*, ATBC, DINX, and TPIB, and only industry (DINX, TPIB) or government (TOTM) data were available. In cases in which peer-reviewed data were not available, the CHAP made executive decisions on a case-by-case basis as to whether non-peer-reviewed data would be used in making their recommendations to the CPSC.

Another level of uncertainty derives from the fact that the NOAELs used in the HI analysis and risk assessment were derived entirely from studies conducted in one species, the rat. Although some of the phthalates have been tested in mice, the available data are insufficient to derive a separate set of NOAELs.

4.1.2 Exposure Scenarios

The overall level of uncertainty in the analyses the CHAP conducted for the 14 phthalates, and the non-phthalate substitutes under consideration varied for each compound. For some compounds, the toxicological, exposure and epidemiological information had major gaps which led to a large degree of uncertainty in the estimated risk. In other cases the uncertainties were driven by the lack of information for assessing either the hazard or the exposure. The nature of these gaps is reflected in two ways: 1. the comments associated with recommendations for the use or ban of a compound in children's toys and other products under the jurisdiction of the CPSC, and 2. the actual recommendations for an action or the lack of a recommendation for an action made by the CHAP on the use of a compound in children's toys or other products under the jurisdiction of CPSC.

Further complicating the analyses was the charge to the CHAP to conduct a cumulative risk analysis. This led to additional uncertainties since data on the exposures associated with all routes of entry into the body were not consistent for each potential source of one or more compounds. In addition, the toxicological data were normally obtained via exposures administered by one route, or there were too few studies associated with each end point.

In the future, the government agencies need to consider how to work collaboratively and efficiently collect the information needed to allow for detailed quantitative analysis of the exposure and hazard for use in quantitatively defining the risk to phthalates or other compounds of concern. In the case of phthalates we were dealing with consumer products and not the raw form of the material or process intermediates. Thus, the data collected from toxicological testing and exposure measurements (biomonitoring and external sources), and risk characterization procedures, must take into account both realistic hazards and exposures. In this way Congressional mandates can be achieved with higher degrees of confidence for the specific or overall recommendations.

Within this process the CPSC must be given the resources to test the products under its jurisdiction as an initial step toward obtaining the information to conduct a characterization of exposure for a source. The lack of exposure information for the current CHAP phthalate analysis leaves large uncertainties, especially for some of the items that were deemed critical to the completion of our tasks. Without information on the use and release rates of the phthalates from the products during use, it is difficult to properly employ exposure modeling tools to complete a thorough exposure characterization for risk assessment Further, lack of such data from the exposure characterizations completed by the CHAP for phthalates, weakens the analyses that couple biomonitoring data to external exposure characterizations to define the percent contribution of children's toys and etc. to cumulative risk.

4.1.3 **HBM Data, Daily Intake Calculations, Hazard Index Calculations**

Human biomonitoring data, daily intake calculations based on HBM data, and, therefore, also the HI approach based on HBM data are subject to several sources of uncertainty and variability that will be named and discussed in the following paragraphs. The CHAP will also attempt to describe the numerical magnitude of the variability, as a factor, increasing or decreasing the daily intake and resulting hazard index calculations.

<u>Analytical variability/uncertainty</u>: The analytical variability of the phthalate measurements in urine (in both NHANES (CDC, 2012b) and SFF (Sathyanarayana *et al.*, 2008a; 2008b)) have a standard deviation of below 20%, but in most cases is below 10% (Silva *et al.*, 2008). Therefore, from the analytical perspective the maximum factor contributing to both over- or underestimating exposure (and finally the HI) would be 1.2 but probably more in the region of 1.1. Recently, the CDC issued correction factors for two of its metabolites covered in the NHANES program, i.e., correction factors 0.66 for MEP and 0.72 for MBZP. All NHANES calculations were redone to include the revised data, post March 2012. In general, the standard purity can be assumed to be 95% and above. Usually the purity of the analytical standard is included in the analytical result and therefore reflected in the analytical result and the SD of the method.

<u>Individual variability in metabolism</u>: The metabolite conversion factors for the individual metabolites have been determined in human metabolism studies (usually after oral dosing different doses of the labeled parent phthalate to human volunteers). For DEHP and DINP Koch *et al.*, (2004a; 2007a) published urinary metabolite conversion factors of 64.9% for DEHP (4 metabolites) and 43.61% for DINP (3 metabolites), were based on one volunteer. Anderson *et al.*, (2011) published conversion factors based on 20 individuals (10 male 10 female) and two dose levels and found conversion factors of 47.1 ± 8.5% (4 DEHP metabolites) and 32.9 ± 6.4% (3 DINP metabolites) over all volunteers (males and females) and over 2 different concentrations. The mean factors of Anderson *et al.*, (2011) were used for our DI and HI calculations. As can be seen from the variability of the Anderson results, these mean excretion factors could over- or underestimate exposure by a factor of 1.2. The variability of the conversion factors for the other metabolites is probably in the same region. For example, for DBP and DIBP a conversion factor of 69% has been used for the monoester metabolites. Assuming a hypothetical conversion factor of 100% (which is unrealistic) would mean that we would have overestimated the DI by a factor of 1.3 at the maximum; assuming a hypothetical conversion factor of less than 69% would mean that we would have underestimated the DI and consequently the HI.

Temporal variability of metabolite levels (exposure driven): Several studies have shown that although the day-to-day and month-to-month variability in each individual's urinary phthalate metabolite levels can be substantial, a single urine sample was moderately predictive of each subject's exposure over 3 months. The sensitivities ranged from 0.56 to 0.74. Both the degree of between- and within-subject variance and the predictive ability of a single urine sample differed among phthalate metabolites. In particular, a single urine sample was most predictive for MEP and least predictive for MEHP (Hauser *et al.*, 2004). In general, for the low molecular weight phthalates (DMP, DEP, DBP, DIBP), a single urine sample has been shown to be more reliable in predicting exposure over a certain time span than for the high molecular weight phthalates (DEHP, DINP, DIDP). Braun *et al.*, (2012) state: "Surrogate analyses suggested that a single spot-urine sample may reasonably classify MEP and MBP concentrations during pregnancy, but >1 sample may be necessary for MBZP, DEHP…". The variability issue has also been thoroughly investigated by Preau *et al.*, (2010) on spot urine samples collected continuously over 1 week for 8 individuals: they confirm the above statements: "Regardless of the type of void (spot, first morning, 24-hr collection), for MEP, interperson variability in concentrations accounted for > 75% of the total variance. By contrast, for MEHHP, within-person variability was the main contributor (69-83%) of the total variance". However, since the DI calculations and the HI approach is population based we can assume that the NHANES and SFF (Sathyanarayana *et al.*, 2008a; 2008b) data accurately reflects the variability of exposure relevant for the investigated population subset.

However, Preau et al reported another interesting finding: "… for MEHHP, the geometric mean concentration of samples collected in the evening (33.2 µg/L) was significantly higher ($p < 0.01$) than in samples collected in the morning (18.7 µg/L) or in the afternoon (18.1 µ g/L)." Since neither NHANES nor SFF samples have been collected in the evening (representing exposure events that took place in the afternoon) there are indications that both NHANES and SFF samples might underestimate exposure to DEHP and other food-borne high molecular weight phthalates like DINP and DIDP. This would indicate a factor of 1.5 for underestimation of the DI (and the HI) for the HMW phthalates.

Another indication for a possible underestimation (in NHANES samples) is mentioned in Lorber *et al.*, (2011): "As much as 25% of all NHANES measurements contain metabolites whose key ratio suggest that exposure was "distant," that is, occurred more than 24 hours before the sample was taken. This leads over to another issue with NHANES samples:

Variability/uncertainty due to fasting: Most of the morning urine samples in NHANES are collected after a fasting period (first described by Stahlhut *et al.*, 2009). Fasting will certainly have an impact on food-borne contaminants, as some of the phthalates are. In the 2007– 2008 NHANES sample, the 50^{th} percentile of reported fasting times was approximately 8 h (Aylward *et al.*, 2011). The authors could actually confirm the influence of fasting in the metabolites of DEHP: "Regression of the concentrations of four key DEHP metabolites *vs*. reported fasting times between 6 and 18 h in adults resulted in apparent population-based urinary elimination half-lives, consistent with those previously determined in a controlled-dosing experiment, supporting the importance of the dietary pathway for DEHP." Correction factor for influence of fasting (relevant for food borne phthalates): underestimation, but difficult to give a factor, probably less than 2. Fasting is not an issue in the SFF samples.

Variability/uncertainty due to elimination kinetics and spot samples: Spot samples can over or underestimate the mean daily exposure due to the fast elimination kinetics of the phthalates. Aylward *et al.*, (2011) state, based on elimination kinetics, void volume and last time of voiding that theoretically "the potential degree of over- or underestimation is in the range of up to approximately four-fold in either direction. That is, at short time since last exposure (2 to 4 h), estimated intakes based on spot sample concentrations may be overestimated by up to approximately four-fold. At long time since last exposure (>14 h), the actual intakes may be underestimated by up to four-fold. They further state that the estimation of intake rates […] in NHANES 2007–2008 spot samples […] may be more likely to over- than underestimate actual exposures to DEHP, assuming fasting time is an appropriate surrogate for time since last exposure." : overestimation possible, but difficult to give a factor, probably less than 2.

Creatinine correction model (used in the CHAP approach) versus volume based model: Both Koch *et al.*, (2007) and Wittassek *et al.*, (Wittassek *et al.*, 2007b) report that the creatinine based daily intake calculations produce lower estimated intakes compared to the volume model. Daily intake values by the creatinine model were lower by a factor of 2 compared to the volume model. The creatinine model might therefore underestimate exposure by a factor of 2.

Overall, the uncertainties regarding HBM data and dose extrapolations based on HBM data are within one order of magnitude, and certain factors for the possibility of overestimation of daily intake (and therefore the HI) seem to be balanced by factors for the underestimation of the DI/HI. Human biomonitoring data therefore provides a reliable and robust measure of estimating the overall phthalate exposure and resulting risk.

4.2 Species Differences in Metabolism, Sensitivity, and Mechanism

When given to pregnant rats in controlled experimental exposures, phthalates produce a series of effects in the male offspring (phthalate syndrome) that has similarities with disorders observed in humans, termed Testicular Dysgenesis Syndrome (TDS) (Skakkebaek *et al.*, 2001). In both cases, deficiency of androgen action in fetal life is strongly implicated, and for this reason, the rat has been regarded as the appropriate animal model for making extrapolations to phthalate risks in humans. However, recent comparative studies in mice, marmosets and with human fetal testis explants grafted onto mice have purportedly called this assumption into question.

The primary mechanism leading to phthalate-induced developmental and reproductive disorders in the rat is thought to be via suppression of testosterone synthesis in fetal life. Testosterone is a key driver of the normal differentiation of male reproductive tissues (Gray *et al.*, 2000; Scott *et al.*, 2009). Phthalates with ortho substitution and a side chain length of between 4 and 6 carbon atoms (Foster *et al.*, 1980) can drive down the expression of genes involved in cholesterol homeostasis (cholesterol is a precursor of androgens) and steroidogenesis genes in Leydig cells, where androgen synthesis takes place. Phthalates with shorter side chains, such as DEP, are unable to induce these effects in the rat. The active principle is not the parent compound, but a mono-ester produced during hydrolytic reactions. Phthalate metabolites can also suppress expression of a key factor responsible for the first phase of testis descent (insl3), leading to cryptorchidism (reviewed by Foster, 2005; 2006). The typical spectrum of effects observed in male rats after *in utero* phthalate exposure involves altered seminiferous cords, multi-nucleated gonocytes, epididymal agenesis, retained nipples, shortened anogenital distance, cryptorchidism and hypospadias.

The majority of studies examining the effects of phthalates have been conducted in the rat. More recently, comparative studies with other species have been undertaken, with the aim of examining whether the mechanisms and responses seen in the rat are species specific, or whether they are of a more general nature.

Similar to the rat, *in utero* exposure to the phthalate DBP in mice led to disruptions in seminiferous cord formation and the appearance of multi-nucleated gonocytes. However, unlike the rat, these effects were not accompanied by suppressed fetal testosterone synthesis, or by reduced expression of genes important in steroid synthesis (Gaido *et al.*, 2007). These observations were confirmed and extended in a mouse fetal testis explant system with the mono-ester of DEHP (MEHP) as the test substance. Depending on culture conditions, MEHP stimulated or inhibited androgen synthesis in testis explants, but the deleterious effects of MEHP on seminiferous cords and multi-nucleated gonocytes occurred independent of any effects on steroidogenesis (Lehraiki *et al.*, 2009). In common with the rat, MEHP induced suppressions of insL3 in this system.

The effects of phthalate metabolites on human fetal testes explants were investigated in several studies. In one study, fetal explants obtained during the second trimester of pregnancy were treated with MBP, but suppressions of androgen synthesis were not observed, independent of whether the cultures were stimulated with human chorionic gonadotrophin (hCG) or whether they were left unstimulated (in human fetal testes, androgen synthesis depends on exposure to maternal hCG, and later also on luteinizing hormone, LH) (Hallmark *et al.*, 2007). In another study, human fetal testes explants from the first trimester of pregnancy were used and exposed to MEHP (Lambrot *et al.*, 2009). MEHP had no effect on testosterone synthesis, neither after stimulation of androgen synthesis by luteinising hormone (LH) nor in cultures left unstimulated. There were also no effects on the expression of steroidogenic genes, and multi-nucleated gonocytes were not seen. However, reductions in the number of germ cells were noted. These studies are technically very challenging, and there is considerable variation in androgen production by different explants which compromises statistical power and may obscure effects. In contrast to the observations with fetal cultures, DEHP and MEHP were able to induce significant reductions of testosterone synthesis in explants of adult testes (Desdoits-Lethimonier *et al.*, 2012).

A primate species, the marmoset, was investigated in two studies. In the first study (Hallmark *et al.*, 2007), neonatal marmosets were exposed to MBP. The monoester induced suppressions of serum testosterone levels shortly after administration. In the second study, marmosets were exposed to MBP during fetal development and studied at birth. Effects on testosterone production were not seen (McKinnell *et al.*, 2009), but any reductions in testosterone synthesis experienced in fetal life are likely to have disappeared at birth.

Very recently, the results of two experimental studies with human fetal testes grafted onto male mice and exposed to DBP were published (Heger *et al.*, 2012; Mitchell *et al.*, 2012). In one of the two studies (Mitchell *et al.*, 2012) the metabolite MBP was also investigated. It drove down serum testosterone levels by approximately 50%, but the effect did not reach statistical significance, due to high experimental variation and a small number of repeats. DBP did not affect testosterone levels. In the second of these studies (Heger *et al.*, 2012), testosterone was not measured. Instead, changes in testosterone synthesis were inferred from analysing the expression of genes involved in testosterone production. DBP exposure did not affect any of these genes.

Both groups concluded that DBP exposure of normal functioning human fetal testes is probably without any effect on steroidogenesis. However, several issues, confounding factors and disparities with other reports (discussed by the authors) must be considered before firm conclusions can be drawn.

Firstly, in both studies the human fetal material was obtained at ages where the male programming of the testes had already occurred. This raises the possibility that DBP may in reality compromise testosterone synthesis, but that the effect was missed due to the age of the explants. The observations in cultured human fetal explants, where effects on testosterone did not occur, independent of whether they were obtained during the first or second trimester (Hallmark *et al.*, 2007; Lambrot *et al.*, 2009) would argue against this possibility, but it cannot be excluded at present.

Secondly, the outcome of the testosterone assay in Mitchell *et al.*, (2012) was highly variable, a result of inherent biological variability and the technical difficulties of these studies. The obvious way of dealing with experimental variability by including larger numbers of replications cannot be readily pursued with human fetal material, due to technical, practical and ethical considerations. For these reasons, results that did not reach statistical significance, as in Mitchell *et al.*, (2012) have to be interpreted with great caution. At this stage, the outcome of these studies has to be regarded as inconclusive.

Thirdly, the observations of associations between phthalate exposure in fetal life and anogenital distance (Swan *et al.*, 2005; Swan, 2008) are difficult to reconcile with the results of the xenograft and human fetal explant experiments. Changes in anogenital distance are a robust read-out of diminished androgen action *in utero* and these observations give strong indications that phthalates are capable of driving down fetal androgen synthesis in humans.

As proposed by Mitchell *et al.*, and Heger *et al.*,, more mechanistic studies are needed to resolve these issues. In view of these discrepancies, and until further evidence is available, the CHAP regards it as premature to assume that phthalate exposure in fetal life is of no concern to humans. In the species examined thus far, mouse, rat and human, multinucleated gonocytes are a consistent feature of phthalate exposure *in utero*. These disruptions of gonocyte differentiation may have significant, although largely unexplored, implications for the development of carcinoma *in situ* (Lehraiki *et al.*, 2009). The long-term consequences of these abnormal germ cells are unknown, but raise concerns. To dispel these concerns, further extensive studies are required.

The experimental findings in the rat and the marmoset show that neonatal exposure to certain phthalates suppresses testosterone synthesis in the testes. These observations are highly relevant considering the high phthalate exposures that may occur in some neonates.

5 Recommendations

5.1 Criteria for Recommendations

The CHAP was charged with making recommendations on specific phthalates and phthalate substitutes. At the present time, these chemicals exist in one of three categories: 1) permanent ban (permanently prohibits the sale of any “children’s toy or child care article” individually containing concentrations of more than 0.1% of DBP, BBP or DEHP; 2) interim ban (prohibits on an interim basis the sale of “any children’s toy that can be placed in a child’s mouth” or “child care article” containing concentrations of more than 0.1% of DNOP, DINP, or DIDP; and 3) currently unrestricted under section 108 of the Consumer Product Safety Improvement Act of 2008. As part of its report, the CHAP will make recommendations on chemicals in each of these three categories. The recommendation may be to impose a permanent ban or an interim ban on a chemical or to take no regulatory action at this time. The recommendation for a ban or no action may be an extension of a current regulatory status or a new action.

The CPSIA prohibits the use of certain phthalates at levels greater than 0.1 percent, which is the same level used by the European Commission. When used as plasticizers for PVC, phthalates are typically used at levels greater than 10 percent. Thus, the 0.1 percent limit prohibits the intentional use of phthalates as plasticizers in children’s toys and child care articles, but allows trace amounts of phthalates that might be present unintentionally. There is no compelling reason to apply a different limit to other phthalates that might be added to the current list of phthalates that are permanently prohibited from use in children’s toys and child care articles.

The recommendations are based on a review of the toxicology literature, exposure data, and other information such as a calculated Hazard Index. The primary criteria for recommendations include the following:

1. What is the nature of the adverse effects reported in animal and human studies of toxicity? Did the findings include evidence of the Phthalate Syndrome or other evidence of reproductive or developmental toxicity?
2. What is the relevance to humans of findings in animal studies? Findings would generally be ascribed to one of three categories: a) known to be relevant, b) known to be irrelevant, or c) assumed to be relevant to humans.
3. What is the weight of the evidence? Is the experimental design of the study appropriate for the purpose of the study? Did the study have adequate power? Were confounders adequately controlled? Were findings replicated in other studies or other laboratories/populations?
4. What is the likely risk to humans? What are the exposures of concern—sources and levels? What are the hazards identified in animal studies? What are the dose-response data? What are the NOAELS? What is the relationship between levels of human exposure and NOAELS? What are the results of the Hazard Index calculations?
5. What is the recommendation? Permanent ban, interim ban, or no action at this time?
6. Would this recommendation, if implemented, affect exposure of children to this chemical? Yes, perhaps, unlikely, no, unknown?

5.2 Recommendations on Permanently Banned Phthalates

5.2.1 Di-n-butyl Phthalate (DBP) (84-74-2)

5.2.1.1 Adverse Effects

5.2.1.1.1 Animal

5.2.1.1.1.1 Reproductive

- Over 20 animal studies were reviewed in the NTP-CERHR report (NTP, 2000). Many studies showed similar effects at high doses (~ 2000 mg/kg-d) in rats. The panel's conclusions were that DBP could probably affect human development or reproduction and current exposures were possibly high enough to cause concern. The NTP concurred with the NTP-CERHR DBP panel. Both stated that there was minimal concern for developmental effects for pregnant women exposed to DBP levels estimated by the panel (2-10 µg/kg-day).
- Studies cited in the NTP-CERHR (NTP, 2000) report have been confirmed and extended by more recent reports of Mahood *et al.*, (2007) showing decreased male fertility and testicular testosterone and increased testicular toxicity, Gray *et al.*, (2006) showing decrease in number of pregnant rats and live pups, decreased serum progesterone, and increased hemorrhagic corpora lutea, and Ryu *et al.*, (2007) documenting changed steroidogenesis and spermatogenesis gene expression profiles. Recently, a study by McKinnel *et al.*, (2009) using marmosets, did not show any effect on testicular development or function, even into adulthood.

5.2.1.1.1.2 Developmental

- The NTP-CERHR (NTP, 2000) reviewed the reproductive and developmental toxicity of DBP and concluded at the time of the report that the panel could locate "no data on the developmental or reproductive toxicity of DBP in humans". The panel concluded, however, that, based on animal data, it "has high confidence in the available studies to characterize reproductive and developmental toxicity based upon a strong database containing studies in multiple species using conventional and investigative studies. When administered via the oral route, DBP elicits malformations of the male reproductive tract via a disturbance of the androgen status: a mode of action relevant for human development. This anti-androgenic mechanism occurs via effects on testosterone biosynthesis and not androgen receptor antagonism. DBP is developmentally toxic to both rats and mice by the oral routes; it induces structural malformations. A confident NOAEL of 50 mg/kg-day by the oral route has been established in the rat. Data from which to confidently establish a LOAEL/NOAEL in the mouse are uncertain." These statements are made primarily on the basis of studies by Ema *et al.*, (1993; 1994; 1998) and Mylchreest *et al.*, (1998; 1999; 2002). Finally, studies by Saillenfait *et al.*, (1998) and Imajima *et al.*, (1997) indicated that the monoester metabolite of DBP is responsible for the developmental toxicity of DBP.
- Studies cited in the NTP-CERHR (NTP, 2000) report have been confirmed and extended by more recent reports of Zhang *et al.*, (2004) documenting effects on the

epididymis, testis, and prostate, Lee *et al.,* (2004) reporting reduced spermatocyte and epididymal development, decreased AGD, and increased nipple retention, Howdeshell *et al.,* (2007) showing reduced AGD, increased number of areolae per male, and increased number of nipples per male, Jiang *et al.,* (2007) reporting an increased incidence of cryptorchidism and hypospadias and decreased AGD and serum testosterone, Mahood *et al.*, (2007) reporting an increased incidence of cryptorchidism and multinucleated gonocytes and decreased testosterone, Struve *et al.,* (2009) documenting decreased AGD, fetal testicular testosterone, and testicular mRNA concentrations scavenger receptor class B, member1; steroidogenic acute regulatory protein, cytochrome P45011a1, and cytochrome P45017a1, and Kim *et al.,* (2010) reporting an increased incidence of hypospadias and cryptorchidism, decreased testis and epididymal weights, and decreased AGD and testosterone levels.

5.2.1.1.2 Human

- Several epidemiologic studies measured urinary concentrations of MBP. Of those that did, there were associations of maternal urinary MBP concentrations with measures of male reproductive tract development (specifically shortened AGD) (Swan *et al.*, 2005; Swan, 2008). However, other studies did not find associations of urinary MBP with shortened AGD (Huang *et al.*, 2009; Suzuki *et al.*, 2012). Several studies reported associations of MBP with poorer scores on neurodevelopment tests (Engel *et al.*, 2010; Swan *et al.*, 2010; Kim *et al.*, 2011; Miodovnik *et al.*, 2011; Whyatt *et al.*, 2011) whereas others did not (Engel *et al.*, 2009; Cho *et al.*, 2010; Kim *et al.*, 2011).

5.2.1.2 **Relevance to Humans**

The reported animal studies are assumed to be relevant to humans.

5.2.1.3 **Weight of Evidence**

5.2.1.3.1 Experimental Design

Animal reproductive and developmental toxicology studies covered a broad range of species and methods and clearly support the overall conclusion that DBP has antiandrogenic properties. Although several of these studies report a specific NOAEL, not all studies were amenable to the calculation of a NOAEL. For example, the studies of Carruther and Foster (2005) and Howdeshell *et al.,* (2007), were designed to obtain mechanistic data and therefore did not include multiple doses. The study by Higuchi *et al.,* (2003) is interesting because it demonstrates that DBP produces effects in rabbits similar to those seen in the rat, but again, only one dose was used, thus precluding the determination of a NOAEL. Other studies (Lee *et al.*, 2004; Jiang *et al.*, 2007; Struve *et al.*, 2009), which did use at least 3 doses, used fewer than the recommended number of animals/dose (20/dose). The study by Kim *et al.,* (2010)used multiple doses; however, it was difficult to ascertain how many animals were used per dose. The studies of Mylchreest *et al.,* (2000) and Zhang *et al.,* (2004), on the other hand, used multiple doses and approximately 20 animals/dose. In the absence of maternal toxicity, Mylchreest reported an increase in nipple retention in male pups at 100 mg/kg-d, whereas Zhang *et al.,* reported increased male AGD at 250 mg/kg-day. In both studies, these LOAELs correspond to a NOAEL of 50 mg/kg-day. A NOAEL of 50 mg/kg-day is supported by the study of Mahood *et al.,* (2007), which reported a LOAEL of 100 mg/kg-day for decreased fetal testosterone production after exposure to DBP. Using the data of Mylchreest *et al.*, (2000) and Zhang *et al.*, (2004) the CHAP committee assigns a NOAEL of 50 mg/kg-day for DBP. Human correlation studies suggested that subjects with higher levels of DBP metabolites were associated with reproductive impairments. Some of these studies (i.e., Murature *et al.*, 1987), however, did not adequately consider or describe potential confounders.

5.2.1.3.2 Replication

A sufficient number of studies were replicated to confirm study findings and endpoints.

5.2.1.4 Risk Assessment Considerations

5.2.1.4.1 Exposure

No quantifiable exposures associated with toys and children's personal care products were located. DBP is used in nail polish. DBP metabolites (MBP) have been detected in human urine samples in the U.S. general population (Blount *et al.*, 2000; NHANES 1999-2000, 2001-2002, 2003-2004, CDC, 2012b), New York city pregnant women (Adibi *et al.*, 2003), Japanese adults (Itoh *et al.*, 2005), and infertility clinic patients in Boston (men; Duty *et al.*, 2004; Hauser *et al.*, 2007). When compared to children 6-11 years old, urine concentrations for MBP were 50% lower in neonates and 6-fold higher in toddlers (Brock *et al.*, 2002; Weuve *et al.*, 2006). In another study, geometric mean levels of MBP in the urine were significantly higher in children 6-11 years old when compared to adolescents or adults (Silva *et al.*, 2004). MBP urine levels have also been reported to differ by gender (Silva *et al.*, 2004). CHAP calculations estimate that the median/high intake (95th percentile) from NHANES biomonitoring data for DBP is 0.6/4 µg/kg-day, respectively.

5.2.1.4.2 Hazard

A relatively complete dataset suggests that exposure to DBP can cause reproductive or (non-reproductive) developmental effects. DBP can also induce other target organ effects, such as changes in body weight and liver weight.

5.2.1.4.3 Risk

Both animal and human data support maintaining the permanent ban on DBP in children's toys and child care articles. Currently, DBP is not allowed in these articles at levels greater than 0.1 %.

The MoEs from biomonitoring estimates range from 8,000 to 83,000 using median exposures and from 1300 to 13,000 using 95th percentiles. Typically, MoEs exceeding 100-1000 are considered adequate for public health; however, the cumulative risk of DBP with other anti-androgens should also be considered.

5.2.1.5 Recommendation to CPSC regarding children's toys and child care articles

The CHAP recommends no further action regarding toys and child care articles at this time, because it is already permanently banned in children's toys and child care articles at levels greater than 0.1 percent.

However, CHAP recommends that U.S. agencies responsible for dealing with DBP exposures from food, pharmaceuticals, and other products conduct the necessary risk assessments with a view to supporting risk management steps.

5.2.1.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DBP?

No, because DBP is already permanently banned in children's toys and child care articles.

5.2.2 Butylbenzyl Phthalate (BBP) (85-68-7)

5.2.2.1 Adverse Effects

5.2.2.1.1 Animal

5.2.2.1.1.1 Reproductive

- The NTP-CERHR reviewed the reproductive and developmental toxicity of BBP (NTP, 2003a). The panel's conclusions were that BBP could probably affect human development or reproduction, but that current exposures were probably not high enough to cause concern. The NTP stated that there was minimal concern for developmental effects in fetuses and children and that there was negligible concern for adverse reproductive effects in exposed men.
- Two 2-generation reproductive toxicity studies not reviewed in the 2003 NTP CERHR document reported that BBP exposure lead to decreased ovarian and uterine weights (F0 females), decreased mating and fertility indices (F1 males and females), decreased testicular, epididymal, seminal vesicle, coagulating gland, and prostate weights, increased reproductive tract malformations (i.e., hypospadias), decreased epididymal sperm number, motility, progressive motility, and increased histopathologic changes in the testis and epididymis (F1 males). In the F2 generation, AGD was reduced in male pups and male pups also had increased nipple/areolae retention.

5.2.2.1.1.2 Developmental

- The NTP-CERHR (2003a) reviewed the reproductive and developmental toxicity of BBP and, as with DBP, concluded at the time of the report that the panel could locate "no data on the developmental or reproductive toxicity of BBP in humans". The panel concluded, however, that, based on animal data, there was an adequate amount of data in rats and mice to do an assessment of "fetal growth, lethality and teratogenicity", but that none of the studies included a postnatal evaluation of "androgen-regulated effects (e.g., nipple retention, testicular descent, or preputial separation)", and that prenatal studies with the monoesters were adequate to conclude " that both metabolites (monobutyl phthalate and monobenzyl phthalate) contribute to developmental toxicity". These statements were based on studies by Ema *et al.,* (1990; 1992; 1995), Field *et al.,* (1989), and Price *et al.,* (1990). Developmental NOAELs in these studies ranged from 420 to 500 mg/kg-d and the panel caveated conclusions by saying it was not confident in the NOAELs because the studies would not detect postpubertal male reproductive effects (i.e., decreased AGD, increased incidence of retained nipples, etc.).

- Several studies subsequent to the NTP-CERHR (2000) extended the reports cited in this document with studies in which exposures occurred during late gestation and into the postnatal period. Gray *et al.,* (2000) reported that BBP increased the incidence of areolas/nipples, decreased testes weights, and increased the incidence of hypospadias, Nagao *et al.,* (2000) reported reduced AGD, delayed preputial separation, and reduced serum testosterone in male pups and increased AGD in female pups, Piersma *et al.,* (2000) reported increased frequency of developmental anomalies (increased incidence of fused ribs and reduced rib size, anopthalmia, cleft palate) and also increased the incidence of retarded fetal testicular caudal migration, Saillenfait *et al.,* (2003) reported increase in exencephalic fetuses in rats and an increase in exencephaly, facial cleft, meniogocele, spina bifida, onphalocele, and acephalostomia in mice. Ema found increased incidence of undescended testes and decreased AGD at 500 mg/kg-d or greater in one study (Ema and Miyawaki, 2002), and at doses of 250 mg/kg-d or greater in a subsequent study (Ema *et al.*, 2003). Tyl *et al.,* (2004) reported reduced AGD in F1 and F2 male offspring, delayed acquisition of puberty in F1 males and females, increased retention of nipples and areolae in F1 and F2 males, and increased incidence of abnormal male reproductive organs (hypospadias, missing epididymides, testes, prostate. BBP significantly reduced fetal testosterone production in male pups at 300 mg/kg-d or greater in SD rats (Howdeshell *et al.*, 2008).

5.2.2.1.2 Human

- Several epidemiologic studies measured urinary concentrations of MBZP. Of those that did there were no associations of maternal urinary MBZP concentrations with measures of male reproductive tract development (specifically shortened AGD) (NTP, 2000; Swan, 2008; Huang *et al.*, 2009; Suzuki *et al.*, 2012). A few studies reported associations of MBzP with poorer scores on neurodevelopment tests (Whyatt *et al.*, 2011) whereas others did not (Swan *et al.*, 2010).

5.2.2.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.2.2.3 Weight of Evidence

5.2.2.3.1 Experimental Design

The study of Gray *et al.,* (2000) could not be used to generate a NOAEL because only one dose was used, whereas, the study by Saillenfait *et al.,* (2003) could not be used because the sensitive period for the disruption of male fetal sexual development in the rat (GD 15-21) was not included in the study's exposure protocol (GD 7-13). The remaining studies were judged to be adequate for determining a NOAEL for BBP. The CHAP committee determined a NOAEL of 100 mg/kg-d from the Nagao *et al.,* (2000) study. Piersma *et al.,* (2000) calculated a benchmark dose of 95 mg/kg-d, and a NOAEL of 250 mg/kg-d was determined from the data of the Ema and Myawaki study (2002) and 167 mg/kg-d from the data of Emma *et al.,*, (2003). Tyl *et al.,* (2004) determined a NOAEL of 50 mg/kg-d from data generated in their two-generation study. Thus, the NOAELs range from a low of 50 to a high of 250 mg/kg-d. Finally, Howdeshell et al., (2008) reported significantly reduced fetal testosterone production at 300 mg/kg-d or greater. The CHAP committee decided to take the conservative approach and recommends a NOAEL of 50 mg/kg-d for BBP.

5.2.2.3.2 Replication

A sufficient number of studies demonstrating similar adverse reproductive and developmental endpoints have been performed.

5.2.2.4 Risk Assessment Considerations

5.2.2.4.1 Exposure

Little to no exposure is known to occur in children, toddlers and infants derived from toys or children's personal care products (BBP is not found in these articles at levels greater than 0.1 %): however, BBP is found in the diet. BBP metabolites (MBZP) have been detected in human urine samples in the U.S. general population (NHANES 1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007-2008; (Blount *et al.*, 2000), New York city pregnant women (Adibi *et al.*, 2003), infertility clinic patients in Boston (men; Duty *et al.*, 2004; Hauser *et al.*, 2007), young Swedish men (Jönsson *et al.*, 2005), German residents (Koch *et al.*, 2003a; Wittassek *et al.*, 2007b), and women in Washington D.C. (CDC, 2005; Hoppin *et al.*, 2004). When compared to children 6-11 years old, urine concentrations for MBzP were similar in children younger than 2 years. In general, levels of MBZP were higher in females when compared to males and children > adolescents > adults (Silva *et al.*, 2004). MBZP levels have decreased consistently over the survey periods for the total (geometric mean; 15.3 to 10.0 µg/L), all age, gender, and race classes. CHAP calculations estimate that the median/high (95^{th} percentile) intake from NHANES biomonitoring data for BBP is 0.3/1.3 µg/kg-day, respectively, in pregnant women and that MoEs for modeling and biomonitoring range from 6,800 to 147,000.

5.2.2.4.2 Hazard

A relatively complete dataset suggests that exposure to BBP can cause reproductive or (non-reproductive) developmental effects. BBP can also induce other target organ effects, such as changes in body weight and liver weight.

5.2.2.4.3 Risk

Both animal and human data support maintaining the permanent ban on BBP in children's toys and child care articles.

The margin of exposure for total BBP exposure in infants (SFF; Sathyanarayana *et al.*, 2008a; 2008b), at the 95th percentile of exposure) was 770 to 10,000. MoEs were slightly higher in pregnant women, ranging from 5000 to 66,000. Typically, MoEs exceeding 100-1000 are considered adequate for public health; however, the cumulative risk of BBP with other anti-androgens should also be considered.

5.2.2.5 Recommendation to CPSC regarding children's toys and child care articles:

The CHAP recommends no further action regarding toys and child care articles at this time, because it is already permanently banned in children's toys and child care articles at levels greater than 0.1 percent.

However, CHAP recommends that U.S. agencies responsible for dealing with BBP exposures from food and other products conduct the necessary risk assessments with a view to supporting risk management steps.

5.2.2.6 Would this recommendation, if implemented, be expected to reduce exposure of children to BBP?

No, because BBP is already permanently banned in children's toys and child care articles.

5.2.3 Di(2-ethylhexyl) Phthalate (DEHP) (117-81-7)

5.2.3.1 Adverse Effects

5.2.3.1.1 Animal

5.2.3.1.1.1 Reproductive

- The NTP-CERHR (2006) reviewed developmental and reproductive effects of DEHP. The panel's conclusions were that DEHP could probably affect human development or reproduction, and that current exposures were high enough to cause concern. The NTP concurred with the panel and stated that there was serious concern for DEHP exposures during certain intensive medical treatments for male infants and that these exposures may result in levels high enough to affect development of the reproductive tract. They also concurred that there was concern for adverse effects on male reproductive tract development resulting from certain medical procedures to pregnant and breast feeding women, that there was concern for male infants (<1 year old) reproductive tract development following exposure, that there was some concern for male children (> 1 year old) reproductive tract development following exposure, that there was some concern for male offspring reproductive tract development following exposures to pregnant women not exposed via medical procedures, and that there is minimal concern for reproductive toxicity in adults who are exposed medically or non-medically. Sixty eight (predominately rodent) studies were reviewed by the NTP-CERHR panel.

5.2.3.1.1.2 Developmental

- The NTP-CERHR (NTP, 2002) reviewed developmental and reproductive effects of DEHP. Forty-one animal prenatal developmental toxicity studies "were remarkably consistent" and "DEHP was found to produce malformations, as well as intrauterine death and developmental delay. The NOAEL based upon malformations in rodents was ~40 mg/kg-d and a NOAEL of 3.7 - 14 mg/kg-d was identified for testicular development/effects in rodents".
- The NTP-CERHR (2006) update on the developmental and reproductive effects of DEHP reviewed multiple human studies and concluded that there is "insufficient evidence in humans that DEHP causes developmental toxicity when exposure is prenatal…or when exposure is during childhood". The panel reviewed animal studies as well and concluded that there is "sufficient evidence that DEHP exposure in rats causes developmental toxicity with dietary exposure during gestation and/or early postnatal life at 14-23 mg/kg-d as manifest by small or absent male reproductive organs" (NOAEL = 3-5 mg/kg-d).
- Three developmental toxicity reports have appeared since the 2006 NTP-CERHR, which confirmed and extended the studies already reviewed. These latest studies show that DEHP exposure delays the age of vaginal opening and first estrus in females, delays male preputial separation, increases testis weight and nipple retention and decreased AGD (Grande *et al.*, 2006; Andrade *et al.*, 2006a; Christiansen *et al.*, 2010).

5.2.3.1.1.3 Human

- Several epidemiologic studies measured urinary concentrations of metabolites of DEHP, including MEHP, MEHHP, MEOHP and MECPP. Of those that did there were associations of maternal urinary MEHP, MEHHP and MEOHP concentrations with measures of male reproductive tract development (specifically shortened AGD) (Swan *et al.*, 2005; Swan, 2008; Suzuki *et al.*, 2012). However, one other study did not find associations of urinary MEHP with AGD (Huang *et al.*, 2009). Several studies reported associations of MEHP with poorer scores on neurodevelopment tests (Engel *et al.*, 2009; Kim *et al.*, 2009; Swan *et al.*, 2010; Kim *et al.*, 2011; Miodovnik *et al.*, 2011; Yolton *et al.*, 2011) whereas others did not (Engel *et al.*, 2010; Whyatt *et al.*, 2011).

5.2.3.2 **Relevance to Humans**

The reported animal studies are assumed to be relevant to humans.

5.2.3.3 Weight of Evidence

5.2.3.3.1 Experimental Design

The Gray *et al.,* (2000) study could not be used to determine a NOAEL because only one dose was used. The studies of Moore *et al.,* (2001), Borch *et al.,* (2004), and Jarfelt *et al.,* (2005) could not be used because in each case the lowest dose used produced a significant effect and therefore a NOAEL could not be determined. The studies of Grande *et al.*, (2006), Andrade *et al.*, (2006a), Gray *et al.*, (2009), and Christian *et al.*, (2010) are all well designed studies employing multiple doses at the appropriate developmental window and using relatively large numbers of animals per dose group. Although different phthalate syndrome endpoints were used to set a NOAEL, the resulting NOAELs cluster tightly around a value of 3-11 mg/kg-d. It is noteworthy that this cluster is consistent with the NOAEL identified in the NTP study (4.8 mg/kg-d; Foster *et al.*, 2006). In contrast, using fetal testosterone production as an endpoint, Hannas *et al.*, (2011b) reported a LOAEL of 300 mg/kg-d and a NOAEL of 100 mg/kg-d, a NOAEL approximately 10 times the one derived using morphological endpoints. Using a weight-of-evidence approach, the CHAP committee has conservatively set the NOAEL for DEHP at 5 mg/kg-d.

5.2.3.3.2 Replication

A sufficient number of animal studies demonstrating similar adverse reproductive and developmental endpoints have been performed.

5.2.3.4 Risk Assessment Considerations

5.2.3.4.1 Exposure

Currently, DEHP is not allowed in children's toys and child care products at levels greater than 0.1%. The frequency and duration of exposures have not been determined; however; metabolites of DEHP (MEHP, MEHHP, MEOHP, MECPP) have been detected in human urine samples in the U.S. general population (NHANES 1999-2000, 2001-2002, 2003-2004; CDC, 2012b), New York city pregnant women (Adibi *et al.*, 2003), women in Washington D.C. (Hoppin *et al.*, 2004), people in South Korea (Koo and Lee, 2005), Japanese adults (Itoh *et al.*, 2005), Swedish military recruits (Duty *et al.*, 2004; Duty *et al.*, 2005b), infertility clinic patients (men; Hauser *et al.*, 2007), plasma and platelet donors (Koch *et al.*, 2005a; Koch *et al.*, 2005b), and people in Germany (Koch *et al.*, 2003a; Becker *et al.*, 2004; Koch *et al.*, 2004b; Preuss *et al.*, 2005; Wittassek *et al.*, 2007b). Trends over time for these metabolites are unclear. CHAP calculations estimate that the median/high (95^{th} percentile) intake from NHANES biomonitoring data for DEHP is 3.5/181 µg/kg-day.

5.2.3.4.2 Hazard

A complete dataset suggests that exposure to DEHP when *in utero* can induce adverse developmental changes to the male reproductive tract. Exposure to DEHP can also adversely affect many other organs such as the liver, thyroid, etc.

5.2.3.4.3 Risk

Both animal and human data support maintaining the permanent ban on DEHP in children's toys and child care articles

The margin of exposure for total DEHP exposure in infants (SFF; Sathyanarayana *et al.*, 2008a; 2008b), at the 95th percentile of exposure) was 116-191. MoEs were similar in pregnant women, ranging from 17-28. The margins of exposure for total DEHP exposure are insufficient considering the severity of the effects described above. Furthermore, DEHP dominates the hazard index for cumulative exposure to antiandrogenic phthalates. Based on NHANES data (NHANES 2005-2006; CDC, 2012b), the CHAP estimates that about 10% of pregnant women exceed a cumulative hazard index of 1.0, which is largely due to DEHP exposure.

5.2.3.5 Recommendation to CPSC regarding children's toys and child care articles

The CHAP recommends no further action regarding toys and child care articles at this time, because DEHP is permanently banned in children's toys and child care articles at levels greater than 0.1 percent.

However, CHAP recommends that U.S. agencies responsible for dealing with DEHP exposures from all sources conduct the necessary risk assessments with a view to supporting risk management steps.

5.2.3.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DEHP?

No, because DEHP is already permanently banned in children's toys and child care articles.

5.3 Recommendations on Interim Banned Phthalates

5.3.1 Di-*n*-octyl Phthalate (DNOP) (117-84-0)

5.3.1.1 Adverse Effects

5.3.1.1.1 Animal

5.3.1.1.1.1 Systemic

- Hardin *et al.*, (1987) reported on a developmental screening toxicity test in female CD-1 mice in which DNOP (0, 9780 mg/kg-day) was administered via gavage during GD 6-13. DNOP administration did not change the number of maternal deaths or body weight.
- Heindel *et al.*, (1989) (and Morrissey *et al.*, 1989) conducted a one generation continuous breeding reproductive toxicity test in CD-1 Swiss mice in which DNOP (0, 1800, 3600, and 7500 mg/kg-day) was administered in the diet for 7 days prior and 26 weeks following cohabitation. Treatment with DNOP did not affect body weight gain or food consumption, but did significantly increase liver weight (F1,

LOAEL = 750 mg/kg-day) and kidney weight (female F1, LOAEL = 750 mg/kg-day).

- (Hinton *et al.*, 1986) reported on short-term toxicity testing in Wistar rats in which DNOP (0, 2%) was administered in the feed for 3, 10, or 21 days. Treatment with DNOP caused hepatomegaly, a changed liver texture and appearance, hepatic fat accumulation, peroxisome proliferation, smooth endoplasmic reticulum proliferation, a decrease in serum thyroxine (T_4) and increased triidothyronine (T_3).
- Khanna *et al.*, (1990) reported on the subchronic kidney toxicity in albino rats (10 male/group) in which DNOP (0, 100, 300, 600 mg/kg) was administered via intraperitoneal injection once daily for 5 days a week for 90 days. Dose-dependent changes in kidney histopathology were noted and suggested that irreversible nephrotoxicity was occurring.
- Lake *et al.*, (1984) reported on intermediate-term toxicity in male Sprague-Dawley rats (6/group) in which DNOP (0, 1000, 2000 mg/kg-day) was administered via gavage daily for 14 days. Exposure to DNOP significantly increased the relative liver weight and altered liver enzyme activities.
- Lake *et al.*, (1986) reported on the intermediate-term liver toxicity in male Sprague Dawley rats in which DNOP (0, 1000 mg/kg-day) was administered daily via gavage for 14 days. As with Lake's previous study, DNOP exposure increased rat relative liver weight and altered liver enzyme functions.
- Mann *et al.*, (1985) reported on short- and intermediate-term liver toxicity in male Wistar rats in which DNOP (0, 2%; ~2000 mg/kg-day) was administered via the diet for 3, 10, or 21 days. DNOP increased the relative liver weight, changed the texture and appearance of the liver, changed the liver ultrastructurally and enzymatically, and marginally increased the peroxisome number.
- Poon *et al.*, (1997) conducted a subchronic toxicity study in Sprague-Dawley rats (10/sex/group) in which DNOP (0, 0.4/0.4, 3.5/4.1, 36.8/40.8, 350.1/402.9 mg/kg-day; M/F) was administered via the diet for 13 weeks. DNOP exposure did not alter body weight, food consumption, liver weight, kidney weight, or the number or distribution of peroxisomes, but did alter liver enzyme activity and liver ultrastructure. Reduced thyroid follicle size (F, 40.8 mg/kg-day), and decreased colloid density (M/F; 3.5/40.8 mg/kg-day) were observed in dosed groups.
- Smith *et al.*, (2000) reported on the intermediate-term toxicity in male Fischer-344 rats and B6C3F1 mice in which DNOP (0, 1000, 10000 mg/kg [rats], and 0, 500, 10000 mg/kg [mice]) was administered via the diet for 2 and 4 weeks. In rats, DNOP exposure increased the relative liver weight, peroxisomal activity, and periportal hepatocellular replicative activity, but didn't change gap junctional intercellular communication. In mice, only peroxisomal activity was altered following exposure to DNOP.
- Saillenfait *et al.*, (2011) conducted a prenatal developmental toxicity test in Sprague-Dawley rats in which DNOP (0, 250, 500, and 1000 mg/kg-day) was administered via gavage once a day on GD 6-20. DNOP exposure did not affect maternal feed consumption, body weight, body weight change, or liver histopathology, but did significantly increase the liver weight and liver weight normalized to body weight on GD21 (LOAEL = 1000 mg/kg-day). DNOP also significantly increased various liver biochemical markers such as ASAT, ALAT, and cholesterol.

5.3.1.1.1.2 Reproductive

- Heindel *et al.*, (1989) (and Morrissey *et al.*, 1989) conducted a one generation continuous breeding reproductive toxicity test in CD-1 Swiss mice in which DNOP (0, 1800, 3600, and 7500 mg/kg-day) was administered in the diet for 7 days prior and 26 weeks following cohabitation. Reproductive parameters were not affected by dosing with DNOP.
- Poon *et al.*, (1997) conducted a subchronic toxicity study in Sprague-Dawley rats in which DNOP (0, 0.4/0.4, 3.5/4.1, 36.8/40.8, 350.1/402.9 mg/kg-day; M/F) was administered via the feed for 13 weeks. No reproductive parameters were affected by dosing with DNOP.
- Foster *et al.*, (1980) conducted a short-term toxicity test in male Sprague-Dawley rats in which DNOP (0, 2800 mg/kg-day) was administered via gavage once a day for 4 days. Changes in testis weight or pathology were not observed.

5.3.1.1.1.3 Developmental

- The NTP-CERHR reviewed the reproductive and developmental toxicity of DNOP in 5 animal studies (Singh *et al.*, 1972; Gulati *et al.*, 1985; Hardin *et al.*, 1987; Heindel *et al.*, 1989; Hellwig *et al.*, 1997) and concluded that “available studies do suggest a developmental toxicity response with gavage or i.p. administration with very high doses”.
- Saillenfait *et al.*, (2011) conducted a prenatal developmental toxicity test in Sprague-Dawley rats in which DNOP (0, 250, 500, and 1000 mg/kg-day) was administered via gavage once a day on GD 6-20. A dose-related increase in the incidence of supernumerary ribs was noted at non-maternally toxic doses. The authors calculated BMD_{05} and $BMDL_{05}$ values for supernumerary ribs (58/19 mg/kg-day, respectively). No adverse effects on reproductive tissue were observed.

5.3.1.1.2 Human

- No published human studies.

5.3.1.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.3.1.3 Weight of Evidence

5.3.1.3.1 Experimental Design

In the Heindel and Poon studies, the number of animals dosed was insufficient to have high confidence in the data (n=20 breeding pairs per dose group and n=13 animals per dose group, respectively). Further, dosing schedule for these studies (and the Foster *et al.*,, 1980 study) did not cover the standard length of time needed to determine male reproductive effects or reproductive effects resulting from developmental issues (10 weeks of dosing pre-mating). In all but one study of the 5 reviewed by NTP, exposure occurred before GD15 (rat) and GD13 (mouse). The NTP panel noted that limited study design “do not provide a basis for comparing consistency of response in two species, nor do they allow meaningful assessment of dose-response relationships and determination of either LOAELs or NOAELs with any degree of certainty". The recently published Saillenfait study was of appropriate design to have confidence in observed toxicologic effects. The Khanna study utilized an exposure route (IP) that was not relevant to common human exposure scenarios.

5.3.1.3.2 Replication

No published full reproduction studies exist. Further replication is needed for the one developmental study (Saillenfait). DNOP-induced systemic adverse effects were noted in animal test subject's thyroid, immune system, kidney, and liver in two, three, three, and eight published studies, respectively. Sufficient data were available from the studies reporting DNOP-induced liver toxicity to calculate a subchronic oral ADI of 0.37 mg/kg-day (Carlson, 2010a), based on a NOAEL of 37 mg/kg-d (Poon *et al.*, 1997) and an overall uncertainty factor of 100.

5.3.1.4 Risk Assessment Considerations

5.3.1.4.1 Exposure

Undetermined frequency and duration of exposures, but metabolites of DNOP (MNOP, MCPP) have been detected in human urine samples in the U.S. (NHANES 1999-2000, 2001-2002, 2003-2004; CDC, 2012b), Washington D.C. (Hoppin *et al.*, 2002), and Germany (Koch *et al.*, 2003a). However, based on HBM data exposure seems to be negligible with 99% of the samples having MNOP concentrations below the LOQ. Trends over time for these metabolites are unclear. Based upon aggregate exposure estimates, for women of reproductive age and children, most DNOP exposure is from food. For infants and toddlers, child care articles are the greatest potential source of exposure. Modeled DNOP exposures for infants and toddlers ranges from 4.5 µg/kg/d (average, infants) to 16 µg/kg/d (upper bound, toddlers) (Table 2.11).

5.3.1.4.2 Hazard

On the one hand, a limited developmental toxicity dataset did not identify DNOP as an anti-androgen; however, with the exception of the Saillenfait study, the developmental toxicity studies making up this dataset all have major limitations. Although DNOP was not anti-androgenic in the Saillenfait study, exposure to this phthalate was associated with developmental toxicity, i.e., supernumerary ribs, although developmental toxicologists are divided as to whether this effect is a malformation or a minor variation. On the other hand, a systemic toxicity dataset, although incomplete, suggests that exposure to DNOP can induce adverse effects in the liver, thyroid, immune system, and kidney.

5.3.1.4.3 Risk

Based on a point of departure (POD) of 37 mg/kg-d (0.037 µg/kg-d) (see above), the CHAP estimates that Margins of Exposure for infants and toddlers range from 2,300 to 8,200.

5.3.1.5 Recommendation

DNOP does not appear to possess anti-androgenic potential; nonetheless, the CHAP is aware that DNOP is a potential developmental toxicant, causing supernumerary ribs, and a potential systemic toxicant, causing adverse effects on the liver, thyroid, immune system, and kidney. However, because the Margins of Exposure in humans are likely to be very high, the CHAP does not find compelling data to justify maintaining the current interim ban on the use of DNOP in children's toys and child care articles. Therefore, the CHAP recommends that the current ban on DNOP be lifted, but that U.S. agencies responsible for dealing with DNOP exposures from food and child care products conduct the necessary risk assessments with a view to supporting risk management steps.

5.3.1.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DNOP?

No. DNOP use would be allowed in children's toys and child care articles.

5.3.2 Diisononyl Phthalate (DINP) (28553-12-0 and 68515-48-0)

5.3.2.1 Adverse Effects

5.3.2.1.1 Animal

5.3.2.1.1.1 Systemic

- DINP was tested in two chronic studies in Fischer 344 rats (Lington *et al.*, 1997; Moore, 1998b) and one in B6C3F1 mice (Moore, 1998a). Systemic effects in the liver and kidney were reported.
- Kidney effects included increased kidney weight (rats and female mice), increased urine volume, increased mineralization (male rat), and progressive nephropathy (female mice). The NOAEL for kidney effects was 88 mg/kg-d (male rat) (Moore, 1998b).
- Liver effects included hepatomegaly, hepatocellular enlargement, peroxisome proliferation, focal necrosis, and spongiosis hepatis (microcystic degeneration) (reviewed in, CPSC, 2001; Babich and Osterhout, 2010). Increased levels of liver-specific enzymes were also reported. The NOAEL for liver effects was 15 mg/kg-d (Lington *et al.*, 1997).
- Peroxisome proliferation, hepatocellular adenomas, and hepatocellular and carcinomas were found in the livers of both mice and rats. The CHAP on DINP attributed the hepatocellular tumors to peroxisome proliferation, which is not expected to occur in humans (CPSC, 2001) (see also, Klaunig *et al.*, 2003).
- A low incidence of renal tubular cell carcinomas was observed in male rats only (Moore, 1998b). These tumors were shown to be result from the accumulation of α2u-globulin (Caldwell *et al.*, 1999), a mode of action that is unique to the male rat .
- The incidence of mononuclear cell leukemia was elevated in Fischer 344 rats (Lington *et al.*, 1997; Moore, 1998b). This lesion is commonly reported in Fischer rats. The CHAP on DINP concluded that mononuclear cell leukemia is of uncertain relevance to humans (CPSC, 2001).

- The NOAEL for non-cancer effects was 15 mg/kg-d. The CHAP on DINP (CPSC, 2001) derived an ADI of 0.12 mg/kg-d, based on a benchmark dose analysis of the incidence of spongiosis hepatis in the Lington *et al.* (1997) study.

5.3.2.1.1.2 Reproductive

- The NTP-CERHR (2003c) reviewed developmental and reproductive effects of DINP. The panel's conclusions were that DINP could probably affect human development or reproduction, but that current exposures were probably not high enough to cause concern. The NTP stated that there was minimal concern for DINP causing adverse effects to human reproduction or fetal development.
- Since the 2003 NTP-CERHR report, one reproductive study in Japanese medaka fish showed no effects on survival, fertility or other factors associated with reproduction (Patyna *et al.*, 2006).

5.3.2.1.1.3 Developmental

- The 2003 summary of the NTP-CERHR report on the reproductive and developmental toxicity of diisononyl phthalate (DINP) (NTP, 2003c) concludes that, as of their report, there were "no human data located for Expert Panel review." The panel did review two rat studies evaluating prenatal developmental toxicity of DINP by gavage on gd 6-15 (Hellwig *et al.*, 1997; Waterman *et al.*, 1999), the developmental toxicity of DINP in a two-generation study in rats (Waterman *et al.*, 2000), and a prenatal developmental toxicity of isononyl alcohol, a primary metabolite of DINP (Hellwig and Jackh, 1997). The two rat prenatal studies showed effects on the developing skeletal system and kidney following oral exposures to DINP from gd 6-15, while in the two-generation study in rats effects on pup growth were noted. The prenatal developmental toxicity study with isononyl alcohol provided evidence that this primary metabolite of DINP "is a developmental and maternal toxicant at high (~1000mg/kg) oral doses in rats." From these studies, the panel concluded that the toxicology database "is sufficient to determine that oral maternal exposure to DINP can result in developmental toxicity to the conceptus." The panel also noted that "some endpoints of reproductive development that have been shown to be sensitive with other phthalates were not assessed." Therefore, the panel recommended that "a perinatal developmental study in orally exposed rats that addresses landmarks of sexual maturation such as nipple retention, anogenital distance, age at testes descent, age at prepuce separation, and structure of the developing reproductive system in pubertal or adult animals exposed through development" should be considered.

The perinatal studies recommended by the NTP-CERHR panel have now been performed. Five such studies have shown that DINP exposure in rats during the perinatal period is associated with increased incidence of male pups with areolas and other malformations of androgen-dependent organs and testes (Gray *et al.*, 2000), reduced testis weights before puberty (Masutomi *et al.*, 2003), reduced AGD (Lee *et al.*, 2006), increased incidence of multinucleated gonocytes, increased nipple retention, decreased sperm motility, decreased male AGD, and decreased testicular testosterone (Boberg *et* *al.*, 2011), and reduced fetal testicular testosterone production, and decreased StaR and Cyp11a mRNA levels (Adamsson *et al.*, 2009; Hannas *et al.*, 2011b). Although the Hannas et al., 2011 study was not designed to determine a NOAEL, a crude extrapolation of their dose response data (Figure 6) suggests that the NOAEL is approximately 100 mg/kg/day for reduced fetal testicular testosterone production. This NOAEL would be higher by a factor of 20 compared to the NOAEL of DEHP (for gross reproductive tract malformations (RTMs) associated with the ''phthalate syndrome''of 5 mg/kg-d; Blystone et al. 2010). In the same paper, however, Hannas et al. 2011, based upon their dose-response assessment of fetal testosterone production found that DINP reduced fetal testicular T production with an only 2.3-fold lesser potency than DEHP. This would lead to a NOAEL of 11.5 mg/kg-d for DINP extrapolated from the NOAEL of DEHP. In more recent studies, Clewell et al., 2013a, b reported a NOEL of ~50 mg/kg/day for DINP-induced multinuclear gonocytes (MNGs) and a NOEL of ~250 mg/kg/day for reduced AGD. However, even in the highest dose group (750 mg/kg-d) Clewell et al. 2013 reported no effect on fetal testicular T production, contrary to Boberg et al. 2011, Hannas et al. 2011 and Hannas et al. 2012.

5.3.2.1.2 Human

No epidemiologic studies measured metabolites of DINP in relation to male reproductive health or neurodevelopment endpoints.

5.3.2.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.3.2.3 Weight of Evidence

5.3.2.3.1 Experimental Design

Several of the studies were judged to be inadequate for ascertaining a NOAEL for DINP. The Gray *et al.*, (2000) study used only one dose and the Masutomi *et al.*, (2003), Borch *et al.*, (2004), and the Adamsson *et al.*, (2009), studies used relatively small numbers of animals per dose group. Further, the Lee *et al.*, (2006) study used the individual fetus rather than the litter as the unit of measurement, thus calling into question their conclusions. In contrast, the Boberg *et al.*, (2011) study used multiple doses (4 plus control), exposure occurred during the developmentally sensitive period (GD 7-PND 17), and used a relatively high number of dams per dose (16). On the basis of increased nipple retention at 600 mg/kg-d, the authors report a NOAEL of 300 mg/kg-d. However, the same authors also observed a dose dependent reduction in testicular testosterone production that was still evident in the low dose group (300 mg/kg-d), as shown in figure 2A of Boberg *et al*., (2011). Furthermore, several of the other studies provide additional data that the CHAP considered relevant. The Hannas *et al.*, (2011b) study found a LOAEL of 500 mg/kg-d based on decreased fetal testosterone production, suggesting that the NOAEL for this endpoint is clearly below this level. Extrapolation of their dose response data (Figure 6) suggests that the NOAEL is approximately 100 mg/kg/day. In addition, data from Clewell *et al.*, (2013b) show that the NOEL for DINP-induced MNGs is approximately 50 mg/kg/day. Taken together, the data from Boberg et al., (2011), Hannas et al., (2011b), and Clewell et al., (2013a; 2013b) indicate that the developmental

NOAEL based upon anti-androgenic endpoints (nipple retention, fetal testosterone production, and MNGs) is somewhere between 50 and 300 mg/kg/day. Taking a conservative approach, the CHAP committee assigns the NOAEL for DINP at 50 mg/kg/day. However, the CHAP also wants to point out that a simple extrapolation based upon relative potencies (as described by Hannas *et al*., 2011b) with 2.3-fold lesser potency of DINP than DEHP (in terms of fetal testicular T reduction), would lead to a NOAEL of 11.5mg/kg-d for DINP. This scenario is reflected in Case 2 of the HI approach.

5.3.2.3.2 Replication

Although the developmental toxicity literature for DINP is not data rich, a number of animal studies demonstrating adverse reproductive and developmental endpoints (antiandrogenic) have beenreported.NOAELs for DINP-induced antiandrogenic toxicities range from 50 mg/kg/day (MNGs) to 300 mg/kg/day (nipple retention). In addition, the CHAP is aware that DINP is a systemic toxicant, e.g., inducing significant liver toxicity. CPSC has calculated an ADI of 0.12 mg/kg/day using the lowest NOAEL (12 mg/kg/day) for DINP-induced liver toxicity (Babich and Osterhout, 2010). Like DIDP, the NOAEL for liver toxicity (12 mg/kg/day) is lower than the lowest NOAEL for antiandrogenic toxicity (50 mg/kg/day for MNGs).

5.3.2.4 Risk Assessment Considerations

5.3.2.4.1 Exposure

DINP has been used in children's toys and child care articles in the past. The CHAP estimates that infants' exposure to DINP from mouthing soft plastic articles may range from 2 (mean) to 9 (upper bound) µg/kg-d. The frequency and duration of exposures have not been determined; however metabolites of DINP (MCOP) have been detected in human urine samples in the U.S. general population (NHANES 2005-2006, 2007- 2008; CDC, 2012b). Although only two survey durations have been monitored, MCOP levels have slightly increased in the last survey period for the total (geometric mean; 5.39 to 6.78 µg/L), all age, gender, and race classes. Another urinary metabolite of DINP (MINP) has also been detected infrequently in human urine samples in the U.S. general population (NHANES 1999-2000, 2001-2002, 2003-2004, 2005-2006, 2007- 2008; CDC, 2012b). Most MINP samples, however, have been lower than the limit of detection. CHAP calculations estimate that the median and high intake (95^{th} percentile) from NHANES biomonitoring data for DINP is 1.0 and 11.1 µg/kg-day, respectively.

5.3.2.4.2 Hazard

A relatively complete dataset suggests that exposure to DINP can cause reproductive or (non-reproductive) developmental effects, although it is less potent than other active phthalates, for example, DEHP.

5.3.2.4.3 Risk

5.3.2.4.3.1 Male Developmental Effects

In infants in the SFF study, the MoE for total exposure ranged from 640 to 42,000 using 95th percentile estimates of exposure. For pregnant women, the MoE for total DINP exposure ranged from 1,000 to 68,000. Typically, MoEs exceeding 100-1000 are considered adequate for public health; however, the cumulative risk of DINP with other anti-androgens should also be considered.

5.3.2.4.3.2 Systemic Effects (Liver)

In infants in the SFF study, the estimated total DINP exposure ranged from 3.6 to 18.0 µg/kg-d (median and 95th percentile) (Table 2.7). For women in NHANES (2005-6), the estimated total exposure ranged from 1.0 to 9.4 µg/kg-d (Table 2.7). Using the NOAEL of 15 mg/kg-d for systemic toxicity, the MoE for infants ranges from 830 to 4,200. The MoE for women ranges from 1,600 to 15,000. Typically, MoEs exceeding 100-1000 are considered adequate for public health.

5.3.2.5 Recommendation

The CHAP recommends that the interim ban on the use of DINP in children's toys and child care articles at levels greater than 0.1 percent be made permanent. This recommendation is made because DINP does induce antiandroenic effects in animals, although at levels below that for other active phthalates, and therefore can contribute to the cumulative risk from other antiandrogenic phthalates.

Moreover, CHAP recommends that U.S. agencies responsible for dealing with DINP exposures from food and other products conduct the necessary risk assessments with a view to supporting risk management steps.

5.3.2.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DINP?

No, because DINP is currently subject to an interim ban on use in children's toys and child care articles at levels greater than 0.1 percent.

5.3.3 Diisodecyl Phthalate (DIDP) (26761-40-0 and 68515-49-1)

5.3.3.1 Adverse Effects

5.3.3.1.1 Animal

5.3.3.1.1.1 Systemic

- BIBRA reported on a 21-day feeding study, in which Fischer 344 rats (5/sex/dose) were fed 300, 1000 or 2000 mg/kg/day DIDP. The NOAEL for both sexes was 300 mg/kg/day based on increased absolute and relative liver weights, increased cyanide-insensitive palmitoyl-CoA oxidation, increases in the number and size of hepatocyte peroxisomes, change in serum triglycerides and cholesterol, a change in hepatocyte cytoplasm staining properties, and increased relative kidney weights.
- An abstract by Lake *et al.,* described (1991) a 28-day feeding study of male Fischer 344 rats (5/sex/dose) that were fed approximately 25, 57, 116, 353, and 1287 mg DIDP/kg/day. A no observed effect level (NOEL) of 57 mg/kg/day is assumed based on a statistically significant increase in relative liver weight 116 mg/kg/day. Liver palmitoyl-CoA oxidation activity at increased at 353 mg/kg/day, as did absolute liver weights. Testicular atrophy was not observed at any dose.
- BASF fed Sprague Dawley rats 0, 800, 1600, 3200, and 6400 ppm DIDP (approximately 55, 100, 200, and 400 mg/kg/day for males and 60, 120, 250, and 500 mg/kg/day for females) for 90 days. Relative liver weights were significantly increased in all males; absolute liver weights were significantly increased only in males at 6400 ppm. In females, relative and absolute liver weights were significantly increased at >1600 ppm and >3200 ppm respectively. Relative kidney weights were significantly increased at all treated doses in males. In females, relative kidney weights were significantly increased in a non-dose dependent manner at 1600 ppm and 3200 ppm, but not at 6400 ppm. There were no observed pathological abnormalities. Peroxisome proliferation was not studied. A NOAEL of 200 mg/kg/day for males and 120 mg/kg/day for females was determined by CERHR (NTP, 2003b).
- In a three-month feeding study, 20 Charles River CD rats were given 0, 0.05, 0.3, or 1% DIDP (approximately 28, 170, and 586 mg/kg/day for males and 35, 211, and 686 mg/kg/day for females) (Hazleton, 1968a). Absolute and relative liver weights were significantly increased in both sexes at 1% DIDP (586 and 686 mg/kg/day for M and F). Relative kidney weights were significantly increased in males at 0.3% and 1% DIDP (170 and 586 mg/kg/day). There were no effects on food consumption, body weight, or clinical chemistry. There were no histological changes in liver, kidney or testes. Peroxisome proliferation was not studied. A NOAEL was reported as 170 and 211 mg/kg/day for males and females, respectively. The LOAEL was 586 and 686 mg/kg/day for males and females respectively for increased liver weight.
- In a 13-week diet study, Beagle dogs (3/sex/group) were given approximately 0, 15, 75 and 300 mg/kg/day DIDP (Hazleton, 1968b). A NOAEL of 15 mg/kg/day was reported based on increased liver weights and histological changes. A LOAEL was reported at 75 mg/kg/day for increased liver weight and slight to moderate swelling and vacuolation of hepatocytes.

- In a two-year oral toxicity/carcinogenicity study of DIDP Fischer 344 rats were exposed to 0, 400, 2000 or 8000 ppm DIDP (0.85, 4.13, 17.37 mg/kg/day for males and 0.53, 3.03, 13.36 mg/kg/day for females). At the high dose, there was a significant decrease in the overall survival and body weight with a significant increase in relative liver and kidney weights in males and females. No treatment-related neoplastic lesions observed in internal organs including the liver of either sex (Cho *et al.*, 2008).
- Cho *et al.*, (2008) also fed 50 rats/dose 0, 400, 2000, or 8000 ppm DIDP or 12000 ppm DEHP, as a positive control and sacrificed after 12 or 32 weeks. After 12 weeks the levels of catalase in the 8000 ppm DIDP group were increased compared to controls, yet after 32 weeks there were no differences in the catalase levels and activity. In the positive DEHP treated control animals, catalase levels and activity were increased at both 12 and 32 weeks.
- An inhalation study exposed Sprague Dawley rats to 505 mg/m^3 DIDP vapor for two weeks, six hours per day for five days per week. No systemic effects were reported (GMRL, 1981).

5.3.3.1.1.2 Reproductive

- Systemic studies summarized above (Hazleton, 1968a; Hazleton, 1968b; BIBRA, 1986; Lake *et al.*, 1991) reported no changes histopathology of testes. However, relative testes weights were significantly increased at 2000 mg/kg/day DIDP in a 21-day feeding study in Fisher 344 rats (BIBRA, 1986).
- In a Hershberger assay, castrated prepubertal SD Crl:CD rats (6/group) were given 0, 20, 100, and 500 mg/kg/day DIDP by gavage in combination with 0.4 mg/kg/day testosterone. Treatment with 500 mg/kg/day DIDP led to a significant decrease in ventral prostate and seminal vesicle weight compared to the testosterone positive control, suggesting that DIDP does possess anti-androgenic activity. The NOAEL for this study was set at 100 mg/kg/day (Lee and Koo, 2007).
- One single-generation and two multi-generation animal studies were completed by Exxon Biomedical Sciences (Exxon, 1997; ExxonMobil, 2000). In the one-generation study, rats received dietary levels of 0, 0.25, 0.5, 0.75, and 1% DIDP. In the first study multi-generation study Crl:CD BR-VAF/Plus (Sprague Dawley) rats (30/sex/dose) were given 0, 0.2, 0.4, or 0.8% DIDP in their diet for ten weeks prior to and during mating. Females continued to receive DIDP throughout gestation and lactation. The second multi-generation study was identical to the first except that rats received 0, 0.02, 0.06, 0.2, or 0.4% DIDP. DIDP did not appear to have effects on male reproductive tract development or function. There was a significant decrease in ovary weight (parental) and significant increases in F1 males' relative testes, epididymis and seminal vesicle weights without accompanying changes in histology or reproductive function at 0.8%. There was a non-reproducible increase in the age at vaginal opening at doses of 0.4% and 0.8% in the first multi-generation study only. There was a non-dose related decreased in the number of normal sperm of F0 treated males in the first study, and an increase in the length of the estrous cycle in the F0 females treated with 0.8% DIDP; neither effects was observed in the F1 generation. There were no effects on mating, fertility, or gestational indices in any generation. The CERHR (NTP, 2003b) considered the reproductive NOAEL to be the highest

dose (0.8%), or 427−929 mg/kg bw/day for males and 508−927 mg/kg bw/day for females.

5.3.3.1.1.3 Developmental

- A one generational comparative developmental screening test was performed on Wistar rats (10/dose). DIDP, at doses of 0, 40, 200, and 1000 mg/kg/day, was given by gavage two weeks prior to mating for a total of 29 days for males or until PND 6 for females (BASF, 1995; Hellwig *et al.*, 1997). Fetuses were examined on GD 20 for weight, external, visceral and skeletal malformations. Maternal toxicity was observed in the high dose group with significantly reduced feed consumption, significantly increased absolute and relative liver weight and vaginal hemorrhage in three dams. Maternal kidney weight was unaffected. There were increases in fetal variations per litter (rudimentary cervical and/or accessory 14th ribs) reaching statistical significance at the top two doses. The Expert Panel for the Center for the Evaluation of Risks to Human Reproduction (NTP, 2003b) set the developmental NOAEL at 40 mg/kg/day and the maternal NOAEL at 200 mg/kg/day.
- Sprague-Dawley rats (25/dose) were given DIDP by gavage at 0, 100, 500, or 1000 mg/kg/day from GD 6-15 (Waterman *et al.*, 1999). Maternal toxicity was seen at 1000 mg/kg/day and included weight gain and decreased food consumption. Effects on fetal weight, mortality, mean numbers of corpora lutea, total implantation sites, post implantation loss and viable fetuses of treated animals were comparable with controls. A dose-related increase in percent fetuses with a supernumerary (7th) cervical rib and incidence of rudimentary lumbar (14th) ribs was observed and was statistically significant at 500 mg/kg/day (on a per fetus basis) and 1000 mg/kg/day (on a per litter and fetus basis). Waterman *et al.*, assigned a LOAEL for maternal and developmental toxicity at 1,000 mg/kg bw/day and a NOAEL of 500 mg/kg bw/day, whereas the CERHR (NTP, 2003b), using a different approach to the linearized data model, selected a developmental NOAEL of 100 mg/kg bw/day based on the significant incidence of cervical and accessory 14th ribs.
- Two multi-generational animal studies were completed by Exxon Biomedical Sciences and were published by (Hushka *et al.*, 2001). In the first study (study A) Crl:CD BR-VAF/Plus (Sprague Dawley) rats (30/sex/dose) were given 0, 0.2, 0.4, or 0.8% DIDP in their diet for ten weeks prior to and during mating. Females continued to receive DIDP throughout gestation and lactation. There was significantly decreased F1 pup survival at birth and on PND 4 in the 0.8% treatment group. In the F2 generation, there was a significant decrease in pup survival in all treatment groups on PND 1 and 4. This decrease in pup survival was also observed on PND 7 and at weaning in the high dose group. Postnatal body weight gain was reduced at the high dose in F1 and F2 pups. Liver weight (mean relative) was increased in F1 male pups at 0.8%, and F1 female pups at 0.4 and 0.8%. Hepatic hypertrophy and eosinophilia were seen in F1 and F2 pups at 0.4 and 0.8%. A developmental NOAEL was not established due to decreased pup survival at all doses in the F2 offspring generation. The 0.2% dose (131-152 mg/kg/day and 162-319 mg/kg/day in F0 and F1 dams during gestation and lactation respectively as calculated by Hushka *et al.*, (2001)) was identified as the developmental LOAEL.

- The second multi-generation Exxon Biomedical Sciences study (2000) was identical to the first except that rats received 0, 0.02, 0.06, or 0.2 or 0.4% DIDP. In the F1 pups, there were no effects on survival, body weight gain, organ weight, anogenital distance, nipple retention, preputial separation, or vaginal opening. In the F2 pups there was significantly decreased pup survival on PND 1 and 4 at 0.2 and 0.4% DIDP. In the F2 generation, significantly decreased pup body weight was observed at 0.2% and 0.4% on PND 14 (females) and PND 35 (males). There were no differences in anogenital distance or nipple retention of the F2 pups. The age of preputial separation was increased by 1.2 days in the F2 pups at 0.4% DIDP but the difference was not statistically significant. Overall NOAEL and LOAEL for offspring survival effects were 0.06% and 0.2% respectively (approximately 50 mg/kg/day and 165 mg/kg/day). A developmental NOAEL was set at 0.06% by the authors (38-44 mg/kg/day and 52-114 mg/kg/day during pregnancy and lactation, respectively).
- Cross-fostering and switched diet studies were completed to determine if postnatal developmental effects in pups were due to lactational transfer. Twenty CRl:CDBR VAF Plus rats per group were fed 0 or 0.8% DIDP for ten weeks prior to mating through gestation and lactation. For the cross-fostered study, pups from ten treated dams were switched with pups from ten control dams. After weaning, the diet of the pups continued as per dam exposure. For the diet switch portion of the study, pups from control dams were fed the DIDP diet after weaning, and pups from the treated dams were given the control diet after weaning. Results show that control pups switched to a 0.8% DIDP fed dam had significantly lower body weight on PND 14 and 21 due to lactational exposure. Pups exposed to DIDP *in utero* but nursed by a control dam did not show body weight changes. In the switched diet study, pups exposed to DIDP *in utero* and while nursing recovered body weight after receiving control diets after weaning (Hushka *et al.*, 2001).

5.3.3.1.2 Human

- No published human studies.

5.3.3.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans. However it should be noted that peroxisome proliferation has questionable relevance to hazard characterization in humans.

5.3.3.3 Weight of Evidence

5.3.3.3.1 Experimental Design

Some of the systemic studies and all of the reproductivestudies described were conducted according to GLP standards using relevant exposure routes. Although some of the studies had small dose groups (particularly the BASF 90-day dog study and the Hellwig developmental study), results were consistent and reproducible indicating a reasonable experimental design.

5.3.3.3.2 Replication

The liver was identified as a target organ based on results in rats and dogs that were qualitatively consistent. Furthermore, NOAELs were fairly consistent for all dietary rat studies (116–264 mg/kg bw/day). From these studies CPSC calculated an ADI of 0.15 mg/kg-day using the lowest NOAEL (15 mg/kg-day) for DIDP-induced liver effects (Hazleton, 1968b). CPSC also calculated an ADI of 0.13-0.17 mg/kg-day using the lowest dose (13.36-17.37 mg/kg-day that led to significant DIDP-induced kidney toxicity(Cho *et al.*, 2008). Similarly, the developmental studies by Waterman *et al.*, (1999)and Hellwig *et al.*, (1997) yielded similar effects (increases in lumbar and cervical ribs) at similar dose levels. Using these studies, the CPSC calculated an ADI of 0.4 mg/kg-day using the lowest developmental NOAEL of 40 mg/kg-day for DIDP-induced supernumerary ribs. Three well-conducted rat studies suggest that oral DIDP exposure is not associated with reproductive toxicity at the levels tested.

5.3.3.4 **Risk Assessment Considerations**

5.3.3.4.1 Exposure

DIDP is used in the PVC used to manufacture flooring, film, and coating products. Consumers may also be exposed via food, food packaging, clothing, and children's vinyl toys. Oxidative metabolites of DIDP found in urine samples indicate exposure to this compound is prevalent. CHAP calculations estimate that the median and 95^{th} percentile intake from NHANES biomonitoring data (pregnant women) for DIDP are 1.5 and 4.6 µg/kg-day, respectively, and that the median and 95^{th} percentile intake from SFF biomonitoring data are 1.9 and 14.2 (women) and 6.0 and 16.5 (infants) µg/kg-day, respectively. Based upon aggregate exposure estimates the following intakes are estimated:women median: 3.2, 95^{th} percentile: 12.2; infants median: 10; 95^{th} percentile 26.4 µg/kg/day.

5.3.3.4.2 Hazard

CPSC staff has previously concluded that DIDP may be considered a "probable toxicant" in humans by the oral route, based on sufficient evidence of systemic, reproductive and developmental effects in animals.

5.3.3.4.3 Risk

Based on the lowest POD (15 mg/kg/day) the Margins of Exposure range from 2,500 to 10,000 for median intakes and 586to 3,300 for 95^{th} percentile intakes

5.3.3.5 **Recommendation**

DIDP does not appear to possess anti-androgenic potential; nonetheless, the CHAP is aware that DIDP is a potential developmental toxicant, causing supernumerary ribs, and a potential systemic toxicant causing adverse effects on the liver and kidney. However, sinceDIDP is not considered in a cumulative risk with other anti-androgens, its Margin of Exposure in humans is considered likely to be relatively high. The CHAP does not find compelling data to justify maintaining the current interim ban on the use of DIDP in children's toys and child care articles. Therefore, the CHAP recommends that the current ban on DIDP be lifted, but that U.S. agencies responsible for dealing with DIDP exposures from food and child care products conduct the necessary risk assessments with a view to supporting risk management steps.

5.3.3.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DIDP?

No. DIDP use would be allowed in children's toys and child care articles.

5.4 Recommendations on Phthalates Not Banned

5.4.1 Dimethyl Phthalate (DMP) (131-11-3)

5.4.1.1 Adverse Effects

5.4.1.1.1 Animal

5.4.1.1.1.1 Reproductive

- No single or multiple generation guideline reproduction studies have been published. No reproductive effects were observed in developmental studies.

5.4.1.1.1.2 Developmental

- Although an early study (Singh *et al.*, 1972) reported dose-dependent increase in the incidence of skeletal defects after rats were dosed intraperitoneally on GD 5, 10, and 15 with DMP (0, 400, 800, 1340 mg/kg-d), other studies (Plasterer *et al.*, 1985; Hardin *et al.*, 1987; NTP, 1989; Field *et al.*, 1993) observed no developmental or reproductive abnormalities after rats and mice were dosed by gavage during GD 6-15 and 6-13, respectively. Likewise, no developmental effects were observed after rats were dosed by gavage from GD 14 to PND 3 (Gray *et al.*, 2000).

5.4.1.1.2 Human

- Only a few epidemiologic studies measured urinary concentrations of MMP. In those that did, there were no associations of maternal urinary MMP concentrations with measures of male reproductive tract development (specifically shortened AGD) (Swan *et al.*, 2005; Swan, 2008; Huang *et al.*, 2009; Suzuki *et al.*, 2012). No human studies reported associations of MMP with neurodevelopment. Three publications (Engel *et al.*, 2009; Engel *et al.*, 2010; Miodovnik *et al.*, 2011) measured MMP but reported associations of neurodevelopmental tests with a summary measure of low molecular weight phthalates (included MEP, MMP, MBP, and MIBP).

5.4.1.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.1.3 Weight of Evidence

5.4.1.3.1 Experimental Design

No published reproductive toxicity studies exist. One full developmental study in Sprague Dawley rats (Field, 1993) and one study in CD-1 mice (Plasterer *et al.*, 1985)*et al.*, had sufficient numbers of animals (29-30 on full study, n=8 on range finder, n=43-50, respectively) and experimental design to support overall conclusions. The other identified studies have lower confidence since the dosing route in one study was not relevant to anticipated human exposures (Singh *et al.*, 1972; intraperitoneal), and the number of dosed litters was low (Gray *et al.*, 2000; 4 litters treated [21 male pups]).

5.4.1.3.2 Replication

No published full reproduction studies exist. “The available [developmental] data, particularly the studies of (Field *et al.*, 1993) (GD 6-15 exposure) and (Gray *et al.*, 2000) (GD 14-PND 3 exposure), support the conclusion that DMP is not a developmental toxicant.” The CHAP concludes that the male reproductive effect has a NOAEL = 750 mg/kg-d (Appendix A, Table 7).

5.4.1.4 Risk Assessment Considerations

5.4.1.4.1 Exposure

Although the frequency and duration of exposures and the quantification of exposures from children’s toys and personal care products have not been determined, DMP metabolites (MMP) have been detected in human urine samples in the U.S. (NHANES 2001-2002, 2003-2004; CDC, 2012b) and in 75% of the men attending an infertility clinic in Boston (Hauser *et al.*, 2007). Adjusted concentrations of urinary MMP were higher in children 6-11 when compared to juveniles 12-19, or adults 20+ years old. In addition, women participants had higher urinary concentrations than men (NHANES 2005-2006; CDC, 2012b). CHAP calculations estimate that the median/high (95^{th} percentile) intake from NHANES biomonitoring data for DMP is 0.05/0.55 µg/kg-day, respectively in pregnant women.

5.4.1.4.2 Hazard

An incomplete dataset suggests that exposure to DMP does not induce reproductive or developmental effects in animals. DMP may induce other effects, however, such as changes in body weight, liver weight, and blood composition.

5.4.1.4.3 Risk

Risks to humans are currently indeterminate due to the lack of relevant data.

5.4.1.5 Recommendation to CPSC regarding children’s toys and child care articles

The CHAP recommends no action at this time.

5.4.1.6 **Would this recommendation, if implemented, be expected to reduce exposure of children to DMP?**

No. However, the CHAP concludes that MMP is not a reproductive or development toxicant in animals or humans.

5.4.2 **Diethyl Phthalate (DEP) (84-66-2)**

5.4.2.1 **Adverse Effects**

5.4.2.1.1 Animal

5.4.2.1.1.1 Reproductive

- High-dose F1 mouse sexually-mature males had significantly decreased sperm concentration and increased absolute and relative prostate weights after exposure to DEP in a continuous breeding study (Lamb *et al.*, 1987).
- Fujii *et al.*, (2005) conducted a two-generation reproductive toxicity study in Sprague-Dawley rats in which DEP was administered 10 weeks prior to mating and continued through mating, gestation, and lactation. A substantial dose-related increase in the number of tailless sperm was reported in the F1 generation. In F1 parental females, the high dose group had shortened gestation lengths. Increased age at pinna detachment and decreased age at incisor eruption was seen in high dose F0 males, and an increase in the age of vaginal opening was noted in F1 female pups. A dose-related decrease in absolute and relative uterus weight was reported for F2 weanlings.
- Oishi and Hiraga (1980) conducted a short-term study in Wistar rats in which DEP (0 and 1000 mg/kg-d) was administered in the diet for 7 days. Dietary exposure to DEP significantly decreased serum testosterone, serum dihydrotestosterone, and testicular testosterone.

5.4.2.1.1.2 Developmental

- As with DMP, studies by Singh (1972) and Field *et al.*, (1993) reported an increased incidence of skeletal defects (rudimentary ribs) in rats after exposure to DEP by gavage or through the diet during early gestation (GD 5-15). Exposure to DEP by gavage during late gestation and early post natal periods did not significantly affect any developmental parameters in male pups (Gray *et al.*, 2000).

5.4.2.1.2 Human

- Several epidemiologic studies measured urinary concentrations of MEP. Of those that did, some reported associations of maternal urinary MEP concentrations with measures of male reproductive tract development (specifically shortened AGD) (Swan *et al.*, 2005; Swan, 2008), whereas other studies did not find associations with AGD (Huang *et al.*, 2009; Suzuki *et al.*, 2012). Several studies reported associations of poorer scores on neurodevelopment tests with MEP (Miodovnik *et al.*, 2011) or with a summary measure of low molecular weight phthalates that was largely explained by MEP concentrations (Engel *et al.*, 2010).

5.4.2.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.2.3 Weight of Evidence

5.4.2.3.1 Experimental Design

Two reproduction studies of sufficient design (Lamb *et al.*, 1987; Fujii *et al.*, 2005) are available to support conclusions. In Oishi and Hiraga (1980), decreases in testosterone are reported after dosing with phthalates that inhibit testosterone production. Increases in testicular testosterone, however, are reported following exposure to DBP, DIBP, and DEHP, phthalates that have been reported to decrease testicular testosterone in other studies. This finding decreases confidence in conclusions regarding DEP-induced testosterone inhibition.

One full developmental study in Sprague Dawley rats (Field *et al.*, 1993) has sufficient numbers of animals (n=31-32) and experimental design to support overall conclusions. The other identified studies have lower confidence since the dosing route in one study was not relevant to anticipated human exposures and had low n (Singh *et al.*, 1972; intraperitoneal; 5 rats per dose group), and the number of dosed litters was low (Gray *et al.*, 2000; 3 litters treated).

Epidemiological studies have drawn conclusion from small populations of exposed humans.

5.4.2.3.2 Replication

Reproductive toxicity results are sufficiently replicated in more than one study. Only one standard developmental study is available and replicate epidemiology studies are not available. The available [developmental] data, particularly the studies of Field *et al.*, (1993) (GD 6-15 exposure) and (Gray *et al.*, 2000) (GD 14-PND 3 exposure), support the conclusion that DEP is not a developmental toxicant for reproductive systems. Data from two studies, however, suggest that DEP may increase the incidence of extra rudimentary ribs.

5.4.2.4 Risk Assessment Considerations

5.4.2.4.1 Exposure

Some exposure results from contact with personal care products in infants and toddlers, mostly cosmetics in older children. DEP metabolites (MEP) have been detected in human urine samples in the U.S. general population (NHANES 1999-2000, 2001-2002, 2003-2004), New York city pregnant women (Adibi *et al.*, 2003), women in Washington, D.C, (Hoppin *et al.*, 2004), German residents (Koch *et al.*, 2003a), Swedish military recruits (Duty *et al.*, 2004), and infertility clinic patients in Boston (men; Hauser *et al.*, 2007). A small study suggested that MEP levels in children <2 years old were about twice as high as that in children 6-11 years old (Brock *et al.*, 2002). Further, MEP concentrations in the urine increased with age, were dependent on sex and race ethnicity, and were less in juveniles 6-11 years old when compared to other age classes (CDC, 2012a). CHAP calculations estimate that the median/high (95^{th} percentile) intake from NHANES biomonitoring data for DEP is 3.4/75 µg/kg-day, respectively in pregnant women.

5.4.2.4.2 Hazard

A relatively complete dataset suggests that exposure to DEP can induce reproductive or (non-reproductive) developmental effects in humans. DEP can also induce other target organ effects, such as changes in body weight and liver weight. Changes in AGD and AGI and sperm parameters have been correlated to MEP concentration in humans. For the most part, these have not been confirmed in animal studies.

5.4.2.4.3 Risk

There are indications from epidemiological studies that DEP exposures are associated with reproductive and developmental outcomes. These observations take precedent over findings in animal experiments where comparable effects could not be recapitulated and suggest that harmful effects in humans have occurred at current exposure levels. There is therefore an urgent need to implement measures that lead to reductions in exposures, particularly for pregnant women and women of childbearing age.

5.4.2.5 Recommendation to CPSC regarding children's toys and child care articles

Since DEP exposures from articles under the jurisdiction of CPSC are currently negligible, CHAP recommends no further action.

CHAP recommends that U.S. agencies responsible for dealing with DEP exposures from food, pharmaceuticals, and personal care products conduct the necessary risk assessments with a view to supporting risk management steps.

5.4.2.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DEP?

There would be no reduction in exposure for the articles under CPSC jurisdiction. However, exposures from personal care products, diet, some pharmaceuticals, food supplements, etc., can be substantial. There is a case for other competent authorities in the U.S. to conduct thorough risk assessments for DEP, especially for women of reproductive age.

5.4.3 Diisobutyl Phthalate (DIBP) (84-69-5)

5.4.3.1 Adverse Effects

5.4.3.1.1 Animal

5.4.3.1.1.1 Reproductive

- One short-term toxicity study showed that DIBP exposure caused a significant decrease in testis weight, an increase in apoptotic spermatogenic cells, and disorganization or reduced vimentin filaments in Sertoli cells (Zhu *et al.*, 2010), and a subchronic toxicity study showed that DIBP exposure via the diet caused reduced absolute and relative testis weights (Hodge, 1954).

5.4.3.1.1.2 Developmental

- Six studies in which rats were exposed to DIBP by gavage during late gestation showed that this phthalate reduced AGD in male pups, decreased testicular testosterone production, increased nipple retention, increased the incidence of male fetuses with undescended testes, increased the incidence of hypospadias, reduced the expression of P450scc, insl-3, genes related to steroidogenesis, and StAR protein (Saillenfait *et al.*, 2006; Borch *et al.*, 2006a; Boberg *et al.*, 2008; Howdeshell *et al.*, 2008; Saillenfait *et al.*, 2008; Hannas *et al.*, 2011b).

5.4.3.1.2 Human

Several epidemiologic studies measured urinary concentrations of MIBP. Of those that did, there were associations of maternal urinary MIBP concentrations with measures of male reproductive tract development (specifically shortened AGD) (Swan *et al.*, 2005; Swan, 2008). Several studies reported associations of MBP with poorer scores on neurodevelopment tests (Engel *et al.*, 2010; Swan *et al.*, 2010; Kim *et al.*, 2011; Miodovnik *et al.*, 2011; Whyatt *et al.*, 2011) whereas others did not (Engel *et al.*, 2009).

5.4.3.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.3.3 Weight of Evidence

5.4.3.3.1 Experimental Design

The Boberg *et al.*,, 2008 study results could not be used to determine a NOAEL because only one dose was used. The Howdeshell *et al.*, (2008)study, which used multiple doses but small numbers of animals per dose group, was designed, as the authors point out " to determine the slope and ED_{50} values of the individual phthalates and a mixture of phthalates and not to detect NOAELs or low observable adverse effect levels." The same is true for the Hannas *et al.*, (2011b) study, which also used multiple doses but small numbers of animals per dose group. The two Saillenfait studies (Saillenfait *et al.*, 2006; 2008) both included multiple doses, exposure during the appropriate stage of gestation and employed relatively large numbers of animals per dose. Using the more conservative of the two NOAELs from the 2008 Saillenfait study, the CHAP committee assigns a NOAEL of 125 mg/kg-day for DIBP.

5.4.3.3.2 Replication

No published full reproductive toxicity studies exist. At least 4 developmental toxicity studies (3 from different labs) confirmed that DIBP has anti-androgenic properties.

5.4.3.4 Risk Assessment Considerations

5.4.3.4.1 Exposure

While DIBP has not been detected frequently in toys and child care articles in the U.S. (Chen, 2002; Dreyfus, 2010), DIBP has been detected in some toys during routine compliance testing. No quantifiable exposures to infants, toddlers or children from toys or children's personal care products were located. DIBP has many of the same properties as DBP, so can be used as a substitute. In general, DIBP is too volatile to be used in PVC, but is a component in nail polish, cosmetics, lubricants, printing inks, and many other products. DIBP metabolites (MIBP) have been detected in human urine samples in the U.S. general population (NHANES 2001-2002, 2003-2004, 2005-2006, 2007-2008; CDC, 2012b), and in Germany (Wittassek *et al.*, 2007a). Urinary MIBP levels have increased over the past 4 surveys in all age groups, genders, and races, and in total. Total levels (geometric means) during the last sample duration (2007-2008; 7.16 µg/L) are two- to three-fold higher than the earliest monitoring year (2001-2002; 2.71 µg/L) at all percentiles. CHAP calculations estimate that the median/high (95th percentile) intake from NHANES biomonitoring data for DIBP is 0.17/1.0 µg/kg-day, respectively in pregnant women.

5.4.3.4.2 Hazard

Animal and human studies suggest that exposure to DIBP can cause reproductive and developmental effects.

5.4.3.4.3 Risk

The margins of exposure (95th percentile total DIBP exposure) for pregnant women in the NHANES study range from 5,000 to 125,000. For infants in the SFF study, the MoE (95th percentile total DIBP exposure) ranged from 3,600 to 89,000. The values are larger using the median exposure estimates. Typically, MoEs exceeding 100-1000 are considered adequate for public health; however, the cumulative risk of DBP with other anti-androgens should also be considered.

5.4.3.5 Recommendation

Current exposures to DIBP alone do not indicate a high level of concern. DIBP is not widely used in toys and child care articles. However, CPSC has recently detected DIBP in some children's toys. Furthermore, the toxicological profile of DIBP is very similar to that of DBP and DIBP exposure contributes to the cumulative risk from other antiandrogenic phthalates. The CHAP recommends that DIBP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 percent.

5.4.3.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DIBP?

There would be little reduction in exposure. However, the recommendation, if implemented, would prevent future exposure from this chemical in such products.

5.4.4 Di-*n*-pentyl Phthalate (DPENP) (131-18-0)

5.4.4.1 Adverse Effects

5.4.4.1.1 Animal

5.4.4.1.1.1 Reproductive

- The CHAP has not written a summary on reproductive toxicity studies using DPENP.
- Heindel *et al.*, (1989) conducted a continuous breeding toxicity test in CD-1 mice in which DPENP (0.5, 1.25, 2.5%) was administered in the diet 7 days pre- and 98 days post-habitation. DPENP exposure reduced fertility in a dose-related fashion (LOAEL = 0.5%), decreased testis and epididymal weights, decreased epididymal sperm concentration, and increased the incidence of seminiferous tubule atrophy.

5.4.4.1.1.2 Developmental

- Howdeshell *et al.*, (2008) and Hannas *et al.*, (2011a) conducted developmental toxicity studies in pregnant Sprague-Dawley rats in which was administered via gavage on GD. DPENP exposure reduced fetal testicular testosterone production, StAR, Cyp11a, and ins13 gene expression, and increased nipple retention.

5.4.4.1.2 Human

No published human studies.

5.4.4.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.4.3 Weight of Evidence

5.4.4.3.1 Experimental Design

No published multigeneration reproductive toxicity studies exist. There are only two studies available describing the effects of DPENP on reproductive development in rats after *in utero* exposure during late gestation. Although these studies were not designed to determine NOAELs, the data presented on the effects of DPENP on fetal testosterone production and gene expression of target genes involved in male reproductive development revealed that reduction in testosterone production was the most sensitive endpoint, with a LOAEL of 33 mg/kg-day (Hannas *et al.*, 2011a). Thus, on the basis of this study, the CHAP committee assigns the NOAEL for DPENP at 11 mg/kg-day.

5.4.4.3.2 Replication

No published multigeneration reproductive toxicity studies exist. Developmental studies reported similar toxicologic endpoints using similar dosing strategies. Because many of the same authors are present on both developmental studies, verification of these results from an independent laboratory would be beneficial.

5.4.4.4 Risk Assessment Considerations

5.4.4.4.1 Exposure

DPENP is currently not found in children's toys and child care articles, and it is not widely found in the environment. DPENP is primarily used as a plasticizer in nitrocellulose. The metabolite MHPP has been proposed as an appropriate biomarker for DPENP exposure and has been detected in human urine (Silva *et al.*, 2010).

5.4.4.4.2 Hazard

DPENP is clearly among the most potent phthalates regarding developmental effects.

5.4.4.4.3 Risk

DPENP is the most potent phthalate with respect to developmental toxicity. However, it is currently not found in children's toys and child care articles, and it is not widely found in the environment. Due to low exposure, current risk levels are believed to be low.

5.4.4.5 Recommendation

The CHAP recommends that DPENP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 percent. The toxicological profile of DPENP is very similar to that of the other antiandrogenic phthalates and DPENP exposure contributes to the cumulative risk.

5.4.4.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DPENP?

No. However, the recommendation, if implemented, would prevent future exposure from this chemical in such products.

5.4.5 Di-*n*-hexyl Phthalate (DHEXP) (84-75-3)

5.4.5.1 Adverse Effects

5.4.5.1.1 Animal

5.4.5.1.1.1 Reproductive

- A comparative study by Foster *et al.*, (1980) indicated that di-n-hexyl phthalate (DHEXP) caused the second most severe testicular atro(NTP, 1997)phy in rats, after diamyl phthalate. Following exposure to 2400 mg/kg bw/day, relative testis weights were significantly lower than those of control rats, with atrophy of the seminiferous tubule and few spermatogonia and Sertoli cells. Leydig cell morphology was normal. An accompanying increase in urinary zinc was noted, likely the result of a concomitant depression in gonadal zinc metabolism (Foster *et al.*, 1980).
- The NTP-CERHR reviewed a study of DHEXP (NTP, 2003d) in which reproductive toxicity was assessed using the Fertility Assessment by Continuous Breeding protocol in Swiss CD-1 mice (NTP, 1997). The reproductive NOAEL of the one-generation study was determined to be less than the lowest dose of ~380 mg/kg/day based on significant decreases in the mean number of litters per pair, the number of live pups/litter, and the proportion of pups born alive, all of which occurred in the absence of an effect on postpartum dam body weights. Results of a follow up crossover mating experiment using control and high-dose (~1670 mg/kg/day) mice indicated that the toxicity of DHEXP to fertility was strongly but not exclusively a result of paternal exposure; both sexes were effectively infertile at this level of DHEXP exposure. Necropsy of these mice revealed lower uterine weights, but no treatment-related microscopic lesions in the ovaries, uterus, or vagina. Males had lower absolute testis weights, and lower adjusted epididymis and seminal vesicle weights, as well as reduced epididymal sperm concentration and motility. The percentage of abnormal sperm was equivalent to that of controls (NTP, 1997).
- The NTP-CERHR panel concluded that data are sufficient to indicate that DHEXP is a reproductive toxicant in both sexes of two rodent species following oral exposure.

5.4.5.1.1.2 Developmental

- The NTP-CERHR (NTP, 2003d) reported on DHEXP and indicated that no human developmental toxicity data were located by the panel. They described that only one animal developmental screening test was available. In this study, mice were administered DHEXP (0, 9900 mg/kg-d) via gavage from GD 6 through 13. Pregnant dams that were treated did not give birth to any live litters. The panel concluded that “the database is insufficient to fully characterize the potential hazard. However, the limited oral developmental toxicity data available (screening level assessment in mouse) are sufficient to indicate that DHEXP is a developmental toxicant at high doses (9900 mg/kg-d). These data were inadequate for determining a NOAEL or LOAEL because only one dose was tested.” Since the NTP-CERHR report, one developmental toxicity study has reported that DHEXP exposure reduced the AGD in male pups in a dose-related fashion and increased then incidence of male fetuses with undescended testes (Saillenfait *et al.*, 2009).

5.4.5.1.2 Human

- No published human studies.

5.4.5.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.5.3 Weight of Evidence

5.4.5.3.1 Experimental Design

The NTP (NTP, 1997) continuous breeding fertility study used an established protocol with high sample sizes (20 mice/sex/dose) and a concurrent 40 pairs of controls. A NOAEL was not established because effects on fertility were observed at the lowest dose. Furthermore, the mid- and low-dose groups were not evaluated at necropsy. Therefore, the NTP-CERHR Panel concluded that their confidence in the LOAEL was only moderate-to-low, although the study itself was of high quality. Based on this study, a single dose study of male reproductive toxicity in rats, and *in vitro* evidence in rats, the panel concluded that data were sufficient to determine that DHEXP acts as a reproductive toxicant in males and females of two rodent species.

When considering developmental studies, the one by Saillenfait *et al.*, (2009) is fairly robust (i.e., multiple doses, number of animals per dose group (20-25), and appropriate exposure time), but a NOAEL for AGD could not be determined because the lowest dose tested was the LOAEL. The other study cited by the NTP-CERHR had only one dose and a dosing strategy (GD 6-13) that may have missed the sensitive window for antiandrogenic impairment in mice. These reasons made it less useful than the Saillenfait study for determining the developmental effects of DHEXP.

5.4.5.3.2 Replication

Verification of multi-generation reproduction and developmental studies is needed.

5.4.5.4 Risk Assessment Considerations

5.4.5.4.1 Exposure

DHEXP is currently not found in children’s toys and child care products, and it is not widely found in the environment. DHEXP is primarily used in the manufacture PVC and screen printing inks. It is also used as a partial replacement for DEHP.

5.4.5.4.2 Hazard

An incomplete dataset suggests that exposure to DHEXP can induce adverse effects in reproductive organs and is a developmental toxicant.

5.4.5.4.3 Risk

DHEXP is believed to induce developmental effects similar to other active phthalates. Due to low exposure, current risk levels are believed to be low.

5.4.5.5 Recommendation

The CHAP recommends that DHEXP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 percent. The toxicological profile of DHEXP is very similar to that of the other antiandrogenic phthalates and DHEXP exposure contributes to the cumulative risk.

5.4.5.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DHEXP?

No. However, the recommendation, if implemented, would prevent future exposure from this chemical in such products.

5.4.6 Dicyclohexyl Phthalate (DCHP) (84-61-7)

5.4.6.1 Adverse Effects

5.4.6.1.1 Animal

5.4.6.1.1.1 Reproductive

- In one reproductive toxicity study, DCHP exposure increased the atrophy of the seminiferous tubules, decreased the spermatid head count in F1 males and increased the estrus cycle length in F0 females (Hoshino *et al.*, 2005).

5.4.6.1.1.2 Developmental

- Two studies in rats exposed to DCHP by gavage during late gestation showed that this phthalate prolonged preputial separation, reduced AGD, increased nipple retention, and increased hypospadias in male offspring (Saillenfait *et al.*, 2009; Yamasaki *et al.*, 2009). In one study in rats exposed to DCHP in the diet showed that DCHP decreased the AGD and increased nipple retention in F1 males (Hoshino *et al.*, 2005).

5.4.6.1.2 Human

- No published human studies.

5.4.6.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.6.3 Weight of Evidence

5.4.6.3.1 Experimental Design

Only one multigeneration reproduction study was determined. Two of the three studies (Hoshino *et al.*, 2005; Yamasaki *et al.*, 2009) available report DCHP-induced effects on male reproductive development (decreased anogenital distance and nipple retention in males) and the third study (Saillenfait *et al.*, 2009) reported only the former. The

Saillenfait study could not be used to determine a NOAEL because the lowest dose used in their study was a LOAEL. Of the two remaining studies, the two-generation study by Hoshino *et al.*,, (2005) reported adverse effects on male reproductive development at a calculated dose of 80-107 mg/kg-d; NOAEL of 16-21 mg/kg-d, whereas the Yamasaki *et al.*, (Yamasaki *et al.*, 2009) prenatal study reported adverse effects on male reproductive development at dose of 500 mg/kg-d; NOAEL of 100 mg/kg-d. Using the more conservative of the two NOAELs, the CHAP committee assigned a NOAEL of 16 mg/kg-d for DCHP.

5.4.6.3.2 Replication

Only one multigeneration reproduction study was found, and therefore, conclusions as to the reproductive toxicity of DCHP need to be verified. Similar adverse developmental effects (i.e., decreased male pup AGD) were reported in three independent studies.

5.4.6.4 **Risk Assessment Considerations**

5.4.6.4.1 Exposure

DCHP is currently not found in children's toys and child care articles, and it is not widely found in the environment. DCHP is FDA-approved for use in the manufacture of various articles that are associated with food handling and contact. Studies have reported migration of DCHP from the product (food wrap, printing ink, etc.) into food substances. DCHP is also the principal component in hot melt adhesives (>60%). MCHP, the metabolite of DCHP, has been found infrequently in the urine of U.S. residents (NHANES 1999-2000, 2001-2002, and 2003-2004; CDC, 2012b).

5.4.6.4.2 Hazard

An incomplete reproductive toxicity dataset suggests that exposure to DCHP can induce adverse effects in reproductive organs and is a developmental toxicant.

5.4.6.4.3 Risk

DCHP induces developmental effects similar to other active phthalates. Due to low exposure, current risk levels are believed to be low.

5.4.6.5 **Recommendation**

The CHAP recommends that DCHP should be permanently banned from use in children's toys and child care articles at levels greater than 0.1 percent. The toxicological profile of DCHP is very similar to that of the other antiandrogenic phthalates and DCHP exposure contributes to the cumulative risk.

5.4.6.6 **Would this recommendation, if implemented, be expected to reduce exposure of children to DCHP?**

No. However, the recommendation, if implemented, would prevent future exposure from this chemical in such products.

5.4.7 Diisooctyl Phthalate (DIOP) (27554-26-3)

5.4.7.1 Adverse Effects

5.4.7.1.1 Animal

5.4.7.1.1.1 Reproductive

- No published single or multigeneration reproduction studies.

5.4.7.1.1.2 Developmental

Grasso (1981) conducted a study in which DIOP (0, 4930, 9860 mg/kg-d) was injected intraperitoneally into female rats on GD 5, 10, and 15. Both treated groups had a higher incidence of soft tissue abnormalities (quantitative information for this study is not available).

5.4.7.1.2 Human

- No epidemiologic studies measured metabolites of DIOP in relation to male reproductive health or neurodevelopment endpoints.

5.4.7.2 Relevance to Humans:

The reported animal studies are assumed to be relevant to humans.

5.4.7.3 Weight of Evidence

5.4.7.3.1 Experimental Design

The one relevant study dosed animals via a route of exposure (i.p.) that is not relevant to exposures from consumer products under the U.S. CPSC's jurisdiction. Further, quantitative information was not available for the summarized results and it is unclear if tissue abnormalities were reproductive in nature.

5.4.7.3.2 Replication

No published full reproduction or full developmental studies exist.

5.4.7.4 Risk Assessment Considerations

5.4.7.4.1 Exposure

Undetermined frequency and duration of exposures. DIOP it is primarily used in the manufacture of wire insulation. It is also approved for various food-associated products by the FDA and has been found in teethers and pacifiers (check reference). The primary metabolite of DIOP (MIOP) may have co-eluted with MEHP in many samples (including controls) in a small human study by Anderson *et al.*, (2001).

5.4.7.4.2 Hazard

Unknown; minimal data do not demonstrate anti-androgenic hazard. However, the isomeric structure of DIOP suggests that DIOP is within the range of the structure-activity characteristics associated with antiandrogenic activity.

5.4.7.4.3 Risk

Currently, there is a lack of exposure data for DIOP. Human exposure to DIOP appears to be negligible. Toxicity data are limited, but structure-activity relationships suggest that antiandrogenic effects are possible.

5.4.7.5 Recommendation

The CHAP recommends that DIOP be subject to an interim ban from use in children's toys and child care articles at levels greater than 0.1 percent until sufficient toxicity and exposure data are available to assess the potential risks.

5.4.7.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DIOP?

Yes. The recommendation, if implemented, would prevent exposure from DIOP in such products.

5.4.8 Di(2-propylheptyl) Phthalate (DPHP) CAS 53306-54-0

5.4.8.1 Adverse Effects

5.4.8.1.1 Animal

5.4.8.1.1.1 Reproductive

- One industry conducted subchronic study in rats showed that DPHP exposure in the diet was associated with up to a 25% reduction in sperm velocity indices (Union Carbide Corporation, 1997).

5.4.8.1.1.2 Developmental

- One industry conducted developmental toxicity study in rats showed that DPHP exposure by gavage was associated with increased incidence of soft tissue variations (dilated renal pelvis) at the maternally toxic high dose (BASF, 2003). In a screening developmental toxicity study, exposure by gavage was not associated with any maternal or fetal effects (Fabjan *et al.*, 2006).

5.4.8.1.2 Human

- No published human studies.

5.4.8.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.4.8.3 Weight of Evidence

5.4.8.3.1 Experimental Design

No published full reproduction studies exist. Results in the BASF developmental study were “preliminary”, even though the number of animals used per dose (n=25) was satisfactory.

5.4.8.3.2 Replication

No published full reproduction or full developmental studies exist.

5.4.8.4 Risk Assessment Considerations

5.4.8.4.1 Exposure

The CHAP is not aware of any uses of DPHP in children’s toys or child care articles. DPHP was not detected in toys and child care articles tested by CPSC (Dreyfus, 2010). Currently, there is an undetermined frequency and duration of exposures; however, analytical methods cannot differentiate DPHP metabolites from DIDP metabolites since they are closely related. DPHP has substantially replaced other linear phthalates as a plasticizer in certain PVC applications. DPHP has increased its proportion in the phthalate production marketplace dramatically between 2005 to 2008 (CEH, 2009). DPHP is approved for use in food packaging and handling. Many uses are at high concentration (30 to 60 percent).

5.4.8.4.2 Hazard

Unknown; minimal data do not demonstrate anti-androgenic hazard.

5.4.8.4.3 Risk

Currently, DPHP metabolites cannot be distinguished from the metabolites of DIDP. Production levels of DPHP have increased in recent years, suggesting that human exposure may also be increasing.

5.4.8.5 Recommendation

Given the general lack of publically available information on DPHP, the CHAP is unable to recommend any action regarding the potential use of DPHP in children’s toys or child care articles at this time. However, the CHAP encourages the appropriate agencies to obtain the necessary toxicological and exposure data to assess any potential risk from DPHP.

5.4.8.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DIDP?

No. DIDP use would be allowed in children’s toys and child care articles.

5.5 Recommendations on Phthalate Substitutes

5.5.1 2,2,4-Trimethyl-1,3 pentanediol diisobutyrate (TPIB) (6846-50-0)

5.5.1.1 Adverse Effects

5.5.1.1.1 Animal

5.5.1.1.1.1 Systemic

- Astill *et al.*, (1972) reported on a 13-week repeat-dose study of TPIB performed by Eastman Kodak Company. Four beagle dogs/sex/group received dietary doses approximately equivalent to 22, 77, and 221 mg/kg bw/day for males and 26, 92, and 264 mg/kg/day for females six days per week for 13 weeks. Based on extensive gross, microscopic, and histopathological analyses, there was no mortality or evidence of neurological stimulation, depression, or reflex abnormality, and no effects on growth or food consumption at any dose. No changes were observed in the hematology, clinical chemistry, histopathology, or urine analyses. Relative organ weights were similar to control animals, except for the liver and pituitary gland in the two higher dose groups, which were increased slightly compared to controls. However, elevated pituitary gland weights were still within the normal range, and the absence of microscopic pathological findings in pituitary and liver indicates that the observed weight change was not adverse. The NOEL for this studied was 22–26 mg/kg/day, and the NOAEL was 221 and 264 mg/kg/day, the highest doses for male and female dogs, respectively.
- Astill *et al.*, (1972) also reported on a feeding study in rats. Ten albino Holtzman rats/sex/dose, received TPIB for 103 days in the diet at doses approximately equivalent to 75.5 and 772 mg/kg/day for males and 83.5 and 858.5 mg/kg/day for females. Appropriate vehicle control groups were also run. Treated and control rats were statistically similar with respect to feed consumption, weight gain, and growth, and no histological differences were observed in the liver, esophagus, small and large intestine, trachea, lung, thyroid, parathyroid, spleen, brain, heart, kidney, bladder, adrenal, gonad, and bone. Relative liver weights in both sexes[*] and absolute liver weights in male rats were slightly significantly higher in high-dose rats compared with controls; however, all weights were within the normal range of values. Study authors derived a NOAEL of 772–858.5 mg/kg bw/day, the highest dose.
- Krasavage *et al.*, (1972) fed Sprague-Dawley rats (10/sex/group) diets containing 0, 147.5, or 1475 mg/kg/day TPIB continuously for 52 days (experiment I), 99 days (experiment II), or for 52 day followed by the control diet for 47 days, or they received control diet for 52 days followed by TPIB diet for 47 days (experiment III). There was no significant treatment-related effect on mean body weight gain, group feed consumption, hematological parameters, alkaline phosphatase activity, tissue histology, or absolute organ weight in any group compared to controls. Serum glutamic oxaloacetic transaminase levels were elevated in all high-dose animals

[*] Astill *et al.*, reported that relative liver weights in females were significantly higher in the high-dose group. In Eastman Chemical's 2007 summary of this study, they note that the laboratory report did not report this result as significant and that the published manuscript contained this finding in error.

relative to controls, except for females in experiment I. However, elevated levels were still within normal ranges. The relative liver weights of high dose rats were significantly greater than controls in all three experiments, except for experiment III rats fed TPIB first and control diet second. Differences in other relative organ weights were not determined to be treatment-related. Likewise, the only consistent finding with respect to microsomal enzymes was an increase in activity at the high-dose level, but only when the animal was consuming TPIB at the time of sacrifice (i.e., not in the experiment III rats that ate a control diet in the second part of the experiment). Temporary liver weight increase and microsomal enzyme activity induction are responses frequently associated with stress. In the absence of hepatic damage, study authors interpreted them as physiological adaptations.

- Krasavage *et al.*, (1972) also injected (ip) groups of six male rats seven times per day with 25 or 100 mg/kg bw TPIB or 2,2,4-trimethyl-1,3-pentanediol (TMPD), the parent glycol and a metabolite of TPIB in rats. At the higher dose, TPIB and TMPD significantly increased P-NDase levels; BG-Tase levels were unaffected. A lower level of enzyme induction by TMPD suggests that TPIB is the active inducer, and not its metabolic product.
- Eastman Chemical (2007a) carried out the combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422) using Sprague-Dawley rats (also summarized in JMHLW, 1993; OECD, 1995). Rats (12/sex/dose) were administered gavage doses of 0, 30, 150 or 750 mg/kg/day TPIB (purity: 99.7%) starting 14 days before mating. Males continued receiving the test substance for 30 days thereafter, and females, through day three of lactation. At the high-dose level, depressed body weight gain (males) and increased food consumption (females) were observed. Rats receiving 150 or 750 mg/kg/day had higher levels of creatinine and total bilirubin, and high-dose males had higher total protein content in the blood, suggesting liver and kidney effects. Indeed, relative liver weights were higher for male rats receiving the two higher doses of TPIB, with discoloration and hepatocellular swelling and decreased fatty change at the highest dose. Absolute and relative kidney weights were elevated in high-dose males and basophilic changes in the renal tubular epithelium and degeneration of hyaline droplet were observed in male rats receiving 150 mg/kg/day or more.

  Additionally, necrosis and fibrosis of the proximal tubule and dilatation of the distal tubule were observed in male rats receiving 750 mg/kg/day. At the lowest dose only, there was a decrease in absolute but not relative thymus weight, which was not considered treatment-related. Eastman Chemical (2007a) determined a NOEL for systemic toxicity of 30 mg/kg/day for males and 150 mg/kg/day for females. The NOAEL was determined to be 150 mg/kg/day based on the assertion that effects seen at this dose were adaptive in nature.

5.5.1.1.1.2 Reproductive

- Eastman Chemical (2007a) conducted a combined reproductive/developmental screening toxicity test in Sprague Dawley rats in which TPIB (0, 30, 150, and 750 mg/kg/day) was administered via gavage for 14 days prior to mating through 30 days post-mating (males) or LD 3 (females). No TPIB-related reproductive effects were observed ($NOAEL_{repro/devel}$ = 750 mg/kg/day). This study is unpublished.

- Eastman Chemical (2001) conducted a combined reproductive/developmental screening toxicity test (OECD GL 421) in Sprague Dawley rats in which TPIB (0, 91, 276, 905 mg/kg/day in males; 0, 120, 359, and 1135 mg/kg/day in females) was administered in the diet for 14 days pre-mating, during mating, through gestation, and through PND 4-5. Changes in epididymal and testicular sperm counts were reported by the authors, but considered not to be adverse. No other TPIB-related male reproductive effects were observed ($NOAEL_{male\ repro/devel}$ = 905 mg/kg/day). This study is unpublished.

5.5.1.1.1.3 Developmental

- See the above Eastman Chemical studies (2001; 2007a) for developmental toxicity screening results.

5.5.1.1.2 Human

- No published human studies.

5.5.1.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.5.1.3 Weight of Evidence

5.5.1.3.1 Experimental Design

The 1972 animal studies by Astill and Krasavage had low sample sizes (4 dogs per dose, 10 rats per dose) and the rat studies used only two dose levels. Adverse, treatment-related effects were not clearly established at any dose level in these studies, with the exception of one of the Krasavage groups. Studies were published in respected journals subject to peer review.

Neither repro-developmental study was published, but they appear to have met OECD GL 421 requirements. As reported in the GL “This test does not provide complete information on all aspects of reproduction and development. In particular, it offers only limited means of detecting post-natal manifestations of prenatal exposure, or effects that may be induced during post-natal exposure. Due (amongst other reasons) to the relatively small numbers of animals in the dose groups, the selectivity of the end points, and the short duration of the study, this method will not provide evidence for definite claims of no effects. Although, as a consequence, negative data do not indicate absolute safety with respect to reproduction and development, this information may provide some reassurance if actual exposures were clearly less than the dose related to the NOAEL.

5.5.1.3.2 Replication

No published full reproduction or full developmental studies exist. As the CHAP has reported, “in neither study is there any indication of any anti-androgenic effects of TPIB when administered to females at doses as high as 1125 mg/kg/day for 14 days before mating, during mating (1–8 day), throughout gestation (21–23 days), and through PND 4–5. Thus, the developmental NOAEL for TPIB is greater than 1125 mg/kg/day."

5.5.1.4 Risk Assessment Considerations

5.5.1.4.1 Exposure

TPIB is a secondary plasticizer used in combination with other plasticizers. While TPIB is not a HPV chemical, it is widely used in many products, including weather stripping, furniture, wallpaper, nail care products, vinyl flooring, sporting goods, vinyl gloves, inks, water-based paints, and toys. TPIB has been detected in indoor air in office building, schools, and residences. TPIB was found in one-quarter of the toys and child-care articles tested by CPSC (Dreyfus, 2010).

Estimates of total TPIB exposure are not available. The mean and 95th percentile exposures to infants from mouthing all soft plastic objects, except pacifiers, are 0.92 to 5.8 µg/kg-d, respectively (Section 2.6; Appendix E2).

5.5.1.4.2 Hazard

The data based is somewhat limited. There is evidence of effects in the liver and kidneys in rats (Eastman, 2007a). The no observed effect level (NOEL) for systemic effects is 30 mg/kg-d in males and 150 mg/kg-d in female rats. The study authors proposed 150 mg/kg-d as the NOAEL.

5.5.1.4.3 Risk

Assuming a point of departure of 30 mg/kg-d, the MOE's for mouthing all soft plastic objects, except pacifiers, by infants range from 5,200 to 33,000.

5.5.1.5 Recommendation to CPSC regarding children's toys and child care articles

Although data are somewhat limited, there is no evidence that TPIB presents a hazard to infants or toddlers from mouthing toys or child care article containing TPIB. Therefore, the CHAP recommends no action on TPIB at this time.

The CHAP recommends that the appropriate U.S. agencies obtain the necessary exposure and hazard data to estimate total exposure to TPIB and assess the potential health risks.

5.5.1.6 Would this recommendation, if implemented, be expected to reduce exposure of children to TPIB?

No.

5.5.2 Di(2-ethylhexyl) adipate (DEHA) CAS 103-23-1

5.5.2.1 Adverse Effects

5.5.2.1.1 Animal

5.5.2.1.1.1 Systemic

- Effects induced by DEHA in 13-week mouse studies are consistent with those of di(2-ethylhexyl)phthalate (DEHP) and other hepatic peroxisome proliferators in rats and mice (Lake, 1995; Cattley *et al.*, 1998; Chevalier and Roberts, 1998; Doull *et al.*, 1999; IARC, 2000a; IARC, 2000b).
- Kang *et al.*, (2006) reported a large (50%) increase in relative liver weight and a decrease in body weight in male F344 rats exposed to 1570 mg/kg-day DEHA in the diet for 4 weeks. There were no effects on serum indicators of hepatotoxicity (ALT, AST, GGT) or light microscopy of the liver. No hepatic changes were observed at 318 mg/kg-day.
- Similarly, Miyata *et al.*, (2006) observed significant increases in relative liver weight without accompanying serum chemistry or histopathology changes in Crj:CD (SD) rats of both sex receiving a gavage dose of 1000 mg/kg-day DEHA, but not in those receiving 200 mg/kg-day or lower, for 28 days or more.
- Dietary 13-week studies performed by NTP (1982) as dose range-finding studies for cancer bioassays in F344 rats and B6C3F1 mice (described below) showed no effects in histopathology of the liver, kidneys or other tissues of males or females of either species exposed to DEHA concentrations as high as approximately 2500 mg/kg-day (rats) and 4700 mg/kg-day (mice). Organ weights were not measured.
- Nabae *et al.*, (2006) also reported no evidence of renal histopathology, serum chemistry, or urinalysis findings indicative of renal pathology in male F344 rats exposed to 1570 mg/kg-day DEHA in the diet for 4 weeks. However, small increases in relative kidney weights were noted.
- Kidney lesions were observed by Miyata *et al.*, (2006) in male, but not female, Crj:CD (SD) rats treated with 1000 mg/kg-day, but not 200 mg/kg-day or lower, of DEHA by gavage for 28 days. The type of lesions (increased eosinophilic bodies and hyaline droplets) and gender-dependent occurrence suggest that this finding may be related to male rat-specific alpha-2u-globulin nephropathy. Small increases in relative kidney weight were also observed treated rats. Miyata *et al.*, (2006) found no effects on hematology or a functional observational battery for neurological effects in treated rats.
- NTP (1982) fed F344 rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) diets containing approximately 2040 or 4250 mg/kg-day (mice), 948 or 1975 mg/kg-day (male rats), or 1104 or 2300 mg/kg/day (female rats) DEHA for 103 weeks followed by a 1-3 week observation period. High-dose rats of both sexes had reduced mean body weights compared to controls. No lesions or other compound-related adverse effects were observed in rats. For mice, mean body weights of all treated animals were lower than controls throughout the study and the decreases were dose-related. Survival did not appear to be affected by DEHA, but liver tumors were induced in both sexes with the combined incidence of hepatocellular adenomas and carcinomas

significantly increased in high-dose males and in all treated females. No compound-related non-neoplastic lesions were observed in the liver or other tissues.

- Hodge *et al.*, (1966) briefly and inadequately reported carcinogenicity results of chronic feeding studies of DEHA in rats and dogs. No compound-related tumors were induced in rats exposed to 0, 0.1, 0.5 or 2.5% DEHA in the diet for 2 years, or in dogs exposed to 0, 0.07, 0.15 or 0.2% DEHA in the diet for 1 year.
- Hodge *et al.*, (1966) also exposed C3H/AnF mice (50/sex/dose) to DEHA by dermal application and subcutaneous injection. In the dermal study, a lifetime weekly application of 0.1 or 10 mg of DEHA in acetone to a clipped area of back skin under non-occlusive conditions caused no gross or histological evidence of tumor formation at the application site. In the subcutaneous study, a single 10 mg dose of DEHA caused no injection site tumors following lifetime observation.

5.5.2.1.1.2 Reproductive

- No published multigenerational reproduction studies.
- The NTP (1982) conducted subchronic and chronic studies in F344 rats and B6C3F1 mice in which DEHA was administered in diet at up to ~2500 mg/kg/day (rats, 13 weeks), ~4700 mg/kg/day (mice, 13 weeks), ~2100 mg/kg/day (rats, 103 weeks), and ~4250 mg/kg/day (mice, 103 weeks). No adverse histopathological changes were reported in either male or female reproductive organs in any of the studies.
- Nabae *et al.*, (2006) and Kang (2006) conducted an intermediate-term study in F344 rats in which DEHA was administered in the diet at 0, 318, and 1570 mg/kg/day for 4 weeks. No changes were seen in spermatogenesis, weight and histology of the testes, epididymides, prostate, or seminal vesicles ($NOAEL_{repro}$ = 1570 mg/kg/day). No DEHA-induced testicular toxicity was seen in rats pretreated with thioacetamide or folic acid (in contrast to DEHP).
- Miyata *et al.*, (2006) conducted an intermediate-term study in Sprague-Dawley rats in which DEHA was administered via oral gavage at 0, 40, 200, or 1000 mg/kg/day for 4 weeks. Increased follicular atresia and prolonged estrous cycle was seen in female rats in the high dose group (F, $NOAEL_{repro}$ =200 mg/kg/day). No reproductive effects were seen in male rats (M, $NOAEL_{repro}$ = 1000 mg/kg/day).

5.5.2.1.1.3 Developmental

- Dalgaard (2002) conducted a pilot developmental study in Wistar rats in which DEHA was administered via oral gavage at 0, 800, and 1200 mg/kg/day on GD 7 through PND 17. Decreased pup weights were seen at 800 and 1200 mg/kg/day. No anti-androgenic effects were observed.
- Dalgaard (2003) conducted a developmental study in Wistar rats in which DEHA was administered via oral gavage at 0, 200, 400, and 800 mg/kg/day on GD7 through PND 17. Postnatal deaths were higher in the 400 mg/kg/day group ($NOAEL_{devel}$ = 200 mg/kg/day). Increased gestation length in the high dose group was reported. No anti-androgenic effects were seen.

5.5.2.2 **Human**

- No published human studies.

5.5.2.3 Relevance to Humans

The reported animal studies are assumed to be relevant to humans. However it should be noted that peroxisome proliferation has questionable relevance to hazard characterization in humans. As well, adverse effects involving alpha-2u-globulin nephropathy in rats are not predictive of renal effects in humans.

5.5.2.4 Weight of Evidence

5.5.2.4.1 Experimental Design

Studies by Nabae, Kang and Miyata each had small dose groups (6 or 10 per group). The Hodge (1966) dog and rat studies were not well reported. The chronic NTP study appears to be of sufficient design and rigor. There were no published reproductive studies. The NTP study had sufficient N per group (n=49-50 for 103 wk) but did not include organ weight measures. The Nabae and Kang studies had only 6 rats per dose group. The Miyata study had only 10 animals per group. Anti-androgenic conclusions are, therefore, weak. The lack of anti-androgenic effects seen in these studies, however, is supported by unpublished findings from a one generation reproduction study (ICI, 1988).

Regarding developmental studies, the Dalgaard (2003) full developmental study (n=20 per dose group) is of sufficient study design and rigor to support the conclusion of no anti-androgenic effects. The pilot study only has n=8 per group, however.

5.5.2.4.2 Replication

Studies consistently show peroxisome proliferation and its associated adverse effects, similar to DEHP. Chronic study showing increased liver tumor incidence in mice has not been replicated, but is a sound study.

No published reproduction studies exist. Because of a low n, only one developmental study can reliably support anti-androgenic conclusions. “The CHAP committee has recommended using a NOAEL of 800 mg/kg/day with an additional uncertainty factor of 10 to be used in the calculation of an RfD.

5.5.2.5 Risk Assessment Considerations

5.5.2.5.1 Exposure

DEHA is a high production volume chemical. It is approved for use in food contact materials. Dietary exposures have been estimated for European (0.7 µg/kg-d) (Fromme *et al.*, 2007b); Japanese (12.5 µg/kg-d) (Tsumura *et al.*, 2003); and Canadian (137 to 259 µg/kg-d (Page and Lacroix, 1995; Carlson and Patton, 2012) populations. DEHA is also found in adhesives, vinyl flooring, carpet backing, and coated fabrics (Versar/SRC, 2010).

DEHA has been found in some toys and child-care articles in the past (Chen, 2002), but was not found in a recent study by CPSC (Dreyfus, 2010). Estimates of exposure from mouthing toys and child care articles are not available.

5.5.2.5.2 Hazard

The toxicity of DEHA has been reviewed by Versar/SRC (Versar/SRC, 2010). NTP conducted a two-year feed study in mice and rats(NTP, 1982). Liver tumors (adenomas plus carcinomas) were elevated in high dose males and in females at all doses. The tumors may be due to peroxisome proliferation. The non-cancer NOAEL in mice was 4,250 mg/kg-d, the highest dose tested.

In a subchronic gavage study in SD rats, increased follicular atresia and prolonged estrous cycle were seen in high dose females. The NOAEL was 200 mg/kg-d.

A developmental study was performed in Wistar rats by gavage (Dalgaard *et al.*, 2003). Gestational length was significantly increased at the high dose (800 mg/kg-d). The developmental NAOEL was 200 mg/kg-d, based on postnatal deaths.

5.5.2.5.3 Risk

Assuming a point of departure of 200 mg/kg-d, the margins of exposure from dietary DEHA exposure range from 770 to 290,000

5.5.2.6 Recommendation to CPSC regarding children's toys and child care articles:

Data on exposure from toys and child care articles are not available. The CHAP recommends that the appropriate U.S. agencies obtain the necessary data to estimate DEHA exposure from diet and children's articles, and assess the potential health risks.

5.5.2.7 Would this recommendation, if implemented, be expected to reduce exposure of children to DEHA?

No.

5.5.3 Di(2-ethylhexyl) terephthalate (DEHT) CAS 6422-86-2

5.5.3.1 Adverse Effects

5.5.3.1.1 Animal

5.5.3.1.1.1 Systemic

- Eastman Kodak Co. (1975) reported an intermediate-term study in male albino rats (5/group) in which DEHT (0, 0.1, 1%; 0, ?, 890 mg/kg-day) was administered in the diet 5 days a week for 2 weeks. DEHT-treated rats were not significantly different than controls. Infection of control and treated rats confounded the interpretation of this study.
- Topping *et al.*, (1987) reported an intermediate-term toxicity study in Sprague Dawley rats (5/sex/group) in which DEHT (0, 0.1, 0.5, 1.0, 1.2, or 2.5%; estimated doses are M: 0, 86, 431, 861, 1033, 2154 mg/kg-day; F: 0, 98, 490, 980, 1176, 2450 mg/kg-day) was administered in the diet for 3 weeks. Exposure to DEHT reduced

body weight gain and feed consumption (M&F; 2154, 2450 mg/kg-day), increased relative liver weight (M; 2154, F; 980, 1176, 2450 mg/kg-day), increased serum cholesterol, triglycerides, liver enzymes, and peroxisomes (M&F; 2154, 2450 mg/kg-day). The review author identified a NOAEL of 1033 (M) and 1176 (F) mg/kg-day based on decrements in body weight gain and food consumption.

- Barber and Topping (1995) reported an intermediate-term toxicity study in Sprague Dawley rats (20/sex/group) in which DEHT (0, 0.1, 0.5, 1%; M: 0, 54, 277, 561 mg/kg-day; F: 0, 61, 309, 617 mg/kg-day) was administered in the diet for 90 days. No changes in body weight gain or food consumption were observed. DEHT exposure significantly increased relative liver weight (M&F 561, 617 mg/kg-day), but not other organ weights. Various hematology parameters (but not serum chemistry) were statistically different than controls. Peroxisomal proliferation was not observed in treated groups. The study authors assigned NOAELs of 277 and 309 mg/kg-day (M&F respectively) based on changes in the liver and hematology.
- Eastman Kodak Co. (1983) conducted an intermediate-term inhalation toxicity study in rats (5/group) in which DEHT (0, 46.3 mg/m^3) was administered 8 hours/day, 5 days/week for 2 weeks. No significant effects were reported in hematology, serum chemistry, or pathology. The study was poorly described, limiting its interpretation.
- Deyo (2008) reported a chronic toxicity study in Fischer-344 rats (50/sex/group) in which DEHT (0, 1500, 6000, 12000 ppm; M: 0, 79, 324, 666 mg/kg-day, F: 0, 102, 418, 901 mg/kg-day) was administered in the diet for 104 weeks. Body weight gain was significantly lower in high-dose animals over the 2 years and lower in the mid-dose rats during the first year. Terminal body weights were significantly different than controls (F, 901 mg/kg-day). Hematology, clinical chemistry, and urinalysis were not consistently affected by DEHT treatment. DEHT increased the relative liver weights in females (significant at 901 mg/kg-day), and males (not significant at 666 mg/kg-day) and increased the incidence of portal lymphoid foci (M, 666 mg/kg-day). Changes in kidney weight were not dose-related or supported by histopathology. The author attributed other organ weight changes to individual variation or secondary to body weight changes. DEHT exposure also increased the incidence of eosinophilic inclusions in the nasal turbinates and atrophy of the outer nuclear layer of the retina (F: 418 mg/kg-day), but the study author regarded these as not toxicologically significant. Changes in the incidence of large granular cell lymphomas were not dose-related.
- Faber *et al.*, (2007b) reported a two generation reproduction study in Sprague Dawley rats (see below). High dose females had more mortalities than controls and high dose males had significant reductions in body weight gain (week 3 and 7). Absolute (F0) and relative (F0, F1) liver weights were increased in mid and high-dose females, but were not correlated to morphological changes in the liver. Maternal body weight gain through gestation, body weight on GD20 through lactation, and feed consumption were significantly reduced in F0 and F1 dams (530 mg/kg-day). Body weight and feed consumption was also reduced during LD 7-14 in mid-dose F1 dams (316 mg/kg-day). Relative spleen and thymus weight was reduced and relative brain weight increased in various populations of rats. The study author identified a NOAEL of 158 mg/kg-day for parental systemic effects.

- Faber *et al.*, (2007a) reported a developmental study in Sprague Dawley rats (see below). Maternal body weight gain was reduced during GD 16-20 in the high DEHT dose group, but body weights were similar to controls during the entire treatment period. A significant increase in absolute liver weight was also reported for high dose rats. The NOAEL was reported to be 458 mg/kg-day based on mean and net maternal body weight decrements.
- Barber (1994) and Divincenzo *et al.*, (1985) reported that reverse mutations were not induced in bacteria, forward mutations in the HGPRT locus of Chinese hamster ovary (CHO) cells, or chromosomal aberrations in CHO cells *in vitro*.

5.5.3.1.1.2 Reproductive

- Faber *et al.*, (2007b) reported a two generation reproduction study in Sprague Dawley rats in which DEHT was mixed in diet at 0, 0.3, 0.6, and 1.0% (F0 males = 0, 158, 316, and 530 mg/kg-day). Males were exposed for 10 weeks prior to and during mating. Females were exposed 70 days prior to mating, during mating, and through gestation and lactation. Weaned offspring were dosed similarly starting PND 22. No reproductive effects were reported at any dose level for any generation ($NOAEL_{repro}$ = 530 mg/kg-day).

5.5.3.1.1.3 Developmental

- Gray *et al.*, (2000) reported a developmental study in Sprague Dawley rats in which DEHT was dosed via gavage at 0 or 750 mg/kg-day on GD14 through PND3. No male reproductive tract malformations were observed in male pups ($NOAEL_{devel}$ = 750 mg/kg-day).
- Faber *et al.*, (2007a) reported a developmental study in Sprague Dawley rats in which DEHT (0, 0.3, 0.6, and 1.0%; 0, 226, 458, and 747 mg/kg-day) was administered via the diet on GD0 through GD20. Adverse reproductive effects were not observed in dosed animals. A dose-related increase in the incidence of 14^{th} rudimentary ribs was observed in treated groups (NOAEL = 458 mg/kg-day).
- Faber *et al.*, (2007a) reported a developmental study in which DEHT was fed via the diet (0, 0.1, 0.3, and 0.7%; 0, 197, 592, and 1382 mg/kg-day) to pregnant ICR mice at GD 0 through GD 18. No antiandrogenic effects were observed in the study ($NOAEL_{devel}$ = 1382 mg/kg-day).

5.5.3.1.2 Human

No published human studies.

5.5.3.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.5.3.3 Weight of Evidence

5.5.3.3.1 Experimental Design

The two generation reproduction and the developmental studies (Faber *et al.*, 2007a; 2007b) had a sufficient number of rats per group (n=25-30) and study design to support the conclusions based on their results. The Gray study had only 8 pregnant rats per treatment group. The chronic and intermediate-term toxicity studies had an acceptable number of animals per dose group (50 and 20/sex/group, respectively). Other studies looking at systemic endpoints generally had lower Ns (5/group).

5.5.3.3.2 Replication

Only one reproduction study (Faber *et al.*, 2007b) has been performed with DEHT. Two full developmental studies in different species were performed by one lab (Faber *et al.*, 2007a) and a targeted developmental study performed by a different lab (Gray *et al.*, 2000). “On the basis of these two [developmental] studies and the results of the two-generation study in rats, the CHAP committee recommends a NOAEL for DEHT of 750 mg/kg/day.” NOTE: The CHAP assessment for reproductive toxicity lists NOAEL = 530 mg/kg-day, and the developmental assessment lists NOAEL as 747 mg/kg-day for Faber *et al.*, (2007b). Systemic toxicity was described by at least 2 larger studies, one long-term, and one intermediate-term and a handful of additional smaller studies. In these studies, DEHT exposure decreased body weight gain (5 studies), feed consumption (2 studies), and increased in liver weight (5 studies), serum cholesterol, triglycerides, liver enzymes, and peroxisomes (1 study). Hepatic changes seen following exposure to DEHT paralleled those seen in rats following ortho phthalate exposures. DEHT-induced adverse changes in nasal turbinates and the retina are not typically described for ortho phthalates.

5.5.3.4 Risk Assessment Considerations

5.5.3.4.1 Exposure

DEHT is a high production volume chemical. It was present in about one-third of the toys and child care articles tested by CPSC (Dreyfus, 2010). The exposure to infants from mouthing all soft plastic articles, except pacifiers, was estimated to be 0.69 µg/kg-d (mean), with an upper bound of 2.8 µg/kg-d. Information on total exposure is not available.

5.5.3.4.2 Hazard

Peer-reviewed toxicological studies on DEHT are available. The reproductive NOAEL was 158 mg/kg-d in a 2-generation study in SD rats, based on parental effects (Faber *et al.*, 2007b). The developmental NOAEL was 458 mg/kg-d in rats, based on increased incidence of 14^{th} rudimentary ribs (Faber *et al.*, 2007a). DEHT did not produce anti-androgenic effects in rats at 750 mg/kg-d (Gray *et al.*, 2000). No developmental effects were observed in mice (Faber *et al.*, 2007a).

5.5.3.4.3 Risk

Assuming a point of departure of 158 mg/kg-d, the margin of exposure for mouthing soft plastic articles is 56,000 to 230,000.

5.5.3.5 Recommendation

There is no evidence that DEHT presents a hazard to infants or toddlers from mouthing toys or child care article containing DEHT. Therefore, the CHAP recommends no action on DEHT.

However, information on total exposure to DEHT is not available. The CHAP recommends that the appropriate U.S. agencies obtain the necessary exposure data to estimate total exposure to DEHT and assess the potential health risks.

5.5.3.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DEHT?

No.

5.5.4 Acetyl Tributyl Citrate (ATBC) CAS 77-90-7

5.5.4.1 Adverse Effects

5.5.4.1.1 Animal

5.5.4.1.1.1 Systemic

- Finkelstein and Gold (1959) exposed small groups of animals (4 rats or 2 cats) to dietary ATBC for 6-8 weeks. Wistar rats were fed approximately 7620 or 15,240 mg/kg/day and cats received 5250 mg/kg-day. Growth was reduced in cats and high-dose rats by 30-35% and both had diarrhea. Treatment with ATBC had no effect on blood counts or on gross or microscopic pathology.
- Sprague-Dawley rats (5/sex/dose) were administered ATBC (purity>98%) in the diet at doses of 0, 1000, 2700 or 5000 mg/kg-day for 14 consecutive days as part of a dose range finding study (Jonker and Hollanders, 1990). Transient dose-related reductions in body weights were reported among all dose groups. Body weights among high-dose rats and mid-dose male rats remained slightly lower than control rats throughout the study, with food consumption in the former group also reduced. Increased cytoplasmic eosinophilia accompanied by reduced glycogen content of periportal hepatocytes was observed in the livers of 2/5 mid-dose male rats and all of the high-dose rats. No further details of this study were available.
- Sprague-Dawley rats (20/sex/dose) were administered ATBC (purity >98%) in the diet *ad libitum* at doses of 0, 100, 300 or 1000 mg/kg-day for 13 weeks (Jonker and Hollanders, 1990). The following endpoints showed no treatment-related changes: mortality, clinical signs, appearance, behavior, motor activity, sensory activity, autonomic activity, body weight, hematology, clinical chemistry and urinalysis. Relative liver weights were higher among mid-dose males and high-dose males and females. There was a slight increase in the relative kidney weights of high-dose male rats, but statistical significance was not reported. It is not clear if absolute organ weights were unchanged or not reported. Gross necropsy and histopathology did not reveal any treatment-related effects in the liver, kidneys or other organs. The high

dose of 1000 mg/kg-day appears to be a NOAEL due to the absence of toxicologically significant findings.

- Soeler *et al.,* (1950) fed three groups of Sherman rats (20 rats/dose) (gender not specified) a diet containing ATBC (99.4% purity) at approximately 0, 10, 100, and 1000 mg/kg-day. There was no ATBC-induced effect on growth. Mortality occurred in 20% of the treated rats (12/60) and the control rats (8/40) prior to study termination, but may have been related to pulmonary infection. Lymphomas were observed in both control and treated rats and were not considered to be related to treatment with ATBC. The NOAEL for this study is 1000 mg/kg-day.

5.5.4.1.1.2 Reproductive

- Robins *et al.*, (1994) conducted a two generation reproduction study in Sprague Dawley rats in which ATBC was mixed in diet at 0, 100, 300, and 1000 mg/kg/day. Males were exposed for 11 weeks and females for 3 weeks prior to mating, then during mating, gestation, and lactation. ATBC was administered to pups for 10 weeks after weaning. No reproductive effects were reported at any dose level ($NOAEL_{repro}$ = 1000 mg/kg/day).
- Chase and Willoughby (2002) conducted a one generation reproduction study in Wistar rats in which ATBC was mixed in diet at 0, 100, 300, and 1000 mg/kg/day. F0 parents were exposed for 4 weeks prior to mating, then during mating, gestation and lactation. No reproductive effects were seen at any dose level ($NOAEL_{repro}$ = 1000 mg/kg/day).

5.5.4.1.1.3 Developmental

- No published animal developmental studies. “Developmental” effects were not observed in the above reproductive studies.

5.5.4.1.2 Human

- No published human studies.

5.5.4.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.5.4.3 Weight of Evidence

5.5.4.3.1 Experimental Design

Repeat dose studies described here are old, have small sample sizes, and are missing methodological and statistical details (Soeler *et al.*, 1950; Finkelstein and Gold, 1959; Jonker and Hollanders, 1990; 1991). The Soeler *et al.,* (1950) study is of limited value as a cancer bioassay because group sizes were relatively small (20 per treated group and 40 in controls), 20% of animals died early from infection, lymphomas were high in control animals, and doses were inadequate (the high dose did not approach the maximum tolerated dose). Furthermore, oral metabolism studies in rats and in rat liver homogenates reveal that ATBC is extensively absorbed and rapidly metabolized and excreted (Davis, 1991; Edlund and Ostelius, 1991; Dow, 1992; CTFA, 1998). Thus, any liver and possibly kidney, enlargement noted in some of these studies may be an adaptive change occurring as a consequence of metabolic load.

As presented, the two generation study by Robins *et al.*, (1994) seems of appropriate rigor to substantiate the lack of ATBC-induced pathologies. The one generation study, however, does not have a sufficient duration of dosing pre-mating (need a minimum of 10 weeks) to adequately assess male reproductive effects.

5.5.4.3.2 Replication

Studies did not adequately replicate the effects observed occasionally in body weight, liver, or kidney. Results from the one generation reproduction study are not directly comparable to the 2 generation reproduction study and therefore, conclusions need to be confirmed. The CHAP committee has recommended using a NOAEL of 1000 mg/kg/day with an additional uncertainty factor of 10 to be used in the calculation of an RfD.

5.5.4.4 Risk Assessment Considerations

5.5.4.4.1 Exposure

ATBC is a high production volume chemical. It is used in food packaging, food (as a flavor additive), medical devices, cosmetics, adhesives, and pesticides (inert ingredient) (Versar/SRC, 2010). ATBC was found in about half of the toys and child care articles tested by CPSC (Dreyfus, 2010). The exposure to infants from mouthing all soft plastic articles, except pacifiers, is estimated to have a mean of 2.3 µg/kg-d, and a 95th percentile of 7.2 µg/kg-d.

5.5.4.4.2 Hazard

The overall NOAEL in a 13-week study in SD rats was 1,000 mg/kg-d, based on systemic effects (Jonker and Hollanders, 1990). The NOAEL was also 1,000 mg/kg-d (the highest dose tested) in two studies: a 2-generation study (Robins, 1994) and a one-generation study (Chase and Willoughby, 2002).

5.5.4.4.3 Risk

Assuming a point of departure of 1,000 mg/kg-d, the MOE for mouthing soft plastic articles by infants is estimated to be 14,000 (upper bound exposure) to 43,000 (mean exposure).

5.5.4.5 Recommendation

Although data are somewhat limited, there is no evidence that ATBC presents a hazard to infants or toddlers from mouthing toys or child care article containing TPIB. Therefore, the CHAP recommends no action on ATBC at this time.

The CHAP recommends that the appropriate U.S. agencies obtain the necessary exposure and hazard data to estimate total exposure to TPIB and assess the potential health risks.

5.5.4.6 Would this recommendation, if implemented, be expected to reduce exposure of children to ATBC?

No.

5.5.5 Diisononyl hexahydrophthalate (DINX) CAS 166412-78-8

5.5.5.1 Adverse Effects

5.5.5.1.1 Animal

5.5.5.1.1.1 Systemic

- No published studies.
- SCENIHR (2007) reported a summary of a 28-day oral toxicity study in an undisclosed species (presumed to be rat at 5 rats/sex/dose) in which DINX was (presumed) to be dosed via the diet at 0, 600, 3000, and 15000 ppm (M/F, 64/66, 318/342, 1585/1670 mg/kg-day). The highest dose of DINX resulted in increased gamma-glutamyl transferase (GGT) and degenerated epithelial cells in the urine. SCENIHR reported 3000 ppm (318/342 mg/kg-day) as the NOAEL, but left open the question of whether these changes were adverse or not.
- SCENIHR (2007) reported a summary of a 90-day oral toxicity study in an undisclosed species (presumed to be rat at 10 rats/sex/dose) in which DINX was (presumed) to be dosed via the diet at 0, 1500, 4500, and 15000 ppm (M/F, 107/128, 325/389, 1102/1311 mg/kg-day). An increase in liver and thyroid weight (absolute or relative not reported), phase I and II liver enzymes, and serum GGT and thyroid stimulating hormone was described as well as hyperplasia/hypertrophy of the thyroid follicles. Relative testis weight was increased at all doses, but did not have a dose-related relationship or associated histopathological changes. Blood and urinary tract transitional epithelial cells were also found in the urine (without histopathological changes in the kidney) and alpha 2_u-globulin accretions in the renal tubules in the rat males. The review author considered the liver changes at which they affected thyroid follicles to be a LOAEL (but did not conclude what this LOAEL was).
- SCENIHR (2007) reported a summary (no quantitative data) of a two generation reproduction study in an unnamed species (presumably rats at 20 rats/sex/dose) in which DINX was mixed in diet at 0, 100, 300, and 1000 mg/kg-day. Although not detailed, it is presumed that males were exposed for at least 10 weeks prior to mating, during mating, and that weaned offspring were dosed similarly (because the study was performed under OECD TG 416). Increased liver, kidney, and thyroid weights in F0 rats were observed at 1000 mg/kg-day. Increased thyroid weight and thyroid hyperplasia/hypertrophy in F1 rats were observed at 300 mg/kg-day and higher (LOAEL = 300 mg/kg-day). Exposure to DINX also increased serum GGT and decreased total bilirubin in F0 females.
- SCENIHR (2007) also reported a summary of a prenatal developmental toxicity study in rats and rabbits that were orally administered DINX at 0, 100, 300, 1000 (1200 – rat) mg/kg-day on GD 6-19 (rat) or GD 6-29 (rabbit). Details on the methodology and

results are not available, but "no effects were observed in either species", suggesting NOAELs of 1200 (rat) and 1000 (rabbit) mg/kg-day for maternal toxicity.

- BASF (2005) reported data for a chronic toxicity/carcinogenicity study in Wistar rats (50/sex/dose) in which DINX (0, 40, 200, 1000 mg/kg-day) was administered in the feed for two years. DINX exposure increased thyroid weight, follicular cell hyperplasia, and follicular adenomas in a dose-related fashion in male and female rats (≥200 and 1000 mg/kg-day, respectively). Urinary tract transitional epithelial cells were also reported (at an unspecified dose), but were considered to be adaptive by the SCENIHR because there was no histopathological changes in the kidney. This study identified a NOAEL (M/F 40/200 mg/kg-day) and LOAEL (M/F, 200/1000 mg/kg-day) for non-neoplastic effects in the thyroid. Note, the SCENIHR suggested that thyroid effects (including adenomas) were not relevant in humans. This is not consistent with the EPA policy (EPA, 1998) which that concludes that rodent noncancer/cancer thyroid effects resulting from disruption of the thyroid-pituitary axis do represent a noncancer/cancer health hazard to humans.
- SCENIHR and BASF report that DINX does not induce mutations in bacteria or Chinese hamster ovary cells *in vitro*. It also does not induce chromosomal aberrations in Chinese hamster V79 cells *in vitro* or micronuclei in mouse bone marrow cells *in vivo*.

5.5.5.1.1.2 Reproductive

- No published reproduction studies.
- SCENIHR (2007) reported a summary of a two generation reproduction study in an unnamed species (presumably rats) in which DINX was mixed in diet at 0, 100, 300, and 1000 mg/kg-day. Although not detailed, it is presumed that males were exposed for at least 10 weeks prior to mating, during mating, and that weaned offspring were dosed similarly (because the study was performed under OECD TG 416). No reproductive effects were reported at any dose level ($NOAEL_{repro}$ = 1000 mg/kg-day).

5.5.5.1.1.3 Developmental

- No published animal developmental studies.
- SCENIHR (2007) reported a summary of a pre- and post-natal developmental toxicity study in rats and rabbits that were orally administered DINX during gestation (at dose levels as high as 1200 mg/kg-day on gestational days 6-19 in the rat and 0, 100, 300 or 1000 mg/kg-day on gestation days 6-29 in the rabbit). Although discrete methods and data were not available in the summary, it was reported that no effects were observed in either species, suggesting apparent $NOAEL_{devel}$s of 1200 mg/kg-day in rats and 1000 mg/kg-day in rabbits.
- SCENIHR (2007) also reported a summary of a developmental toxicity study in rats that were orally administered DINX at 0, 750, and 1000 mg/kg-day from 3 days post-coitum to PND 20. Details on the methodology and results are not available. A 7-8% decrease in AGD in males and the AGD index in both sexes was reported at the high dose on PND 1. This was considered to be a study artifact, however, because other male reproductive parameters were not affected ($NOAEL_{devel}$ = 1000 mg/kg-day).

- No developmental variations or malformations were observed in the SCENIHR reproduction summary.

5.5.5.1.2 Human

- No published human studies.

5.5.5.2 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.5.5.3 Weight of Evidence

5.5.5.3.1 Experimental Design

All studies were unpublished and their experimental design had to be inferred from the SCENIHR review. This reduces the confidence of conclusions drawn by the author.

5.5.5.3.2 Replication

No published studies exist. The available summaries of these studies are brief and generally insufficient with respect to information on experimental design and results, particularly quantitative data and dose-response relationships. While DINX is entering the market as a component of consumer products such as children’s articles, the insufficiency of these study summaries preclude independent evaluation of the results and reliable identification of adverse effect levels. Systemic results that are presented, however, support the conclusion that DINX increases liver weight (2 studies), thyroid weight (4 studies), GGT (3 studies), epithelial cells in the urine (3 studies), and follicular hyperplasia (2 studies).

5.5.5.4 Risk Assessment Considerations

5.5.5.4.1 Exposure

Although DINX is not a high production volume chemical, its production has grown rapidly in recent years (CEH, 2009). DINX is used in food packaging and processing materials. It is a potential substitute for DEHP in medical devices. DINX was present in about one-third of the toys and child care articles tested by CPSC (Dreyfus, 2010). The estimated mean exposure to from mouthing soft plastic articles, except pacifiers, is 1.4 µg/kg-d, with an upper bound of 5.4 µg/kg-d (Section 2.6; Appendix E2). Estimates of total exposure are not available.

5.5.5.4.2 Hazard

The available toxicity studies are proprietary; only summaries prepared by the manufacturer are available. In a 2-year bioassay in Wistar rats (BASF, 2005) DINX exposure led to thyroid hypertrophy, follicular cell hyperplasia, and follicular adenomas in middle and high dose males and females. The non-cancer NOAEL was 40 mg/kg-d (low dose); the LOAEL was 200 mg/kg-d.

Few details were available on a 2-generation study (OECD TG 416). The species and number of animals were not reported (SCENIHR, 2007). The systemic NOAEL was 100 mg/kg-d. Liver, kidney, and thyroid weights were increased in F0 and F1 animals at the middle dose (300 mg/kg-d). Thyroid hyperplasia was reported in F1 animals. Increased serum GGT and decreased bilirubin were reported in F0 females. The reproductive/developmental NOAEL was 1,000 mg/kg-d, the highest dose tested.

5.5.5.4.3 Risk

Assuming a point of departure of 40 mg/kg-d, the MOE for infants mouthing soft plastic articles is between 7,400 (upper bound exposure) and 29,000 (mean exposure).

5.5.5.5 Recommendation

Based on the limited information available, there is no evidence that DINX presents a hazard to infants or toddlers mouthing soft plastic articles. However, given the lack of publically available information on DINX, the CHAP strongly encourages the appropriate agencies to obtain the necessary toxicological and exposure data to any potential risk from DINX.

5.5.5.6 Would this recommendation, if implemented, be expected to reduce exposure of children to DINX?

No.

5.5.6 Tris(2-ethylhexyl) trimellitate (TOTM) CAS 3319-31-1

5.5.6.1 Adverse Effects

5.5.6.1.1 Animal

5.5.6.1.1.1 Systemic

- United Nations Environment Programme (UNEP, 2002) reported an intermediate-term toxicity study in Sprague-Dawley rats (5/sex/group) in which TOTM (0, 100, 300, 1000 mg/kg-day) was administered daily via gavage for 28 days. TOTM exposure did not induce any adverse effects in any treatment groups (NOAEL = 1000 mg/kg-day).
- Nuodex (1983) reported a intermediate-term toxicity study in Fischer-344 albino rats (M, 5/group) in which TOTM (0, 1000 mg/kg-day) was administered via gavage for 5 days/week for 4 weeks. Triglycerides in the treated rats were significantly lower than controls, however, body and organ weights in exposed rats were similar to controls.
- CMA (1986) and Hodgson (1987) reported a short-term feeding study in which Fischer-344 rats (5/sex/group) were administered TOTM (0, 0.2, 0.67, or 2%; M:0, 184, 642, 1826 mg/kg-day, F:0, 182, 666, 1641 mg/kg-day) in the diet for 4 weeks. TOTM significantly reduced red blood cell count and hemoglobin and increased serum albumin (not dose-related). TOTM also significantly increased absolute and

relative liver weights (M&F; dose-related; NOAEL = 184 and 182 mg/kg-day). Biochemically, TOTM increased cyanide-insensitive palmitoyl CoA oxidation (pCoA) and carnitine acetyl transferase activity in the liver (M&F), and catalase activity (M). High dose rats had histopathologically reduced cytoplasmic basophilia (F) and slightly increased centrilobular and periportal peroxisomes in the liver (M&F). The review author considered liver changes of questionable relevance to humans and considered the NOAEL to be 1826 mg/kg-day.

- CMA (1986) and Hodgson (1987) reported an intermediate-term toxicity study in which Fischer-344 rats (5/sex/group) were administered TOTM (0, 200, 700, 2000 mg/kg-day) daily via gavage for 21 days. TOTM significantly increased absolute and relative liver weight (F; not dose-related). Histologically, the quantity of neutral lipid in the liver was reduced. Biochemically, pCoA activity (M&F; 2000 mg/kg-day) and lauric acid 12-hydroxylase activity (M; all doses) was increased. Hepatic peroxisomes were increased in male rats (2000 mg/kg-day). The review author considered 2000 mg/kg-day to be the NOAEL for this study.
- Japan Ministry of Health and Welfare (JMHW, 1998) conducted a one generation reproduction study (see below). No treatment-related effects were reported for body weight or food consumption.
- Huntington Life Sciences (2002) conducted a developmental toxicity test (see below). No significant changes in maternal body weight were observed during gestation or lactation for any dose group.
- UNEP (2002), EPA (1983), CMA (1983; 1985a; 1985b), and Zeiger *et al.*, (1988) reported that TOTM does not induce reverse mutations in various strains of bacteria, forward mutations in the HGPRT locus in Chinese hamster ovary cells, unscheduled DNA synthesis in primary rat hepatocytes, or chromosomal aberrations in Chinese hamster lung cells *in vitro*. TOTM was also negative for dominant lethal mutations in Swiss white mice *in vivo*.

5.5.6.1.1.2 Reproductive

- Japan Ministry of Health and Welfare (JMHW, 1998) reported a one generation reproduction study in rats in which TOTM was administered via gavage at 0, 100, 300, and 1000 mg/kg-day for 46 days to males (including mating) and 14 days prior to mating through LD 3 in females. Mid and high dose males had reduced numbers of spermatocytes and spermatids in the testes ($NOAEL_{repro}$=100 mg/kg-day).

5.5.6.1.1.3 Developmental

- Huntington Life Sciences (2002) reported a pre- and post-natal developmental toxicity study in Sprague Dawley rats dosed with TOTM (0, 100, 500 or 1050 mg/kg-day) on GD 6-19 for the prenatal assessment and GD 6 through LD 20 for the postnatal assessment. Increases in the number of fetuses (from treated dams) exhibiting displaced testes were reported, but these were within historical control ranges. A statistically significant increase was seen in the number of high dose male offspring with retained areolar regions (on PND 13 but not PND 18; a slight developmental delay; NOAEL = 1050 mg/kg-day).

5.5.6.2 Human

- No published human studies.

5.5.6.3 Relevance to Humans

The reported animal studies are assumed to be relevant to humans.

5.5.6.4 Weight of Evidence

5.5.6.4.1 Experimental Design

The number of animals in the Japan Ministry of Health and Welfare study (JMHW, 1998) was small (n=12) when considering standard reproduction studies. The Huntington study (2002) had sufficient number of rats per group and appropriate study design. Studies assessing systemic effects were limited to a handful of short to intermediate duration exposures. These studies primarily were of low N (5 rats/group), suggesting that conclusions made from these studies may be of lower confidence.

5.5.6.4.2 Replication

Studies verifying changes in testicular spermatocytes and spermatids, displaced testes, and areola region development have not been performed. “The CHAP committee recommends that the conservative NOAEL of 100 mg/kg/day derived in the Japanese study be assigned for TOTM.” Systemic effects included increased liver weight (2 studies), increased liver enzymes (2 studies), increased peroxisomes (2 studies), decreased triglycerides (1 study), and changes in hematology (1 study). As with DEHT, hepatic changes seen following exposure to TOTM paralleled those seen in rats following ortho phthalate exposures.

5.5.6.5 Risk Assessment Considerations

5.5.6.5.1 Exposure

TOTM is a high production volume plasticizer used in electrical cable, lubricants, medical tubing, and controlled release pesticide formulations. It is preferred for use in high temperature applications. TOTM was not found in toys and child care articles tested by CPSC. Estimates of daily exposure from toys and child care articles are not available. However, it is expected that TOTM will have a low leaching/migration rate and low volatility because of its high molecular weight and very low vapor pressure. TOTM has a lower migration rate than DEHP when assessed in medical tubing.

5.5.6.5.2 Hazard

Several repeated-dose studies ranging from 21 to 28 days in duration have been reported. In one study in F344 rats (CMA, 1986; Hodgson, 1987), TOTM exposure significantly reduced red blood cell counts and hemoglobin, and increased serum albumin. The NOAEL for these effects was 182 mg/kg-d. Evidence of peroxisome proliferation was also reported. The reproductive NOAEL was 100 mg/kg-d in a one-generation study in rats (JMHW, 1998). The developmental NOAEL was 1,050 mg/kg-d in SD rats exposed on either GD 6-19 or GD 6 to lactational day 20 (Huntingdon Life Sciences, 2002).

Effects in male offspring included displaced testes and retained areolae (PND 13). The authors reported that the incidence of displaced testes was within the range of historical controls, and the retained areolae were absent by PND 18.

5.5.6.5.3 Risk

The margin of exposure cannot be calculated because data on exposure from toys and child care articles are not available.

5.5.6.6 Recommendation

There is insufficient information on exposure to assess the potential risks of the use of TOTM in toys and child care articles. However, the migration of TOTM from PVC products is expected to be relatively low. The CHAP recommends no action on TOTM. However, the CHAP strongly recommends that appropriate exposure information be obtained before using TOTM in toys and child care products.

5.5.6.7 Would this recommendation, if implemented, be expected to reduce exposure of children to TOTM?

No.

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PEER REVIEW DRAFT

Draft Report to the
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by the
CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES

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APPENDIX A

DEVELOPMENTAL TOXICITY

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1 Introduction

1.1 Male Sexual Differentiation in Mammals

Although phthalates can induce a number of types of toxicities in animals, as described in the previous section, the most extensively studied is male developmental toxicity in the rat. As discussed in more detail subsequently, phthalates have been shown to disrupt testicular development as well as subsequent reproductive tract dysgenesis. Because the developmental toxicity studies reviewed in this section relate to various aspects of male sexual differentiation, a brief introduction to this subject, taken directly from the 2008 NRC publication: *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (2008), is herein provided.

"Sexual differentiation in males follows complex interconnected pathways during embryo and fetal developments that have been reviewed extensively elsewhere (see, for example, Capel, 2000; Hughes, 2001; Tilmann and Capel, 2002; Brennan and Capel, 2004).

Critical to the development of the male mammals is the development of the testis in embryonic life from a bipotential gonad (a tissue that could develop into a testis or an ovary). The "selection" is genetically controlled in most mammals by a gene on the Y chromosome. The sex-determining gene (sry in mice and SRY in humans) acts as a switch to control multiple downstream pathways that lead to the male phenotype. Male differentiation after gonad determination is exclusively hormone-dependent and requires the presence at the correct time and tissue location of specific concentrations of fetal testis hormones-Mullerian inhibiting substance (MIS), insulin-like factors, and androgens. Although a female phenotype is produced independently of the presence of an ovary, the male phenotype depends greatly on development of the testis. Under the influence of hormones and cell products from the early testis, the Mullerian duct regresses and the mesonephric duct (or Wolffian duct) gives rise to the epididymis and vas deferens. In the absence of MIS and testosterone, the Mullerian ductal system develops further into the oviduct, uterus, and upper vagina, and the Wolffian duct system regresses. Those early events occur before establishment of a hypothalamic-pituitary-gonadal axis and depend on local control and production of hormones (that is, the process is gonadotropin-independent). Normal development and differentiation of the prostate from the urogenital sinus and of the external genitalia from the genital tubercle are also under androgen control. More recent studies of conditional knockout mice that have alterations of the luteinizing-hormone receptor have shown that normal differentiation of the genitalia, although they are significantly smaller.

Testis descent appears to require androgens and the hormone insulin-like factor 3 (insl3; Adham *et al.*, 2000) to proceed normally. The testis in early fetal life is near the kidney and attached to the abdominal wall by the cranial suspensory ligament (CSL) and gubernaculum. The gubernaculum contracts, thickens, and develops a bulbous outgrowth; this results in the location of the testes in the lower abdomen (transabdominal descent). The CSL regresses through an androgen-dependent process. In the female, the CSL is retained with a thin gubernaculum to maintain ovarian position. Descent of the testes through the inguinal ring into the scrotum (inguinoscrotal descent) is under androgen control.

Because the majority of studies discussed below were conducted in rats, it is helpful to compare the rat and human developmental periods for male sexual differentiation. Production of fetal testosterone occurs over a broader window in humans (gestation weeks 8-37) than in rats (gestation days [GD] 15-21). The critical period for sexual differentiation in humans is late in the first trimester of pregnancy, and differentiation is essentially complete by 16 weeks (Hiort and Holterhus, 2000). The critical period in rats occurs in later gestation, as indicated by the production of testosterone in the latter part of the gestational period, and some sexual development occurs postnatally in rats. For example, descent of the testes into the scrotum occurs in gestation weeks 27-35 in humans and in the third postnatal week in rats. General, the early postnatal period in rats corresponds to the third trimester in humans."

As the authors of the 2008 NRC conclude "…it is clear that normal differentiation of the male phenotype has specific requirements for fetal testicular hormones, including androgens, and therefore can be particularly sensitive to the action of environmental agents that can alter the endocrine milieu of the fetal testis during the critical periods of development."

1.2 The Rat Phthalate Syndrome

Studies conducted over the past 20 plus years have shown that phthalates produce a syndrome of reproductive abnormalities when administered to pregnant rats during the later stages of pregnancy, e.g., GD 15-20. This syndrome of reproductive abnormalities, known as the rat phthalate syndrome, is characterized by malformations of the epididymis, vas deferens, seminal vesicles, prostate, external genitalia (hypospadias), cryptorchidism (undescended testes) as well as retention of nipples/areolae (sexually dimorphic structures in rodents) and demasculinization of the perineum resulting in reduced anogenital distance (AGD). The highest incidence of reproductive tract malformations is observed at higher phthalate dose levels whereas changes in AGD and nipple/areolae retention are frequently observed at lower phthalate dose levels.

Mechanistically, phthalate exposure can be linked to the observed phthalate syndrome abnormalities by an early phthalate-related disturbance of normal fetal testicular Leydig function and/or development (Foster, 2006). This disturbance is characterized by Leydig cell hyperplasia or the formation of large aggregates of Leydig cells at GD 21 in the developing testis. These morphological changes are preceded by a significant reduction in fetal testosterone production, which likely results in the failure of the Wolffian duct system to develop normally, thereby contributing to the abnormalities observed in the vas deferens, epididymis, and seminal vesicles. Reduced testosterone levels also disturb the dihydrotestosterone (DHT)-induced development of the prostate and external genitalia by reducing the amount of DHT that can be produced from testosterone by 5α-reductase. Because DHT is required for the normal apoptosis of nipple anlage in males and also for growth of the perineum to produce the normal male AGD, changes in AGD and nipple retention are consistent with phthalate-induced reduction in testosterone levels. Although testicular descent also requires normal testosterone levels, another Leydig cell product, insl3 (insulin-like factor 3), also plays a role. Phthalate exposure has been shown to decrease insl3 gene expression and mice in which the insl3 gene has been deleted show complete cryptorchidism.

1.3 The Phthalate Syndrome in Other Species (excluding humans)

Although the literature is replete with information about the phthalate syndrome in rats, there is, interestingly, a relative dearth of information about the phthalate syndrome in other species. In a study by Higuchi *et al.*, (2003), **rabbits** were exposed orally to 0 or 400 mg DBP/kg/day from GD 15-29 and male offspring were examined at 6, 12, and 25 weeks of age. The most pronounced effects observed were decreased testes weights at 12 weeks and accessory gland weights at 12 and 25 weeks as well as abnormal semen characteristics, e.g., decreased sperm concentration/total sperm/normal sperm and an increase in acrosome-nuclear defects. In a study by Gaido *et al.,* (2007), **mice** were exposed 0, 250, or 500 mg DBP/kg/day from GD 16-18, male fetuses were collected on day 19, and their testes were removed for histopathology. Similar to the rat, DBP significantly increased seminiferous cord diameter, the number of multinucleated gonocytes per cord, and the number of nuclei per multinucleated gonocyte. In a separate set of experiments, dosing with levels as high as 1500 mg DBP/kg/day from GD 14-16 did not significantly affect fetal testicular testosterone concentration even though the plasma concentrations of MBP in mice were equal to or greater than the concentration in maternal and fetal rats. In a third set of experiments, *in utero* exposure to DBP led to the rapid induction of immediate early genes, similar to the rat; however, unlike the rat, expression of genes involved in cholesterol homeostasis and steroidogenesis were not decreased. In another study, reported only in abstract form, Marsman (1995) exposed **mice** to 0, 1, 250, 2,500, 5,000, 7,500, 10, 000 or 20,000 ppm DBP in feed during gestation and lactation. No pups were delivered in the 20,000 ppm group and only 1 pup survived past lactation day 1 in the 10,000 ppm group. Although the author states that "No treatment-related gross lesions were identified at necropsy, and no histopathological lesions definitively associated with treatment were observed in male or female mice in the 7,500 ppm group," he also states that "Developmental toxicity and fetal and pup mortality were suggested at concentrations as low as 7,500 ppm." Two studies have been published on the toxicity of phthalates (specifically DBP/MBP) in marmosets. In one study (Hallmark *et al*., 2007), 4 day old **marmosets** were administered 500 mg/kg/day MBP for 14 days after which blood was obtained for the measurement of testosterone levels and the testes were removed for histopathological examination. In a second acute study, nine males 2-7 days of age were administered a single oral dose of 500 mg/kg/day, and a blood sample was obtained 5 hours later for measurement of testosterone levels. Results showed that MBP did suppress testosterone production after an acute exposure; however, this suppression of testosterone production was not observed when measurements were taken 14 days after the beginning of exposure to MBP. The authors speculate that the initial MBP-induced inhibition of steroidogenesis in the neonatal marmoset leads to a "reduced negative feedback and hence a compensatory increase in LH secretion to restore steroid production to normal levels." In a follow up study, McKinnell *et al.*, (2009) exposed pregnant marmosets from ~7-15 weeks gestation with 500 mg/kg/day MBP, and male offspring were studied at birth (1-5 days; n= 6). Fetal exposure to 500 mg/kg/day MBP did not affect gross testicular morphology, reproductive tract development, testosterone levels, germ cell number and proliferation, Sertoli cell number or germ:Sertoli cell ratio.

1.4 Mechanism of Action

Initial mechanistic studies centered on phthalates acting as environmental estrogens or antiandrogens; however, data from various estrogenic and antiandrogenic screening assays clearly showed that while the parent phthalate could bind to steroid receptors, the developmentally toxic monoesters exhibited little or no affinity for the estrogen or androgen receptors (David, 2006). Another potential mechanism of phthalate developmental toxicity is through PPARα. Support for this hypothesis comes from data showing that circulating testosterone levels in PPARα-null mice were increased following treatment with DEHP compared with a decrease in wild-type mice, suggesting that PPARα has a role in postnatal testicular toxicity. PPARα activation may play some role in the developmental toxicity of nonreproductive organs (Lampen *et al.*, 2003); however, data linking PPARα activation to the developmental toxicity of reproductive organs is lacking.

Because other studies had shown that normal male rat sexual differentiation is dependent upon three hormones produced by the fetal testis, i.e., anti-Mullerian hormone produced by the Sertoli cells, testosterone produced by the fetal Leydig cells, and insulin-like hormone 3 (insl3), several laboratories conducted studies to determine whether the administration of specific phthalates to pregnant dams during fetal sexual differentiation that caused demasculinization of the male rat offspring would also affect testicular testosterone production and insl3 expression. Studies by Wilson *et al.*, (2004), Howdeshell *et al.*, (2007), and Borch *et al.*, (2006b) reported significant decreases in testosterone production and insl3 expression after DEHP, DBP, BBP, and by DEHP + DBP (each at one half of its effective dose). The study of Wilson *et al.*, (2004) also showed that exposure to DEHP (and similarly DBP and BBP) altered Leydig cell maturation resulting in reduced production of testosterone and insl3, from which they further proposed that the reduced testosterone levels result in malformations such as hypospadias, whereas reduced insl3 mRNA levels lead to lower levels of this peptide hormone and abnormalities of the gubernacular ligament (agenesis or elongated and filamentous) or freely moving testes (no cranial suspensory or gubernacular ligaments). Together, these studies identify a plausible link between inhibition of steroidogenesis in the fetal rat testes and alterations in male reproductive development. In addition, other phthalates that do not alter testicular testosterone synthesis (DEP; Gazouli *et al.*, 2002) and gene expression for steroidogenesis (DEP and DMP; Liu *et al.*, 2005) also do not produce the "phthalate syndrome" malformations produced by phthalates that do alter testicular testosterone synthesis and gene expression for steroidogenesis (Gray *et al.*, 2000; Liu *et al.*, 2005).

Complementary studies have also shown that exposure to DBP *in utero* leads to a coordinated decrease in expression of genes involved in cholesterol transport (peripheral benzodiazepine receptor [PBR], steroidogenic acute regulatory protein [StAR], scavenger receptor class B1 [SR-B1]) and steroidogenesis (Cytochrome P450 side chain cleavage [P450scc], cytochrome P450c17 [P450c17], 3β-hydroxysteroid dehydrogenase [3β-HSD]) leading to a reduction in testosterone production in the fetal testis (Shultz *et al.*, 2001; Barlow and Foster, 2003; Lehmann *et al.*, 2004). Interestingly, Lehmann *et al.*, (2004) further showed that DBP induced significant reductions in SR-B1, 3β-HSD, and c-Kit (a stem cell factor produced by Sertoli cells that is essential for normal gonocyte proliferation and survival) mRNA levels at doses (0.1 or 1.0 mg/kg/day) that approach maximal human exposure levels. The biological significance of these data are not known given that no statistically significant observable adverse effects on male reproductive tract development have been identified at DBP dose <100 mg/kg/day and given that fetal testicular testosterone is reduced only at dose levels equal to or greater than 50 mg/kg/day.

Thus, current evidence suggests that once the phthalate monoester crosses the placenta and reaches the fetus, it alters gene expression for cholesterol transport and steroidogenesis in Leydig cells. This in turn leads to decreased cholesterol transport and decreased testosterone synthesis. As a consequence, androgen-dependent tissue differentiation is adversely affected, culminating in hypospadias and other features of the phthalate syndrome. In addition, phthalates (DEHP, DBP) also alter the expression of insl3 leading to decreased expression. Decreased levels of insl 3 result in malformations of the gubernacular ligament, which is necessary for testicular descent into the scrotal sac.

Summary of Mechanism of Action Studies

PE	1	2	3	4	5	6	7	8	9
DBP	↓	↓		↓		↓	↓	↓	
BBP	↓	↓							
DEHP	↓	↓	↓	↓	↓	↓	↓	↓	↓
DEHP+DBP	↓	↓	↓	↓					
DNOP									
DINP	↓	↑	↓	↓	↑			↑	
DIDP									
DMP									
DEP									
DIBP	↓	↓		↓		↓		↓	↓
DPENP	↓	↓	↓	↓					
ATBC									
DEHA									
DINX									
DEHT									
TOTM									
TPIB									

1 = Testosterone
2 = INSL3 (Insulin-like Factor 3)
3 = CYP11A (Rate-limiting enzyme responsible for the conversion of cholesterol to pregnenolone)
4 = StAR = Steroidogenic Acute Regulated Protein, involved in mitochondrial cholesterol uptake
5 = LH = Lutenizing Hormone
6 = SR-B1 = Scavenger Receptor B-1, responsible for cholesterol uptake by Leydig cells
7 = PBR = Peripheral Benzodiazepene Receptor, involved in mitochondrial cholesterol uptake
8 = CYP450scc = Cytochrome P450 side chain cleavage enzyme, steroid converting enzyme
9 = SF-1 = Nuclear Receptor Steroidogenic Factor-1, regulates expression of genes involved in steroidogenesis

1.5 Cumulative Exposures to Phthalates

In a 2007 study, Howdesheshell et al., reported the results of the cumulative effects of DBP and DEHP on male rat reproductive tract development, steroid hormone production, and gene expression following exposure of Sprague Dawley rats on GD 8-18. Pregnant rats were gavaged with vehicle control, 500 mg/kg DBP alone, 500 mg/kg DEHP alone, or a combination of DBP and DEHP (500 mg/kg for each phthalate). The mixture of DBP + DEHP elicited dose-additive effects, i.e., increased incidence epididymal agenesis and reduced androgen-dependent organ weights as well as decreased fetal testosterone, and expression of insl3 and cyp11a.

In a follow-up publication, Howdeshell *et al.*, (2008) reported studies in which they characterized the dose response effects of six individual phthalates (BBP, DBP, DEHP, DEP, DIBP, and DEP) on GD 18 testicular testosterone production following exposure of Sprague Dawley rats on GD 8-18. Results showed that testosterone production was significantly reduced at doses of 300 mg/kg/day or higher of BBP, DBP, DEHP, and DIDP and at doses as low as 100 mg/kg/day of DPP. In a follow up study, dams were dosed via gavage from GD 8-18 with either vehicle or 7 dose levels of a mixture of BBP, DBP, DEHP, DIBP (each at 300 mg/kg/day) plus DIPENP at 100 mg/kg/day. This mixture was administered at 100, 80, 60, 40, 20, 10, and 5% of the top dose (1300 mg/kg/day). Administration of the mixture of five antiandrogenic phthalates reduced fetal testicular testosterone production at doses of 26 mg/kg/day (20% of the top dose, which contains BBP, DBP, DEHP, and DIBP at 60 mg/kg/day per chemical and 20 mg DIPENP/kg/day) and higher. The authors conclude that their data demonstrate that "individual phthalates with a similar mechanism of action can elicit cumulative, dose additive effects on fetal testosterone production and pregnancy when administered as a mixture."

1.6 Developmental Toxicity of Phthalates in Rats

The goal of this section is to systematically review the published, peer-reviewed literature reporting the *in utero* exposure of phthalates in pregnant rats. After careful consideration by the committee, this review is limited to the 3 permanently banned phthalates (DBP, BBP, and DEHP), the 3 phthalates currently on an interim ban (DNOP, DINP, and DIDP), and 8 other phthalates (DMP, DEP, DPENP/DPP, DIBP, DCHP, DHEXP, DIOP, and DPHP). Because the first six of these phthalates were extensively reviewed by a phthalates expert panel in a series of reports from the NTP Center for the Evaluation of Risks to Human Reproduction in 2002, our review of these phthalates begins with a brief summary of these NTP reports, which is then followed by a review of the literature since those reports. For the 8 other phthalates that were not reviewed by the NTP panel, the following review covers all the relevant studies available to the committee. From the available literature for each of these 10 phthalates, we then identified the most sensitive developmentally toxic endpoint in a particular study as well as the lowest dose that elicited that endpoint (NOAEL). Finally, we evaluated the "adequacy" of particular studies to derive a NOAEL. Our criteria for an adequate study from which a NOAEL could be derived are: 1) at least 3 dose levels and a concurrent control should be used, 2) the highest dose should induce some developmental and/or maternal toxicity and the lowest dose level should not produce either maternal or developmental toxicity, 3) each test and control group should have a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy, and 4) pregnant animals need to be exposed during the appropriate period of gestation. In addition, studies should follow the OECD Guideline For The testing Of Chemicals (OECD 414, adopted 22 January 2001).

As part of the charge to the committee, we were also asked to evaluate the potential developmental toxicity of phthalate substitutes. The phthalate substitutes include acetyl tributyl citrate (ATBC), di (2-ethylhexyl) adipate (DEHA), diisononyl 1,2-dicarboxycyclohexane (DINX), di (2-ethylhexyl) terephthalate (DEHT), trioctyl trimellitate (TOTM), and 2,2,4-trimethyl-1,3-pentanediol-diisobutyrate (TPIB).

2 Permanently Banned Phthalates (DBP, BBP, DEHP)

2.1 Di-n-Butyl Phthalate (DBP) (84-74-2)

2.1.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report on the reproductive and developmental toxicity of Di-n-butyl phthalate (DBP) (NTP, 2000) concludes that, as of their report, the expert panel could locate “no data on the developmental or reproductive toxicity of DBP in humans.” However, on the basis of available animal data the panel concluded that it “has high confidence in the available studies to characterize reproductive and developmental toxicity based upon a strong database containing studies in multiple species using conventional and investigative studies. When administered via the oral route, DBP elicits malformations of the male reproductive tract via a disturbance of the androgen status: a mode of action relevant for human development. This anti-androgenic mechanism occurs via effects on testosterone biosynthesis and not androgen receptor antagonism. DBP is developmentally toxic to both rats and mice by the oral routes; it induces structural malformations. A confident NOAEL of 50 mg/kg bw/day by the oral route has been established in the rat. Data from which to confidently establish a LOAEL/NOAEL in the mouse are uncertain.” These statements are made primarily on the basis of studies by Ema *et al.*, (1993; 1994; 1998) and Mylchreest *et al.*, (1998; 1999; 2000). Finally, studies by Saillenfait *et al.*, (1998) and Imajima *et al.*, (1997) indicated that the monoester metabolite of DBP is responsible for the developmental toxicity of DBP.

2.1.2 Relevant Studies Published Since the 2002 Summary of the NTP-CERHR Report

Zhang *et al.*, (2004) reported a study in which rats were given DBP by gavage at levels of 0, 50, 250 and 500 mg/kg bw/day from GD 1 to PND 21. “Severe damage to the reproductive system of mature F1 male rats included testicular atrophy, underdeveloped or absent epididymis, undescended testes, obvious decline of epididymal sperm parameters, total sperm heads per g testis, decrease of organ/body weight ratio of epididymis and prostate was observed in the group treated with 250 mg/kg bw/day and higher. A NOAEL for developmental toxicity of DBP was 50 mg/kgBW/day was established based upon pup body weight and male reproductive lesions.

Lee *et al.*, (2004) reported a study in which Sprague-Dawley rats were given DBP at dietary concentrations of 0, 20, 200, 2000, and 10,000 ppm from GD 15 to PND 21. At PND 11 in males, a significant reduction of spermatocyte development was observed at 2000 ppm and above, whereas at PND 21 a significant reduction of testicular spermatocyte development was observed at 20 ppm and above and decreased epididymal ductal cross section at 2000 ppm and above. The authors also noted significant adverse effects on mammary gland development in females at 20 ppm and above on PND 21 but not on PND 11 or 20.

Howdeshell *et al.,* (2007) reported a study in which pregnant Sprague Dawley rats were gavaged on GD 14-18 with doses of DBP or DEHP at 500 mg/kg; or a combination of DBP and DEHP (500 mg/kg each chemical). DBP and DEHP significantly reduced anogenital distance on PND 3, number of areolae per PND 14 males, and increased the number of nipples per adult male, whereas the DBP + DEHP dose increased the incidence of these reproductive malformations by more than 50%. They concluded that "individual phthalates with a similar mechanism of action, but with different active metabolites (monobutyl phthalate versus monoethylhexyl phthalate), can elicit dose-additive effects when administered as a mixture.

Jiang *et al.,* (2007) reported a study in which timed-mated rats were given DBP by gastric intubation at doses of 0, 250, 500, 750, or 1000 mg/kg bw/day from GD 14-18. DBP significantly increased the incidence of cryptorchidism in male pups at doses of 250, 500, and 750 mg/kg bw/day and the incidence of hypospadias and a decrease in anogenital distance at doses of 500 and 750 mg/kg bw/day. They also reported significant decreases in serum testosterone concentration in PND 70 male offspring at DBP doses of 250, 500, and 750 mg/kg bw/day.

Mahood *et al.,* (2007) reported a study in which time-mated Wistar rats were given DBP by gavage at doses of 0, 4, 20, 100 or 500 mg/kg/day from GD 13.5 to either 20.5 or 21.5.

Struve *et al.,* (2009) reported a study in which pregnant Sprague Dawley CD rats were given DBP at doses of 0, 100, and 500 mg/kg/day via the diet from GD 12-19. DBP significantly decreased the anogenital distance in male offspring at 500 mg/kg/day, significantly reduced fetal testicular testosterone concentrations at 100 and 500 mg/kg/day when measured at 24 hours after removal of DBP from the diet and at 500 mg/kg/day when measured 4 hours after removal of DBP from the diet, and induced a significant dose-dependent reduction in testicular mRNA concentrations of scavenger receptor class B, member 1; steroidogenic acute regulatory protein; cytochrome P45011a1; and cytochrome P45017a1 at 100 and 500 mg/kg/day when evaluated 4 hr after the end of dietary exposure on GD 19.

Kim *et al.,* (2010) reported a study in which pregnant Sprague Dawley rats were given DBP at doses of 0, 250, 500, or 700 mg/kg/day on GD 10-19. DBP significantly increased the incidence of hypospadias and cryptorchidism in male offspring, decreased the weights of the testis and epididymis, decreased the anogenital distance, and decreased the levels of dihydrotestosterone and testosterone in rats treated with DBP at 700 mg/kg/day.

Studies cited above are summarized in Table A-1.

434 **Table A-1** DBP developmental toxicity studies—antiandrogenic effects.

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Mylchreest *et al.*, (2000)	**DBP**	**S-D**	**0, 0.5, 5, 50, 100, 500 mg/kg/d**	**GD 12-21; gavage**	**19-20; 11@ 500 mg/kg/d**	**19-20; 11@ 500 mg/kg/d**	**no**	**↓male AGD; ↑hypospadias @ 500mg/kg/d; ↑nipple retention @ 100mg/kg/d**	**50 mg/kg/d**
Higuchi *et al.*, (2003)	DBP	Rabbits	0, 400 mg/kg/d	GD 15-29; PNW 4-12	5-8	5-8	no	↑hypospadia, cryptorchid testes; ↓ testes weight, sperm concentration	**NA**
Zhang *et al.*, , (2004)	DBP	S-D	0, 50, 250, 500 mg/kg/d	GD1-PND21 gavage	20	14-16	no	↓Pup body weight; ↓male AGD @PND4; ↓sperm @250mg/kg/d	**50 mg/kg/d**
Lee *et al.*, (2004)	DBP	S-D	0, 20, 200, 2000, 10,000 ppm	GD 15-PND 21 diet	6-8	6-8	Yes; maternal body weight @ 10,000ppm	↓male AGD;↑ nipple retention @ 10,000ppm; ↓Sperm development @ 20ppm	**<20ppm Based upon ↓Sperm development @ 20ppm**
Carruthers & Foster (2005)	DBP	S-D	0, 500 mg/kg/d	GD 14-15, 15-16, 16-17, 17-18, 18-19, 19-20	9-16		no	↓male AGD, ↓epididymal weight, & epididymal agenesis @ 500 mg/kg/d after exposures on GD 16-18	**NA**
Howdeshell *et al.*, (2007)	DBP; DBP+ DEHP	S-D	0, 500 mg/kg/d	GD 14-18 gavage	6	6	no	↓male AGD@ 500mg/kg/d	**NA**
Jiang *et al.*, (2007)	DBP	S-D	0, 250, 500,750, 1000 mg/kg/d	GD 14-18 gavage	10	10	Yes @ 750 & 1000 mg/kg/d	↓male AGD and ↑hypospadias @ 500 & 750 mg/kg/d: ↑ cryptorchidism and serum testosterone concentration @ 250 mg/kg/d	**<250 mg/kg/d based upon ↑ cryptorchidism and serum testosterone concentration @ 250 mg/kg/d**
Mahood *et al.*, (2007)	DBP	Wistar	0, 4, 20, 100, 500 mg/kg/day	GD 13.5-20.5/21.5	3-16	3-16	Not reported	↑Cryptorchidism@ 500mg/kg/day;↑ MNGs@ 100mg/kg/day;↓testostero	**20 mg/kg/d based upon ↓ testosterone@**

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
								ne@ 100mg/kg/day	**100mg/kg/day**
Howdeshell *et al.*, (2008)	DBP	S-D	0, 33, 50, 100, 300, 600 mg/kg/d	GD 8-18	3-4	3-4	no	↓testicular testosterone production @ 300 mg/kg/d and above	
Struve *et al.*, (2009)	DBP	S-D	0, 100, 500 mg/kg/d	GD 12-19 diet	9	9	no	↓male AGD @ 500 mg/kg/d; ↓fetal testosterone @ 100 mg/kg/d @24 hrs	**<100mg/kg/d Based upon ↓fetal testosterone @ 100 mg/kg/d @24 hrs**
Kim *et al.*, (2010)	DBP	S-D	0, 250, 500, 700 mg/kg/d	GD 10-19	?	?	NA	↓male AGD and ↑ nipple retention @ 500 mg/kg/d and above; ↑ cryptorchidism and hypospadias @ 700 mg/kg/d; ↓ serum DHT and testosterone @ 700 mg/kg/d	**250 mg/kg/d based upon ↓male AGD and ↑ nipple retention @ 500 mg/kg/d**

2.1.3 Consensus NOAEL for DBP

The studies listed in Table A-1 clearly indicate that DBP is developmentally toxic when exposure occurs later in gestation (during fetal development). Although several of these studies report a specific NOAEL, not all studies were amenable to the calculation of a NOAEL. For example, the studies of Carruthers and Foster (2005) and Howdeshell *et al.,* (2007) were designed to obtain mechanistic data and therefore did not include multiple doses. The study by Higuchi *et al.,* (2003) is interesting because it demonstrates that DBP produces effects in rabbits similar to those seen in the rat, but again, only one dose was used, thus precluding the determination of a NOAEL. Other studies (Lee *et al.,* 2004; Jiang *et al.,* 2007; Struve *et al.,* 2009), which did use at least 3 doses, used fewer than the recommended number of animals/dose (20/dose). The study by Kim *et al.,* (2010) used multiple doses; however, it was difficult to ascertain how many animals were used per dose. The studies of Mylchreest *et al.,* (2000) and Zhang *et al.,* (2004), on the other hand, used multiple doses and approximately 20 animals/dose. In the absence of maternal toxicity, Mylchreest reported an increase in nipple retention in male pups at 100 mg/kg/d, whereas Zhang *et al.,* reported increased male AGD at 250 mg/kg/day. In both studies, these LOAELs correspond to a NOAEL of 50 mg/kg/day. A NOAEL of 50 mg/kg/d is supported by the study of Mahood *et al.,* (2007), which reported a LOAEL of 100 mg/kg/day for decreased fetal testosterone production after exposure to DBP. Using the data of Mylchreest *et al.,* (2000) and Zhang *et al.,* (2004), the CHAP committee assigns a NOAEL of 50 mg/kg-d for DBP.

2.2 Butyl Benzyl Phthalate (BBP) (85-68-7)

2.2.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report (NTP, 2003a)on the reproductive and developmental toxicity of butyl benzyl phthalate (BBP) concludes that, as of their report, the expert panel could locate “no human data” on the developmental or reproductive toxicity of BBP. However, on the basis of available animal data the panel concluded that (1) “the data in rats and mice are adequate for a prenatal assessment of fetal growth, lethality, and teratogenicity.” (2) “None of the studies included a postnatal evaluation of androgen-regulated effects (e.g., nipple retention, testicular descent, or preputial separation) that were the most sensitive indicators of developmental toxicity of DBP.” (3) “Prenatal studies with BBP monoesters (MBP and MBZP) were sufficient to determine that both metabolites contribute to developmental toxicity.” These statements are based primarily upon the studies by Field *et al.,* (1989), Ema *et al.,* (1990; 1992; 1995), and Price *et al.,* (1990). The studies by Field *et al.,* (1989) and Ema *et al.,* (1992) reported that the developmental NOAELs in Sprague Dawley and Wistar rats ranged from 420 to 500 mg/kg bw/day, respectively. The NTP-CERHR panel noted, however, that it was not confident in these NOAELs because the prenatal studies (GD 7-15) examined would not detect effects such as altered anogenital distance, retained nipples, delays in acquisition of puberty, and malformations of the post-pubertal male reproductive system.

2.2.2 Relevant Studies Published Since the 2002 Summary of the NTP-CERHR Report

Gray *et al.,* (2000) reported a study in which Sprague Dawley rats were given BBP (as well as DEHP, DINP, DEP, DMP, or DOTP) by gavage at 0 or 750 mg/kg/day from GD 14 to PND 3.

Males in the BBP-treated groups exhibited significantly shortened AGD, female-like areolas/nipples, decreased testes weights, and a significant incidence of reproductive malformations (cleft phallus, hypospadias). The authors note that of the phthalates tested, BBP, DEHP, and DINP altered sexual differentiation whereas DOTP, DEP, and DMP did not. They also noted that BBP and DEHP were of equivalent potency, whereas DINP was about an order of magnitude less active.

Nagao *et al.*, (2000) reported a two-generation study in which Sprague Dawley rats were exposed to oral doses of BBP at 0, 20, 100, and 500 mg/kg/day from 2 weeks before mating through cohabitation, gestation, lactation until postpartum day 21. BBP produced a significant reduction in AGD in male pups and increased AGD in female pups at 500 mg/kg/day. In addition, preputial separation in male pups was delayed and serum concentrations of testosterone were decreased at 500 mg/kg/day.

Piersma *et al.*, (2000) reported a study in which Harlan Cpb-WU rats were gavaged with BBP at doses of 0, 270, 350, 450, 580, 750, 970, 1250, 1600, or 2100 mg/kg bw/day for GD 6-15 or GD 6-20. BBP exposure was associated with skeletal anomalies (reduced rib size, fusion of two ribs, and incompletely ossified or fused sternebrae) at the middle or high doses (exact doses not specified). Anopthalmia was found in several pups after exposure to 750 and 970 mg/kg/day after exposure from day 6-15 and 6-20. Cleft palate was found in two cases at 750 mg/kg/day and one at 1250 mg/kg/day after exposure from GD 6-20. Two cases of exencephaly were observed in the 750 mg/kg/day group after exposure from GD6-20. Finally, the incidence of retarded fetal testicular caudal migration increased in a dose-related fashion.

Saillenfait *et al.*, (2003) reported studies in which OF1 mice or Sprague Dawley rats were given oral doses of BBP at 0, 280, 560, 1120, or 1690 mg/kg on GD 8 and 10. Similarly mice and rats were given oral doses of mono-n-butyl phthalate (MBP) at doses of 0, 200, 400, 800, or 1200 mg/kg/day or mono-benzyl phthalate (MBzP) at doses of 0, 230, 460, 920, or 1380 mg/kg/day. In mice external malformations (exencephaly, facial cleft, meningocele, spina bifida, onphalocele, acephalostomia) were seen in animals dosed with 560 mg/kg/day BBP and above, 200 mg/kg MBP and above, and 920 mg/kg/day and above. In rats 5% of fetuses were exencephalic at the highest BBP dose, however, this effect did not appear to reach statistical significance.

Tyl *et al.*, (2004) reported two-generation studies in which rats were exposed to dietary butyl benzyl phthalate (BBP) at concentrations of 0, 750, 3750, and 11,250 ppm during a 10-week pre-breeding period and then during mating, gestation, and lactation. There were no effects on parents or offspring at BBP exposures of 750 ppm (50 mg/kg/day). At 3750 ppm (250 mg/kg/day), BBP induced a reduction in AGD in F1 and F2 male offspring. At 11,250 ppm (750 mg/kg/day), BBP induced a reduction in F1 and F2 male AGD and body weights/litter during lactation, delayed acquisition of puberty in F1 males and females, retention of nipples and areolae in F1 and F2 males, and male reproductive system malformations (hypospadias, missing epididymides, testes, prostate, and abnormal reproductive organ size and/or shape). The authors concluded that the NOAEL for F1 parental systemic and reproductive toxicity was 3750ppm (250 mg/kg/day), the offspring toxicity NOAEL was 3750ppm (250 mg/kg/day), and the NOAEL for offspring toxicity was 750 ppm (50 mg/kg/day).

Studies cited above are summarized in Table A-2.

Table A-2 BBP developmental toxicity studies—antiandrogenic effects.

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Gray *et al.*, (2000)	BBP	S-D	0, 750 mg/kg/d	GD 14-PND 1	8	8	no	↓Male AGD; ↓testes weight; ↑nipple retention;↓ epididymal weight	**NA**
Nagao *et al.*, (2000)	BBP	S-D	0, 20, 100, 500 mg/kg/d	Two generation study; GD 1-PND 21	25	25	Yes; increased liver, kidney & thyroid gland weights @ 500 mg/kg/d	↓Male & female pup weight on PND 0 @ 100mg/kg/d and above; ↓male AGD & ↑female AGD @ 500 mg/kg/d; ↓serum testosterone @ 500 mg/kg/d	**100 mg/kg/d based upon ↓male AGD & ↑female AGD @ 500 mg/kg/d; ↓serum testosterone @ 500 mg/kg/d**
Piersma *et al.*, (2000)	BBP	Harlan Cpb-WU	0, 270, 350, 450, 580, 750, 970, 1250, 1600, 2100 mg/kg/d	GD 6-20 (also GD 6-15)	10		Yes; death @ highest two doses; increased resorptions @ 750 mg/kg/d and above	Dose-dependent retardation of fetal testicular caudal migration & ↓fetal testis weight	**Reported a benchmark dose of 95 mg/kg/d for testicular dislocation**
Ema and Myawaki (2002)	BBP	Wistar rat	0, 250, 500, 1000 mg/kg/d	GD 15-17	16	16	Yes, decreased maternal body weight @ 500 mg/kg/d and above	↑incidence of undescended testes and ↓ male AGD @ 500 mg/kg/d and above	**250 mg/kg/d**
Saillenfait *et al.*, (2003)	BBP	S-D; OF1 mice	0, 280, 560, 1120, 1690 mg/kg/d	GD 8 & 10	Rat 7-13; mice 15-23				**NA**
Saillenfait *et al.*, (2003)	MBP	S-D: OF1 mice	0, 400, 800, 1200 mg/kg/d	GD 8 & 10	Rat 7-13; mice 15-23				**NA**
Saillenfait *et al.*, (2003)	MBzP	S-D; OF1 mice	230, 460, 920, 1380 mg/kg/d	GD 8 & 10	Rat 7-13; mice 15-23				**NA**

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Ema *et al.*, (2003)	MBP	Wistar rat	0, 167, 250, 375 mg/g/d	GD 15-17	16	16	Yes, decreased maternal weight gain on days 18-21 @ 167 mg/kg/d and higher	↑incidence of undescended testes and ↓male AGD @ 250 mg/kg/d and above	**167 mg/kg/d on the basis of ↑incidence of undescended testes and ↓male AGD @ 250 mg/kg/d and above**
Tyl *et al.*, (2004)	BBP	CD	0, 750, 3750, 11,250 ppm	Two generation study; GD 1-PND 21	20	20	Yes; reduced maternal body weight during gestation & lactation @ 11,250 ppm	F1 & F2 ↓ male AGD @ 3750 ppm and above; F1 ↓ testes weight @ 3750 ppm and above; F1 and F2 ↑nipple retention @ 11,250 ppm; F1 ↑male reproductive tract malformations, e.g., hypospadias @ 11,250ppm	**750 ppm (=50 mg/kg/d) on the basis of F1 & F2 ↓ male AGD @ 3750 ppm and above; F1 ↓ testes weight @ 3750 ppm and above**
Howdeshell *et al.*, (2008)	BBP	S-D	0, 100, 300, 600, 900	GD 8-18	2-9	2-9	yes	↓ testicular testosterone production @ 300 mg/kg/d and above	

2.2.3 Consensus NOAEL for BBP

The study of Gray *et al.*, (2000)could not be used to generate a NOAEL because only one dose was used, whereas, the study by Saillenfait *et al.*, (2003) could not be used because the sensitive period for the disruption of male fetal sexual development in the rat (GD 15-21) was not included in the study's exposure protocol (GD 7-13). The remaining studies were judged to be adequate for determining a NOAEL for BBP. In the Nagao *et al.*, (2000) study, the CHAP committee calculated a NOAEL of 100 mg/kg/d, Piersma *et al.*, (2000) calculated a benchmark dose of 95 mg/kg/d, we calculated a NOAEL of 250 mg/kg/d from the data of the Ema and Myawaki (2002) study and 167 mg/kg/d from the data of Ema *et al.*, (2003) and, finally, Tyl *et al.*, (2004), calculate a NOAEL of 50 mg/kg/day from data generated in their two-generation study. Thus, the NOAELs range from a low of 50 to a high of 250 mg/kg/day. The CHAP committee decided to take the conservative approach and recommends a NOAEL of 50 mg/kg/day for BBP.

2.3 Di(2-ethylhexyl) Phthalate (DEHP) (117-81-7)

2.3.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report on the reproductive and developmental toxicity of Di(2-ethylhexyl) phthalate (DEHP) concludes that, as of their report (Kavlock *et al.*, 2002), "There were no studies located on the developmental toxicity of DEHP or its metabolites in humans." In contrast, 41 prenatal developmental toxicity studies in animals in which assessments were made just prior to birth "were remarkably consistent." "DEHP was found to produce malformations, as well as intrauterine death and developmental delay. The pattern of malformations seen in fetuses is consistent across studies. It included morphological abnormalities of the axial skeleton (including tail), cardiovascular system (heart and aortic arch), appendicular skeleton (including limb bones, finger abnormalities), eye (including open eye), and neural tube (exencephaly). The NOAEL based upon malformations in rodents was ~40mg/kg bw/day and a NOAEL of 3.7-14mg/kg bw/day was identified for testicular development/effects in rodents." The panel noted that the examination of effects during late gestation and neonatal periods is "quite recent and incomplete." The panel also expressed concerns about *in utero* exposures in humans given that (1) "exposures may be on the order of 3-30 μg/kg bw/day", (2) "the most relevant rodent data suggest a NOAEL for testis/developmental effects of 3.7-14 mg/kg bw/day," (3) "even time-limited exposures are effective at producing irreversible effects," and (4) the active toxicant MEHP passes into breast milk and crosses the placenta."

In a 2006 NTP-CERHR expert panel update on the reproductive and developmental toxicity of DEHP (NTP, 2006), the panel reviewed several human studies and concluded that there is "insufficient evidence in humans that DEHP causes developmental toxicity when exposure is prenatal … or when exposure is during childhood." These conclusions were based upon the reports of Latini *et al.*, (2003), Swan *et al.*, (2005), Rais-Bahrami *et al.*, (2004), and Colon *et al.*, (2000). The panel also reviewed additional animal studies published since their first report and on the basis of these reports concluded that there is "sufficient evidence that DEHP exposure in rats causes developmental toxicity with dietary exposure during gestation and/or early postnatal life at 14-23 mg/kg bw/day as manifested by small or absent male reproductive organs. Multiple other studies showed effects on the developing male reproductive tract at higher dose levels. These conclusions are supported by studies of Shirota *et al.,* (2005), Moore *et al.,* (2001), Borch *et al.*, (Borch *et al.*, 2003; 2004; 2006b), Jarfelt *et al.,* (2005), Li *et al.,* (2000), Cammack *et al.*, (2003), and Gray *et al.,* (2000).

2.3.2 Relevant Studies Published Since the 2006 Update Summary of the NTP-CERHR Report

Grande *et al.,* (2006) reported studies in which Wistar rats were given DEHP by gavage from GD 6 to lactation day 22 at doses of 0, 0.015, 0.045, 0.135, 0.405, 1.215, 5, 15, 45, 135, and 405 mg/kg bw/day and effects on female rat reproductive development were assessed. DEHP induced a significant delay in the age at vaginal opening at exposures of 15 mg/kg bw/day and above as well as a trend for a delay in the age at first estrus at 135 and 405 mg/kg bw/day. Anogenital distance and nipple development were unaffected. Based upon delayed pubertal development at 15 mg/kg bw/day, the authors set the NOAEL for female reproductive development at 5 mg DEHP/kg bw/day.

Andrade *et al.*, (2006a) reported studies in which Wistar rats were given DEHP by gavage from GD 6 to lactation day 22 at doses of 0, 0.015, 0.045, 0.135, 0.405, 1.215, 5, 15, 45, 135, and 405 mg/kg bw/day and effects on male rat reproductive development were assessed. DEHP induced delayed preputial separation at exposures of 15 mg/kg bw/day and above, increased testis weight on PND 22 at doses of 5, 15, 45, and 135 mg/kg bw/day, and nipple retention and reduced AGD at a dose of 405 mg/kg bw/day. On the basis of increased testis weight on PND 22, the authors set the NOAEL at 1.215 mg DEHP/kg bw/day.

Christiansen *et al.,* (2010) reported studies in which Wistar rats were given DEHP by gavage from GD 7 to PND 16 at doses of 10, 30, 100, 600, or 900 mg DEHP/kg bw/day. DEHP induced decreased AGD, increased incidence of nipple retention, and mild dysgenesis of the external genitalia at 10 mg DEHP/kg bw/day. Higher doses of DEHP induced histopathological effects on the testes, reduced testis weight, and expression of androgen-related genes in the prostate. The authors note that the effects seen at 10 mg/kg bw/day are “consistent with the EU NOAEL of 5 mg/kg bw/day for DEHP.”

Studies cited above are summarized in Table A-3.

605 **Table A-3** DEHP developmental toxicity studies.

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Gray *et al.*, (2000),	DEHP	S-D	0, 750 mg/kg/d	GD 14-PND 1	16	16	Yes, decreased maternal weight gain @ 750 mg/kg/d	Male AGD; testes weight; nipple retention; epididymal weight	**NA**
Moore *et al.*, (2001)	DEHP	S-D	0, 375, 750, 1500 mg/kg/d	GD 3-PND 21	5-8		Yes, decreased maternal weight gain on GD 16-20 at @ 750 and 1500 mg/kg/d	Decreased male AGD; increased nipple retention; increased incidence of permanent nipple retention @ 375 mg/kg/d; increase in incidence of undescended testes; reduced testes, epididymides and glans penis weights; reduced epididymal sperm number @ 750 and 1500 mg/kg/d	**NA**
NTP (2004)	**DEHP**	**S-D**	**1.5, 10, 30, 100, 300, 1000, 7500, 10,000 ppm**					**Increased reproductive organ abnormalities @ 300 ppm (14-23 mg/kg/d) and above**	**100 ppm (3-5 mg/kg/d)**
Borch *et al.*, (2004)	DEHP	Wistar rat	0, 300, 750 mg/kg/d	GD 1- 21	8	8	NA	Decreased testicular testosterone production/content @ 300 & 750 mg/kg/d; reduced male AGD @ 750 mg/kg/d	
Jarfelt *et al.*, (2005)	DEHP	Wistar rat	0, 300, 750 mg/kg/d	GD 7-PND 17	20	11-15	Decreased maternal weight gain @ 300 and 750 mg/kg/d, but not statistically significant	Reduced male AGD, increased incidence of nipple retention & decreased testes and epididymis weights @ 300 and 750 mg/kg/d	

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Shirota *et al.*, (2005)	DEHP	S-D	0, 125, 250, 500 mg/kg/d	GD 7-18	11-12	11	no	↑degeneration of germ cells and hyperplasia of interstitial cells in the fetal testis at 250 mg/kg/d and above	**125 mg/kg/d on basis of ↑degeneration of germ cells and hyperplasia of interstitial cells in the fetal testes at 250 mg/kg/d and above**
Grande *et al.*, (2006)	**DEHP**	**Wistar rat**	**0, .015, .045, .135, 1.215, 5, 15, 45, 136, 405 mg/kg/d**	**GD 6-PND 22**	**11-16**	**11-16**	**no**	**Delay in mean age at vaginal opening @ 15 mg/kg/d and above; no effect on female AGD or nipple retention at any dose**	**5 mg/kg/d based on delay in mean age at vaginal opening @ 15 mg/kg/d**
Andrade et al (2006a)	**DEHP**	**Wistar rat**	**0, .015, .045, .135, 1.215, 5, 15, 45, 136, 405 mg/kg/d**	**GD 6-PND 22**	**11-16**	**11-16**	**no**	**Delay in the age of preputial separation @ 15 mg/kg/d and above; reduced male AGD and increased incidence of nipple retention @ 405 mg/kg/d**	**5 mg/kg/d based on delay in preputial separation**
Howdeshell *et al.*, (2008)	DEHP	S-D	0, 100, 300, 600, 900 mg/kg/d	GD 8-18	4	4	no	↓ testicular testosterone production @ 300 mg/kg/d and above	
Gray *et al.*, (2009)	**DEHP**	**SD rat**	**0, 11, 33, 100, 300 mg/kg/d**	**GD 8-17**	**13-14**	**13-14≤**	**no**	**↑incidence of pups with phthalate syndrome at doses of 11 mg/kg/d and above**	**≤11 mg/kg/d based upon ↑incidence of pups with phthalate syndrome at doses of 11 mg/kg/d and above**
Christiansen *et al.*, (2010)	**DEHP**	**Wistar rat**	**0, 3, 10, 30, 100, 300, 600, 900 mg/kg/d**	**GD 7-21 and PND 1-16**		**13-15 @ 10-100 mg/kg/d; 6-7 @ 300-900 mg/kg/d**	**no**	**Reduced male AGD and increased nipple retention at 10 mg/kg/d**	**3 mg/kg/d based upon ↓male AGD and increased nipple retention LOAEL of 10 mg/kg/d**

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Hannas *et al.*, (2011)	**DEHP**	**SD and Wistar**	**0, 100, 300, 500, 625, 750, 875 mg/kg/day**	**GD 14-18**	**3-6**			**↓testosterone production in both strains @ 300 mg/kg/day and higher;↓expression of insl3 mRNA @ 625 mg/kg/day and higher; ↓ expression of StAR and Cyp11a mRNAs @ 500 mg/kg/day and above**	**100 mg/kg/day based on testosterone LOAEL of 300 mg/kg/day**

2.3.3 Consensus NOAEL for DEHP

The Gray *et al.*, (2000)study could not be used to identify a NOAEL because only one dose was used. The studies of Moore *et al.*, (2001), Borch *et al.*, (2004), Jarfelt *et al.*, (2005), could not be used because in each case the lowest dose used produced a significant effect and therefore a NOAEL could not be determined. The studies of Grande *et al.*, (2006), Andrade *et al.*, (2006a), Gray *et al.*, (2009), and Christiansen *et al.*, (2010) are all well designed studies employing multiple doses at the appropriate developmental window and using relatively large numbers of animals per dose group. Although different phthalate syndrome endpoints were used to set a NOAEL, the resulting NOAELs cluster tightly around a value of 3-11 mg/kg/day. It is noteworthy that this cluster is consistent with the NOAEL identified in the NTP study (4.8 mg/kg-d; Foster *et al.*, 2006). In contrast, using fetal testosterone production as an endpoint, Hannas *et al.*, (2011), reported a LOAEL of 300 mg/kg/day and a NOAEL of 100 mg/kg/day, a NOAEL approximately 10 times the one derived using morphological endpoints. Using a weight-of-evidence approach, the CHAP committee has conservatively set the NOAEL for DEHP at 5 mg/kg/day.

3 Interim Banned Phthalates

3.1 Di-n-octyl Phthalate (DNOP) (117-84-0)

3.1.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report on the reproductive and developmental toxicity of di-n-octyl phthalate (DNOP) (NTP, 2003e) concludes that, as of their report, the expert panel could locate “no data on the developmental or reproductive toxicity of DBP in humans.” The panel reviewed 5 animal studies involving prenatal exposure to DNOP in mice and rats (Singh *et al.*, 1972; Gulati *et al.*, 1985; Hardin *et al.*, 1987; Heindel *et al.*, 1989; Hellwig *et al.*, 1997). It should be noted that in all but one study, exposure to DNOP occurred before gestational day 15 in the rat and day 13 in the mouse. Although they concluded that “available studies do suggest a developmental toxicity response with gavage or i.p. administration with very high doses,” the panel also noted that the limited study designs of the 5 studies reviewed “do not provide a basis for comparing consistency of response in the two species, nor do they allow meaningful assessment of dose-response relationships and determination of either LOAELs or NOAELs with any degree of confidence.” The panel concluded by stating that the “experimental data are insufficient to permit a firm judgment about DNOP’s potential to pose a developmental toxicity hazard to humans.”

3.1.2 Relevant Studies Published Since the 2002 Summary of the NTP-CERHR Report

A PubMed literature search using the terms di-n-octyl phthalate and developmental toxicity or DNOP and developmental toxicity did not uncover any studies since the 2002 summary of the NTP-CERHR report.

3.1.3 Consensus NOAEL for DNOP

Only one study, Saillenfait et al., 2011, was of appropriate design to provide a meaningful NOAEL; however, no anti-androgenic effects were observed in this study. This study did, however, report a dose-related increase in supernumerary ribs at maternally non-toxic doses. Because of the lack of relevant data, a consensus NOAEL could not be determine.

3.2 Diisononyl Phthalate (DINP) (28553-12-0; 68515-48-0)

3.2.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report on the reproductive and developmental toxicity of diisononyl phthalate (DINP) (NTP, 2003c) concludes that, as of their report, the expert panel concluded that there were “no human data located for Expert Panel review.” The panel did review two rat studies evaluating prenatal developmental toxicity of DINP by gavage on GD 6-15 (Hellwig *et al.*, 1997; Waterman *et al.*, 1999), the developmental toxicity of DINP in a two-generation study in rats (Waterman *et al.*, 2000), and a prenatal developmental toxicity of isononyl alcohol, a primary metabolite of DINP (Hellwig and Jackh, 1997). The two rat prenatal studies showed effects on the developing skeletal system and kidney following oral exposures to DINP from GD 6-15, while in the two-generation study in rats effects on pup growth were noted. The prenatal developmental toxicity study with isononyl alcohol provided evidence that this primary metabolite of DINP "is a developmental and maternal toxicant at high (~1000mg/kg) oral doses in rats." From these studies, the panel concluded that the toxicology database "is sufficient to determine that oral maternal exposure to DINP can result in developmental toxicity to the conceptus." The panel also noted that "some endpoints of reproductive development that have been shown to be sensitive with other phthalates, were not assessed." Therefore, the panel recommended that "a perinatal developmental study in orally exposed rats that addresses landmarks of sexual maturation such as nipple retention, anogenital distance, age at testes descent, age at prepuce separation, and structure of the developing reproductive system in pubertal or adult animals exposed through development" should be considered.

3.2.2 Relevant Studies Published Since the 2002 Summary of the NTP-CERHR Report

Gray *et al.,* (2000) reported a study in which Sprague Dawley rats were given DINP (as well as BBP, DEHP, DEP, DMP, or DOTP) by gavage at 0 or 750 mg/kg/day from GD 14 to PND 3. DINP significantly induced increased the incidence of male offspring with areolas (with and without nipple buds) and increased incidence of male offspring with malformations of the androgen-dependent organs and testes The authors note that of the phthalates tested, DINP, BBP, and DEHP altered sexual differentiation whereas DOTP, DEP, and DMP did not. They also noted that DINP was about an order of magnitude less active than BBP and DEHP, which were of equivalent potency.

Masutomi *et al.,* (2003) reported a study in which Sprague-Dawley rats were exposed to DINP in the diet at 0, 400, 4,000, and 20,000 ppm from gestational day 15 to PND 10. DINP significantly reduced maternal weight gain, postnatal weight gain and testis weights before puberty, but did not see any alterations in AGD.

Lee *et al.,* (2006) reported a study in which Wistar-Imamichi rats were exposed to DINP in the diet at 0, 40, 400, 4000, and 20,000 ppm from gestational day 15 to PND 21. The authors reported that DINP induced a reduction in AGD and all levels tested; however, their statistical analyses apparently used the individual fetus rather than the litter as the unit of measurement, thus calling into question their conclusion.

Boberg *et al.,* (2011) reported a study in which Wistar rats were exposed to DINP by gavage at 0, 300, 600, 750, and 900 mg/kg bw/day from gestation day 7 to PND 17. DINP significantly altered testis histology (e.g., multinucleated gonocytes) at 600 mg/kg bw/day and above, increased nipple retention in males at 600 mg/kg bw/day and above, decreased sperm motility at 600 mg/kg bw/day and above, and decreased AGD in males at 900 mg/kg bw/day. The authors also reported a reduction in testicular testosterone levels at all doses tested; however, these reductions did not reach statistical significance, probably due to the small number of litters sampled for this endpoint. On the basis of these results, the authors conclude that the NOAEL for DINP-induced reproductive toxicity in the rat is 300 mg/kg bw/day.

Studies cited above are summarized in Table A-4

Table A-4 DINP developmental toxicity studies.

STUDY	AGENT	STRAIN/ SPECIES	# DOSELEVELS	DOSING REGIMEN	# ANIMALS/ DOSE	# LITTERS/ DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Gray *et al.*, (2000)	DINP	S-D	0, 750	GD 14-PND 3 gavage	14	14	Yes, decreased maternal weight gain @ 750 mg/kg/d	Increased nipple retention	**NA**
Waterman *et al.*, (2000)	DINP	S-D	0, 0.5, 1.0, 1.5 % in one generation study; 0, 0.2, 0.4, 0.8 % in two generation study	One & two generation studies diet	30	?	Yes, decreased maternal weight gain @ 1.0% and above in one generation and 0.8% in two generation studies	CERHR panel concluded that the LOAEL for developmental effects (reduced pup weight) was 143mg/kg/d for the gestational exposure; No effects observed on testicular development, undescended testes, & hypospadias	**CERHR could not establish a NOAEL**
Hass *et al.*, (2003)	DINP	Wistar	0, 300, 600, 750, 900 mg/kg/d	GD 7-17				↑nipple retention on PND 13 @ 600 mg/kg/d and above; ↓male AGD @ 750 mg/kg/d	**300 mg/kg/d based on ↑nipple retention on PND 13 @ 600 mg/kg/d**
Masutomi *et al.*, (2003)	DINP	S-D	0, 400, 4000, 20,000ppm	GD 15-PND 10 diet	5-6	5-6	Yes, decreased maternal weight gain @ 20,000ppm	Decreased absolute & relative prepubertal testes weight @ 20,000ppm	**4000 ppm (?)**
Borch *et al.*, (2004),	DINP	Wistar rat	0, 750 mg/kg/d	GD 1- 21 gavage	8	8	NA	Decreased testicular testosterone production/content	**NA**

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	**NOAEL**
Lee *et al.*, (2006)	DINP	Wistar rat	0, 40, 400, 4000, 20,000ppm	GD 15-PND 21 diet	?	?		Decreased male AGD @ 40ppm and above; increased female AGD @ 20,000ppm; increase in hypothalamic p130 mRNA @ 40 ppm and above	**?**
Adamsson *et al.*, (2009)	DINP	SD	0, 250, 750 mg/kg/d	ED 13.5-17.5 gavage	7-8	7-8	no	Increased P450scc, GATA-4 & Insl-3 mRNAs @ 750mg/kg/d	**250 mg/kg/d on the basis of Increased P450scc, GATA-4 & Insl-3 mRNAs @ 750mg/kg/d**
Boberg *et al.*, (2011)	**DINP**	**Wistar**	**0, 300, 600, 750, 900 mg/kg/d**	**GD 7-PND 17 gavage**	**16**	**10**	**no**	**Increased multinucleated gonocytes & nipple retention @ 600 mg/kg/d and above; decreased testicular testosterone content @ 600 mg/kg/d and AGD @ 900 mg/kg/d**	**300 mg/kg/d reported by authors**
Hannas *et al.*, (2011)	DINP	SD	0, 500, 760, 1000, 1500 mg/kg/day	GD 14-18	3-6	3-6	no	↓fetal testosterone production @ 500 mg/kg/day and above; ↓StaR and Cyp11a mRNA levels @ 1000 mg/kg/day and above	**? somewhere below 500 mg/kg/day based upon testosterone LOAEL**

3.2.3 Consensus NOAEL for DINP

Several of the studies listed in Table A-4 were judged to be inadequate for ascertaining a NOAEL for DINP, e.g., the Gray *et al.*, (2000) study used only one dose and the Matsutomi *et al.*, (2003), Borch *et al.*, (2004), and the Adamsson *et al.*, (2009) studies used relatively small numbers of animals per dose group. In contrast, the Boberg *et al.*, (2011) study used multiple doses (4 plus control), exposure occurred during the developmentally sensitive period (GD 7-PND 17), and used a relatively high number of dams per dose (16). On the basis of increased nipple retention at 600 mg/kg/d, the authors report a NOAEL of 300 mg/kg/d. Furthermore, several of the other studies, although not "adequate" on their own for the determination of a NOAEL for DINP, do provide supporting data. For example, the Hass *et al.*, (2003), 2003 study, reported only as an Abstract, also reported a NOAEL of 300 mg/kg/d based on increased nipple retention. In addition, the Hannas *et al.*, (2011) study found a LOAEL of 500 mg/kg/d based on decreased fetal testosterone production, suggesting that the NOAEL for this endpoint is somewhere below this level. Thus, on the basis of available studies, the CHAP committee assigns the NOAEL for DINP at 300 mg/kg/d.

3.3 Diisodecyl Phthalate (DIDP) (26761-40-0; 68515-49-1)

3.3.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report (NTP, 2003b) on the reproductive and developmental toxicity of diisodecyl phthalate (DIDP) concludes that, as of their report, the expert panel concluded that there were "no human data located for Expert Panel review." The panel did review two developmental toxicity studies in rats (Hellwig *et al.*, 1997; Waterman *et al.*, 1999) and one in mice (Hardin *et al.*, 1987) in which exposure was by gavage from GD 6-15 or 6-13, respectively. The panel also reviewed 2 two-generation reproductive toxicity studies (Exxon, 1997; ExxonMobil, 2000) in which developmental effects were observed. Although prenatal exposures of DIDP to mice did not result in any observable developmental or maternal toxicity, the prenatal rat studies and the two-generation studies did demonstrate developmental toxicity, i.e., increased fetal cervical and lumbar ribs and adverse effects on pup growth and survival, respectively. From these studies, the panel concluded that the "oral prenatal developmental toxicity studies and the oral two-generation reproductive toxicity studies have shown no effects on the reproductive system in rats." In addition, the panel "noted that the endpoints of reproductive development that have been shown to be sensitive with other phthalates were examined in one of the two-generation reproductive toxicity studies. "

3.3.2 Recent Studies Not Cited in the 2002 Summary of the NTP-CERHR Report

Hushka *et al.*, (2001)reported two-generation studies in which Sprague Dawley rats were exposed to DIDP in the feed at approximate doses of 15, 150, 300, or 600 mg/kg/day for 10 weeks prior to mating and throughout mating, gestation, and lactation, until PND 0, 1, 4, 7, 14, and 21. The authors state that there were "no differences in anogenital distance, nipple retention, or vaginal patency in the F2 offspring (Table 7)." Preputial separation was slightly but statistically significantly delayed in the 300 mg/kg/day dose group; however, the authors concluded that this difference "was deemed not adverse because the magnitude was so small."

Studies cited above are summarized in Table A-5.

Table A-5 DIDP developmental toxicity studies.

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Waterman *et al.*, (1999)	DIDP	S-D	0, 100, 500, 1000 mg/kg/day by gavage in one-generation study	GD 6-GD 15	25	22-25	Decreased weight gain, food consumption at 1000 mg/kg-d	Increased incidence of supernumerarycervical (7^{th}) ribs & rudimentary lumbar (14^{th}) ribs	**100 mg/kg-d**
Hushka *et al., (2001)*	DIDP	S-D	0, 0.02, 0.04, 0.2, 0.4 or 0, 0.2, 0.4, 0.8% in two generation studies	GD 1-PND 21 diet	30	?	no	Slight, but significant increase in age of preputial separation @ 0.4% (~300mg/kg/d) (Table 7; deemed "…not adverse because the magnitude was so small.") No observed effects on AGD or nipple retention @ any dose.	**0.2% (~150 mg/kg/d) (?)**

3.3.3 Consensus NOAEL for DIDP

Neither of the published studies reported significant anti-androgenic effects; however, one report did find that DIDP exposure was associated with a dose-related increase in percent fetuses with supernumerary cervical and lumbar ribs (Waterman et al., 1999). A 2003 NTP reevaluation of the Waterman et al. data led the Expert Panel for the Center for the Evaluation of Risks to Human Reproduction to set a NOAEL at 100 mg/kg/day based upon the increased supernumerary ribs.

4 Other Phthalates

4.1 Dimethyl Phthalate (DMP) (131-11-3)

Although an early study by Singh *et al.,* (1972) suggested that gestational exposure to DMP (0.4-1.3 g/kg i.p. on gestational days 5, 10, and 15) increased the incidence of skeletal defects in rats, subsequent studies by Plasterer *et al.,* (1985), Field *et al.,* (1993), and Gray *et al.,* (2000) uniformly found that DMP was not a developmental toxicant in mice (Plasterer) or rats (Field and Gray). Plasterer *et al.,* administered DMP to CD-1 mice by gavage at a single dose (at or just below the threshold of adult lethality) on GD 7-14 and reported that DMP had no effect on maternal or fetal survival and produced no congenital anomalies. Field *et al.,* , exposed rats to DMP from GD 6-15 at doses of 0, 0.25, 1, and 5% in feed (approximately 0.2-4.0 g/kg/day). Although high dose DMP caused maternal toxicity (increased maternal liver weight and reduced weight gain), there was no effect of DMP "on any parameter of embryo/fetal development.." Gray *et al.,* administered DMP to rats at an oral dose of 0.75 g/kg from gestational day 14 to postnatal day 3 and reported that DMP was ineffective in altering sexual differentiation and inducing reproductive malformations observed after exposure to other phthalates (DEHP, BBP, and DINP).

4.1.1 Consensus NOAEL for DMP

The available data, particularly the studies of Field *et al.*, 1993 (GD 6-15 exposure) and Gray *et al.,* , 2000 (GD 14-PND 3 exposure), support the conclusion that DMP is not a developmental toxicant.

4.2 Diethyl Phthalate (DEP)) (84-66-2)

Although an early study by Singh *et al.,* (1972) suggested that gestational exposure to DEP (0.6-1.9 g/kg i.p. on gestational days 5, 10, and 15) increased the incidence of skeletal defects in rats, subsequent studies by Field *et al.,* (1993), and Gray *et al.*, (2000) found that DEP was not a developmental toxicant in rats. Field *et al.,* , exposed rats to DEP from GD 6-15 at doses of 0, 0.25, 2.5, and 5% in feed (approximately 0.2-4.0 g/kg/day). Although high dose DMP caused maternal toxicity (reduced weight gain), there was no effect of DEP "on any parameter of embryo/fetal development.." Gray *et al.,* administered DEP to rats at an oral dose of 0.75 g/kg from gestational day 14 to postnatal day 3 and reported that DEP was ineffective in altering sexual differentiation and inducing reproductive malformations observed after exposure to other phthalates (DEHP, BBP, and DINP).

4.2.1 Consensus NOAEL for DEP

The available data, particularly the studies of Field *et al.*, 1993 (GD 6-15 exposure) and Gray *et al.,* , (2000) (GD 14-PND 3 exposure), support the conclusion that DEP is not a developmental toxicant.

4.3 Diisobutyl Phthalate (DIBP) (84-69-5)

Borch *et al.,* (2006a) exposed pregnant Wistar rats to DIBP at 0 or 600 mg/kg/day from gestation day 7 to either 19 or 20/21. At this dose of DIBP they observed significant reductions in anogenital distance, testicular testosterone production, testicular testosterone content, and expression of P450scc and StAR proteins in Leydig cells. In two different studies, Saillenfait *et al.*, (2006; 2008) exposed pregnant Sprague-Dawley rats from gestation day 6-20 to DIBP at 0, 250, 500, 750, or 1000 mg/kg/d (Saillenfait *et al.*, 2006) or from gestation day 12-21 at 0, 125, 250, 500, or 625 mg/kg/day. In the 2006 study the authors found that the incidence of male fetuses with undescended testes was significantly elevated at 750 and 1000 mg/kg/day. In the later study, the authors found that DIBP caused reduced anogenital distance and increased nipple retention in males at 250 mg/kg/day and higher and hypospadias and undescended testes at 500 mg/kg/day and higher. Boberg *et al.*, (2008) exposed pregnant Wistar rats from gestation day 7-21 to DIBP at 600 mg/kg/day and observed reduce anogenital distance in males, testosterone production, and expression of testicular insl3 and genes related to steroidogenesis. Howdeshell *et al.*, (2008) exposed pregnant Sprague-Dawley rats from gestation day 8-18 to DIBP at 0, 100, 300, 600, or 900 mg/kg/day and observed reduced fetal testicular testosterone production at 300 mg/kg/d and above. Finally, Hannas *et al.*, (2011) exposed pregnant Sprague-Dawley rats from gestation day 14-18 to DIBP at 0, 100, 300, 600, or 900 mg/kg/day and observed reduced fetal testicular testosterone production at 300 mg/kg/d and above.

4.3.1 Consensus NOAEL for DIBP

The Boberg *et al.*, (2008) study results could not be used to determine a NOAEL because only one dose was used. The Howdeshell *et al.*, (2008) study, which used multiple doses but small numbers of animals per dose group, was designed, as the authors point out " to determine the slope and ED50 values of the individual phthalates and a mixture of phthalates and not to detect NOAELs or low observable adverse effect levels." The same is true for the Hannas *et al.*, (2011) study, which also used multiple doses but small numbers of animals per dose group.   The two Saillenfait studies (2006; 2008) both included multiple doses, exposure during the appropriate stage of gestation and employed relatively large numbers of animals per dose. Using the more conservative of the two NOAELs from the 2008 Saillenfait study, the CHAP committee assigns a NOAEL of 125 mg/kg/day for DIBP.

Table A-6 DIBP developmental toxicity studies.

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Borch *et al.*, (2006a)	DIBP	Wistar rat	0, 600 mg/kg/d	GD 7-GD 19 or GD 20/21 gavage	6 or 8 (?)		NA	Decreased testicular production & content; male AGD adjusted for body weight on GD 20/21 A 600 mg/kg/d; increased female ADG adjusted for body weight @ 600 mg/kg/d on GD 20/21	**NA**
Saillenfait *et al.*, (2006)	DIBP	S-D	0, 250, 500, 750, 1000 mg/kg/d	GD 6-20	23-24	20-21	Yes, decreased maternal body weight (GD 6-9) @ 500 mg/kg/d and above	Increase in visceral & skeletal malformation; increase in male fetuses with undescended testes @ 500 mg/kg/d, significant @750 mg/kg/d and above when evaluated on GD 21	**Authors suggest 250 mg/kg/d based on the dose dependent effects on testes migration**
Saillenfait *et al.*, (2008)	DIBP	S-D	0, 125, 250, 500, 625 mg/kg/d	GD 12-21 gavage	11-14	7-14	no	Reduced male AGD (on PND 1), increased nipple retention (PND 12-14) @ 250 mg/kg/d; delayed onset of puberty & increased hypospadias, cleft prepuce & undescended testis @ 500 mg/kg/d and above	**125 mg/kg/d Based on Reduced male AGD (on PND 1), increased nipple retention (PND 12-14) @ 250 mg/kg/d**
Boberg *et al.*, (2008)	DIBP	Wistar rat	0, 600 mg/kg/d	GD 7-21 gavage	8	8		Decreased expression of SR-B1, StAR, P450Scc, CYP17, SF1, Insl3 on GD 19 & GD 20/21; PPARα on GD 19 @ 600 mg/kg/d	**NA**

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
Howdeshell *et al.*, (2008)	DIBP	S-D	0, 100, 300, 600, 900 mg/kg/d	GD 8-18	5-8	5-8		↓fetal testicular testosterone production @ 300 mg/kg/d and above	**100 mg/kg/d based upon ↓fetal testicular testosterone production @ 300 mg/kg/d**
Hannas *et al.*, (2011)	DIBP	S-D	0,100, 300, 600, 900 mg/kg/d	GD 14-18	3-6	3-6		↓fetal testosterone production @ 300 mg/kg/d and above; ↓Cyp11a expression at 100 mg/kg/d and above and ↓expression of StAR at 300 mg/kg/d and above	**100 mg/kg/d based upon ↓fetal testicular testosterone production @ 300 mg/kg/d**

4.4 Dipentyl Phthalate (DPENP/DPP) (131-18-0)

A PubMed search using the terms dipentyl phthalate and developmental toxicity or DPENP and developmental toxicity identified three articles, one by Heindel *et al.*, (1989), one by Howdeshell *et al.*, (2008), and the other by Hannas *et al.*, (2011). Heindel *et al.*, (1989) used a continuous breeding protocol to expose CD-1 mice to 0.5, 1.25, or 2.5% DPENP in the diet from 7 days prior to and during a 98-day cohabitation period. DPENP exposure adversely affected the reproductive system as evidenced by a complete inhibition of fertility at 1.25 and 2.5% DPENP, and reduced fertility at 0.5% DPENP. DPENP treatment was also associated decreased body weight, increased liver weight, decreased testis and epididymis weights, decreased epididymal sperm concentration and elevated seminiferous tubule atrophy. Howdeshell *et al.,* (2008) exposed pregnant Sprague-Dawley rats from gestation days 8-18 to DPENP at doses of 0, 25, 50, 100, 200, 300, 600, and 900 mg/kg/d and then measured fetal testicular testosterone production on gestational day 18. They found that testosterone production was significantly reduced at doses of DPENP at 100 mg/kg/d and above. Hannas *et al.,* (2011) dosed pregnant rats with 0, 300, 600, 900, or 1200 mg/kg on GD 17 or 0, 11, 33, 100, 0r 300 mg/kg on GD 14-18 and then evaluated fetal testicular testosterone production on GD 17.5 or GD 18, respectively. They also dosed pregnant rats on GD 8-18 with 0, 11, 33, 100, 0r 300 mg/kg/day and evaluated early postnatal endpoints in male offspring. Results showed that DPENP significantly reduces fetal testicular testosterone production (at 300 mg/kg/day or higher after 1-day exposure and 33 mg/kg/day after 5-day exposure), StAR, Cyp11a, and ins13 gene expression levels (100 mg/kg/day after a 5-day exposure), and induced early postnatal reproductive alterations in male offspring (anogenital distance at 100 mg/kg/day and nipple retention at 300 mg/kg/day). The authors note that the reduction in fetal testicular testosterone production occurred as early as 5 hours following dosing and at a dose as low as 33 mg/kg/day makes fetal testicular testosterone production a more sensitive endpoint for the antiandrogenic action of phthalate compounds than genomic and early postnatal endpoints. The authors also note that DPENP is 8-fold more potent in decreasing fetal testicular testosterone production, 4.5-fold more potent in inducing nipple retention, and 2-fold more potent in reducing anogenital distance compared with DEHP. Finally, the authors conclude that the "consistency in DPENP potency from fetal endpoints to postnatal effects supports the hypothesis that fetal declines in androgen production are causally linked to postnatal malformations in androgen-sensitive tissues."

4.4.1 Consensus NOAEL for DPENP/DPP

There are only two studies available describing the effects of DPENP on reproductive development in rats after *in utero* exposure during late gestation. Although these studies were not designed to determine NOAELs, the data presented on the effects of DPENP on fetal testosterone production and gene expression of target genes involved in male reproductive development revealed that reduction in testosterone production was the most sensitive endpoint, with a LOAEL of 33 mg/kg/day *et al.*, (Hannas *et al.*, 2011). Thus, on the basis of this study, the CHAP committee assigns the NOAEL for DPENP/DPP at 11 mg/kg/day.

4.5 Dicyclohexyl phthalate (DCHP) (84-61-7)

Hoshino *et al.,* (2005) conducted a two-generation reproductive toxicity study in which male and female Sprague-Dawley rats of parental (F0) and F1 generation were exposed to DCHP in the diet at concentrations of 0, 240, 1200, or 6000 ppm. DCHP caused a decrease in anogenital distance and an increase in nipple retention in F1 males at 6000 ppm and in F2 males at 1200 ppm and above. Based on the LOAEL in F2 males, the authors report a NOAEL of 240 ppm (16-21 mg/kg/day).

Yamasaki *et al.,* (2009) exposed pregnant Sprague-Dawley rats on gestation day 6 to postnatal day 20 to DCHP at 0, 20, 100, or 500 mg/kg/day and observed prolonged preputial separation, reduced anogenital distance, increased nipple retention and increased hypospadias in male offspring in the 500 mg/kg/day group. Using 500 mg/kg/day as the LOAEL, the NOAEL would be 100 mg/kg/day.

Saillenfait *et al.,* (2009) reported a study in which they exposed pregnant Sprague- Dawley rats from gestational day 6-20 to DCHP at 0, 250, 500, or 750 mg/kg/day. Like DHEXP also studied by the same group, DCHP caused a significant and dose-related decrease in anogenital distance in male fetuses at all doses. Unlike DHEXP, DCHP did not cause and a significant increase in the incidence of male fetuses with undescended testis or dose-related increases in cleft palate, eye defects, and axial skeleton abnormalities.

4.5.1 Consensus NOAEL for DCHP

Two of the three studies (Hoshino *et al.*, 2005; Yamasaki *et al.*, 2009) available report DCHP-induced effects on male reproductive development (decreased anogenital distance and nipple retention in males) and the third study (Saillenfait *et al.*, 2009) reported only the former. The Saillenfait (2009) study could not be used to determine a NOAEL because the lowest dose used in their study was a LOAEL. Of the two remaining studies, the two-generation study by Hoshino *et al.*, (2005) reported adverse effects on male reproductive development at a calculated dose of 80-107; NOAEL of 16-21 mg/kg/day, whereas the Yamasaki *et al.,* (2009) prenatal study reported adverse effects on male reproductive development at dose of 500 mg/kg/day; NOAEL of 100 mg/kg/day. Using the more conservative of the two NOAELs, the CHAP committee assigns a NOAEL of 16 for DCHP

Table A-7 DCHP developmental toxicity studies.

Study	Agent	Strain/ Species	Dose levels	Dosing regimen	Animals/ dose	Maternal toxicity	Endpoint	NOAEL
Hoshino *et al.*, (2005)	DCHP	S-D	0, 240, 1200, 6000 ppm	Two generation	20-24		↓AGD and ↑ nipple retention @ 1200ppm and above in F2 males	240 ppm (16-21 mg/kg/day) based upon ↓AGD and ↑ nipple retention @ 1200ppm and above in F2 males
Yamasaki *et al.*, (2009)	DCHP	S-D	0, 20, 100, 500 mg/kg/day	GD 6-PND 20	10		↓ AGD, ↑ nipple retention and hypospadias @ 500 mg/kg/day	100 mg/kg/day based upon ↓ AGD, ↑ nipple retention and hypospadias @ 500 mg/kg/day
Saillenfait *et al.*, (2009)	DCHP	S-D	0, 250, 500, 750 mg/kg/day	GD 6-20	24-25	yes	↓ male AGD @ 250 mg/kg/day and above	NA

4.6 Di-*n*-hexyl Phthalate (DHEXP/DnHP) (84-75-3)

4.6.1 2002 Summary of the NTP-CERHR Report

The 2002 summary of the NTP-CERHR report (Kavlock *et al.*, 2002; NTP, 2003d) on the reproductive and developmental toxicity of di-*n*-hexyl phthalate (DHEXP/DnHP) indicates that no human developmental toxicity data were located by the expert panel. Animal data are limited to one screening assay in which a "massive oral dose (9,900 mg/kg bw/day) was administered to 48 mice on GD 6-13. None of the 34 pregnant dams gave birth to a live litter." Based on the available studies, the panel concludes that the "the database is insufficient to fully characterize the potential hazard. However, the limited oral developmental toxicity data available (screening level assessment in the mouse) are sufficient to indicate that DHEXP is a developmental toxicant at high doses (9900 mg/kg bw/day). These data were inadequate for determining a NOAEL or LOAEL because only one dose was tested."

4.6.2 Relevant Studies Published Since the 2002 Summary of the NTP-CERHR Report

Saillenfait *et al.*, (2009) reported a study in which they exposed pregnant Sprague- Dawley rats from gestational day 6-20 to DHEXP at 0, 250, 500, 0r 750 mg/kg/day. DHEXP caused a significant and dose-related decrease in anogenital distance in male fetuses at all doses and a significant increase in the incidence of male fetuses with undescended testis at 500 mg/kg/day and above. In addition, DHEXP caused dose-related increases in cleft palate, eye defects, and axial skeleton abnormalities.

4.6.3 Consensus NOAEL for DHEXP/DnHP

Although the study by Saillenfait ***et al.,*** (2009) is fairly robust, i.e., multiple doses, number of animals per dose group (20-25), and appropriate exposure time, no NOAEL for the most sensitive developmental reproductive endpoint (anogenital distance) could be ascertained because the lowest dose tested was the LOAEL.

4.7 Diisooctylphthalate (DIOP) (27554-26-3)

The on*l*y available data on dev**e**lopmental effects come from a parental study, in which female rats were administered 0, 5, or 10 mL/kg DIOP (0, 4,930, or 9,860 mg/kg, using the reported density of 986 kg/m3 (NICNAS, 2008) on days 5, 10, and 15 of gestation by intraperitoneal injection (as cited in Grasso, 1981; ECB, 2000). No increase in fetal mortality or skeletal abnormalities was observed. It was reported that there was a high incidence of soft tissue abnormalities in both treated groups, but quantitative data were not provided in the available summary.

4.7.1 Consensus NOAEL for DIOP

The lack of comprehensive d**e**velopmental toxicity studies using DIOP as a test substance supported the conclusion that there was “inadequate evidence” for the designation of DIOP as a “developmental toxicant”.

4.8 Di(2-propylheptyl) phthalate (DPHP) (53306-54-0)

A gestational exposure study of DPHP in **r**ats is available as a brief report of preliminary results (BASF, 2003). Groups of presumed pregnant female Wistar rats (25/group) were administered 0, 40, 200, or 1,000 mg DPHP/kg-day by gavage (vehicle not specified) on gestation days (GDs) 6 through 19. At necropsy (not specified but presumably GD 20), 17–25 females per group had implantation sites. Maternal toxicity occurred in the high-dose group (1,000 mg/kg-day), as evidenced by insufficient care of fur, 32% reduced food consumption on GDs 6–10, and 30% reduced corrected body weight gain. Significant loss of body weight (magnitude not specified) occurred on GDs 6–8. Gross necropsy showed that two high-dose females had hydrometra (accumulation of fluid in the uterus). Examination of the uterus showed that high-dose females had increased postimplantation loss compared with controls (21.3 vs. 6.2%). In addition, 17/20 high-dose females (it is unclear what happened with the remaining five females in this group) had viable fetuses, and in three dams, only resorptions were found in the uterus (2.2 vs. 0.5% in controls). Exposure to DPHP did not cause teratogenicity, but fetuses from high-dose females showed a statistically significant increased incidence in soft tissue variations (dilated renal pelvis), which according to the researchers, was just outside the historical control range. It should be noted that this study is also summarized in the review by Fabjan *et al.,* (2006), which states that the rates of soft tissue, skeletal, and total variations were slightly but statistically significantly increased in high-dose fetuses. Fabjan *et al.,* (2006) also reported a screening developmental toxicity study (citation not provided) in which pregnant rat dams were treated with DPHP on GDs 6–15 by gavage with no maternal or fetal effects at the high dose of 1,000 mg/kg-day. No data were shown and no further details were provided in the available reports of these studies.

4.8.1 Consensus NOAEL for DPHP

Overall, an insufficient amount of animal data and poorly described methodologies in studies using DPHP as a test substance supported the conclusion that there was “insufficient evidence” for the designation of DPHP as a “developmental toxicant”.

Table A-8 Consensus reference doses for antiandrogenic endpoints.

PHTHALATE	NOAEL mg/kg/d	UNCERTAINTY FACTOR	RfD mg/kg-d
DBP	50	100	0.50
BBP	50	100	0.50
DEHP	5	100	0.05
DNOP	NA	NA	
DINP	300	100	3.0
DIDP	≥600	NA	
DMP	≥750	NA	
DEP	≥750	NA	
DIBP	125	100	1.25
DPENP (DPP)	11	100	0.11
DCHP	16	100	0.16
DNHEXP	≤ 250	NA	
DIOP	NA	NA	
DPHP	NA	NA	

Table A-9 Summary of animal male developmental toxicology.

PE	Testis malform. /histopathology	Testis wt.	Seminal vesicle	Epididymal wt.	Cryptorchidism	Hypospadias	Gubernacu-lar malformations
DBP	↑	↓	↓	↓	↑	↑	↑
BBP	↑	↓	↓	↓	↑	↑	↑
DEHP	↑	↓	↓	↓	↑	-	
DNOP							
DINP	-	↓	-	-			
DIDP							
DMP	-	-	-	-			
DEP	-	-	-	-	-	-	**-**
DIBP	↑	↓	↓?	↓	↑	↑	↑**?**
DPP	↑	↓		↓	↑?	↑?	↑**?**
DHEXP					↑		
DCHP					↑	↑	
DIOP							
DPHP							
ATBC							
DEHA		-	-	-			
DINCX					-?	-?	**-?**
DEHT							
TOTM							
TPIB							

↑= INCREASE; ↓= DECREASE; -=NOT AFFECTED

5 Prenatal Phthalate Exposures and Neurobehavioral Effects

Studies reviewed in the previous section have provided extensive documentation that phthalates induce the "phthalate syndrome" in rats, and that one of the early manifestations of this syndrome is the reduction of testosterone production. Because gonadal steroids play an essential role in the process of brain sexual differentiation during embryonic development and early postnatal life, some developmental toxicology studies have also focused on the neurobehavioral effects of prenatal exposures to various phthalates.

Gray *et al.,* (2000) treated pregnant Sprague-Dawley rats from gestation days gestation day 14 to postnatal day 3 with 0 or 750 mg DEHP, BBP, or DINP/kg/day and examined mounting behavior in a subset of control and treated males. The authors report that 4/6 treated males displayed mounts with pelvic thrusts versus 2/3 controls and conclude that "these data do not support the hypothesis that PEs alter sexual differentiation of CNS with respect to male rat sexual behavior."

Moore *et al.*, (2001), treated pregnant Sprague-Dawley rats from gestation day 3 through postnatal day 21 with 0, 375, 750, or 1,500 mg DEHP/kg/day, and males from litters so treated were examined for masculine sexual behaviors as adults. Nine of 16 DEHP-treated males failed to ejaculate during sexual behavior testing compared to one of eight control males. Eight of these nine had no intromissions and five failed to mount a single time. The authors could find no evidence that the abnormal sexual behaviors observed in the DEHP-exposed male rats was caused by effects on androgen concentrations in adulthood or by abnormal male reproductive organs. Instead, they suggest that the *in utero* and lactational DEHP exposure causes incomplete sexual differentiation of the CNS.

Masutomi *et al.,* (2003) fed pregnant Sprague-Dawley rats 400, 4000, or 20,000ppm DINP from gestation day 15 to postnatal day 10 and then did volume measurements on the sexually dimorphic nucleus of the preoptic area (SDN-POA), which is sensitive to exogenous androgens, at prepubertal necropsy. Although the SDN-POA in males was >10 larger than in females, there were no significant differences in SDN-POA values between controls and DINP-treated groups for either sex.

Takagi *et al.,* (2005) fed pregnant CD (SD) IGS rats 4000 or 20,000 ppm DINP/kg/day from gestation 15 to postnatal day 10, at which time pups were killed, brains were fixed and sectioned, the SDN-POA localized and isolated, and total RNA extracted. Using this SDN-POA RNA and Real-time RT-PCR, the authors determined the expression levels for ERα, ERβ, PR, and SRC-1 mRNAs. The only significant change observed was a decreased expression of PR in females after treatment with 20,000 ppm.

Lee *et al.,* (2006) fed pregnant Wistar rats either DBP (20, 200, 2,000, or 10,000 ppm), DINP (40, 400, 4,000, or 20,000 ppm), or DEHA (480, 2,400 or 12,000 ppm) from gestation day 15 to the day of weaning) PND 21). On PND 7 a subset of rats was killed, their brains removed, and the entire hypothalamus removed and frozen for RNA isolation. The RNA was used to determine the expression levels of grn and p130 mRNAs by RT-PCR. DBP induced increased expression of grn in females at 2000 ppm and above and DINP induced increased grn expression in females at all doses except 4000 ppm. In contrast, DBP induced increased expression of p130 in males at low doses (20 and 200 ppm) but not at high doses, whereas DINP induced increased expression of p130 in males at all doses tested. ON PND 20-21, copulatory behavior was assessed for both males and females. Whereas the copulatory behavior of females was significantly inhibited at all doses of DBP and DINP, the effects of these phthalates on male copulatory behavior were complex, e.g., 200 and 2,000 ppm DBP decreased the number of ejaculations while in the 10,000 ppm exposed rats, the number of ejaculations was increased.

Dalsenter *et al.,* (2006) treated pregnant Wistar rats by gavage with 0, 20, 200, or 500 mg/kg/day DEHP from gestational day 14 through postnatal day 3 and adult males were then evaluated for sexual behavior (mount and intromission latencies, number of intromissions up to ejaculation, ejaculatory latency, and intromission frequency). Males exposed utero to 500 mg/kg/day DEHP exhibited impaired sexual behavior as evidenced by increased intromission latency and increased number of intromissions up to ejaculation.

Andrade *et al.,* (2006b) treated pregnant Wistar rats by gavage from gestation day 5 to lactation day 21 with 0, 0.015, 0.045, 0.135, 0.405, 1.215, 5, 15, 45, 135, or 405 mg DEHP/kg bw/day. Males from treated litters were tested as adults on postnatal day 130 for sexual behavior (mount and intromission latencies, number of intromissions up to ejaculation, ejaculatory latency, and intromission frequency). No effects on male sexual behavior were observed at any dose of DEHP tested.

Boberg *et al.,* (2011) reported a study in which Wistar rats were exposed to DINP by gavage at 0, 300, 600, 750, and 900 mg/kg bw/day from gestation day 7 to PND 17. A subset of male and female animals from each dose group was weaned at PND 21 and used for behavioral testing (motor activity and habituation capability and Morris maze learning and memory). Although DINP did not affect male behavior as tested, DINP-exposed females showed a dose-dependent improvement in spatial learning and memory abilities, which was statistically significant at the highest dose.

6 Developmental Toxicity of Phthalate Substitutes

6.1 Acetyl Tributyl Citrate (ATBC) (77-90-7)

A two-generation reproduction study in Sprague-Dawley rats was reported by Robins (1994). ATBC was mixed in the diet at concentrations to give 0, 100, 300, 1000mg/kg/day. Males were exposed for 11 weeks, females for 3 weeks before mating, during mating, and through gestation and lactation. Male and female pups were given diets with ATBC for 10 weeks after weaning. There were no reproductive or developmental effects attributable to ATBC at any dose level.

Chase and Willoughby (2002) reported a one-generation reproduction study (summary only) in Wistar rats given ATBC in the diet at concentrations to provide 0, 100, 300, or 1000mg/kg/day four weeks prior to and during mating plus during gestation and lactation. The f0 parents produced an f1 generation of litters. No systemic or reproductive effects were seen at any dose level.

6.1.1 Consensus NOAEL for ATBC

In both the Chase and Willoughby (2002) and the Robins (1994) studies, the highest dose tested, 1000 mg/kg/day, was also the NOAEL. Although these were not peer-reviewed studies and that ATBC was administered in the diet rather than by gavage, the CHAP committee recommends a NOAEL of 1000 mg/kg/day but with an additional uncertainty factor of 10 being used in calculating the reference dose.

6.2 Di (2-ethylhexyl) Adipate (DEHA) (103-23-1)

Dalgaard (2002; 2003) reported on perinatal exposure of Wistar rats by gavage at dose levels of 0, 800 or 1200mg/kg/day on gestation day 7 through postnatal day 17. This was a dose range finding study to examine pups for evidence of antiandrogenic effects—none were observed. Decreased pup weights were seen at both dose levels. In the main study, DEHA was given by gavage at dose levels of 0, 200, 400 and 800mg/kg/day on gestation day 7 through postnatal day 17. No antiandrogenic effects were seen; a NOAEL of 200mg/kg/day was based on postnatal deaths.

6.2.1 Consensus NOAEL for DEHA

The Dalgaard *et al.,* (2003) study employed 3 dose groups (plus control), 20 dams/ dose, an appropriate exposure regimen (gestation day 7-17), and observed no antiandrogenic effects at any dose. Thus the CHAP committee recommends a NOAEL of 800 mg/kg/day for DEHA but with an additional uncertainty factor of 10 being used to calculate the Reference Dose given that this NOAEL is based upon one unreplicated study.

6.3 Diisononyl 1,2-dicarboxycyclohexane (DINX) (474919-59-0)

PubMed search for diisononyl 1,2-dicarboxycy**c**lohexane and developmental toxicity or DINCH® and developmental toxicity failed to identify any peer-reviewed articles.

A two-generation reproduction study was reported by SCENIHR (2007) in summary form only. Because the study used OECD TG 416, it was likely conducted in rats. Dose levels by diet were 0, 100, 300, or 1000mg/kg/day. There were no effects on fertility or reproductive performance in f0 and f1 parents and no developmental toxicity in f1 or f2 pups. A substudy designed to look for anti-androgenic effects showed no developmental toxicity at any dose level.

Prenatal developmental toxicity was also evaluated (BASF, 2005) in rats and rabbits that were orally administered DINX during gestation (at dose levels as high as 1200 mg/kg/day on gestational days 6-19 in the rat and 0, 100, 300 or 1000 mg/kg/day on gestation days 6-29 in the rabbit). No effects were observed in either species, suggesting apparent NOAELs of 1200 mg/kg/day in rats and 1000 mg/kg/day in rabbits.

6.3.1 Consensus NOAEL for DINX

Although the studies cited **s**uggest a NOAEL in rats of 1000 mg/kg/day, these were not peer reviewed studies; therefore CHAP members did not have access to protocol details or actual data. Given the limitation of non- peer-reviewed studies, the CHAP committee recommends a NOAEL for DINX of 1000 mg/kg/day but with an additional uncertainty factor of 10 being used to calculate the reference dose.

6.4 Di (2-ethylhexyl) Terephthalate (DEHT/DOTP) (6422-86-2)

Gray *et al.,* (2000) reported a study to look for anti-androgenic effects of DEHT. Pregnant Sprague-Dawley rats were dosed by gavage with 0 or 750mg/kg/day on gestation day 14 through postnatal day 3. No anti-androgenic effects were observed.

Faber *et al.*, (2007b) reported the results of a two-generation reproduction study in Sprague-Dawley rats given DEHT in the diet. The dietary admix was given to males and females for 70 days prior to mating plus during pregnancy and lactation. Concentrations in the diet gave O, 158, 316, or 530mg/kg/day to males and 0, 273, 545, or 868mg/kg/day to females. No adverse effects on reproduction were observed in either generation at any dose level. Weight gain was decreased in f0 high dose males. Weight gain was decreased in f1 and f2 males at the top two dose levels. The NOAEL for reproductive effects was 530mg/kg/day; the NOAEL for parental and pup systemic toxicity was 158mg/kg/day.

This same group also reported the results of a developmental toxicity study in which rats or mice were fed DEHT at levels of 0,226, 458, and 747 mg/kg-day (rat) or 197, 592, and 1382 mg/kg/day from GD 0-20 (rat) or 0-18 (mice). Mean numbers of implantation sites, early resorptions, late resorptions, fetal sex ratios, preimplantation loss, malformations, or variations were unaffected at any concentration level in the rat or mouse. There was a slight reduction in maternal weight gain at the highest dose level rat group and the mid- and high-dose mouse groups. The NOAEL for maternal toxicity was 458 mg/kg/day in rats and 197 mg/kg/day in mice.

6.4.1 Consensus NOAEL for DEHT

The Gray *et al.* (2000) study, which used only one dose group and only 8 animals per dose group, reported no antiandrogenic effects of DEHT (DOTP) at the highest and only dose tested, 750 mg/kg/day. The Faber *et al.*, , 2007b prenatal developmental toxicity study, which used multiple doses and 25 animals per dose group, also observed no antiandrogenic effects at the highest dose tested, i.e., 747 mg/kg/day from gestation days 0-20 in Sprague-Dawley rats. On the basis of these two studies and the results of the two-generation study in rats, the CHAP committee recommends a NOAEL for DEHT of 750 mg/kg/day.

6.5 Trioctyl Trimellitate (TOTM)

A one-generation reproduction study was reported in Sprague-Dawley rats given TOTM by gavage at dose levels of 0, 100, 300, or 1000mg/kg/day (JMHW, 1998). Males were dosed for 46 days, females for 14 days prior to mating and during mating through lactation day 3. Histologic examination showed a decrease in spermatocytes and spermatids at the top two dose levels. No other reproductive toxicity was seen. The NOAEL was 100 mg/kg/day.

Pre and postnatal effects of TOTM in Sprague-Dawley rats were reported from Huntington Life Sciences (2002). Rats were given 0, 100, 500, or 1050 mg/kg/day by gavage on days 6-19 of pregnancy or day 3 through day 20 of lactation. There were no significant effects on developmental measures but there was a slight delay in the retention of areolar regions on postnatal day 13 but not day 18 (not considered to be toxicologically significant). The high dose of 1050 mg/kg/day was identified as a NOAEL in this study for developmental effects.

6.5.1 Consensus NOAEL for TOTM (3319-31-1)

As with Like ATBC and DINX, there is a lack of peer-reviewed studies on TOTM. Nevertheless, the data available from the Japanese toxicity testing report showing decreases in spermatocytes and spermatids in males exposed to TOTM and the "slight delay in the retention of areolar regions" (nipple retention?) in the Huntington Life Sciences study suggests at the very least that additional studies are required. Lacking these, the CHAP committee recommends that the conservative NOAEL of 100 mg/kg/day derived in the Japanese study be assigned for TOTM.

6.6 2,2,4-Trimethyl-1,3-pentanediol-diisobutyrate (TPIB) (3319-31-1)

In the combined repeated dose and reproductive/developmental toxicity screening test described in the repeat-dose section above, male and female Sprague-Dawley rats were administered gavage doses of 0, 30, 150, or 750 mg/kg/day TPIB from 14 days before mating until 30 days after (males) or day three of lactation (females) ((JMHLW, 1993; OECD, 1995; Eastman, 2007). TPIB had no significant effect on mating, fertility, the estrous cycle, delivery, or lactation period. Parameters evaluating developmental toxicity were limited to body weights at postnatal days (PND) 0 and 4, and autopsy findings at PND 4; these examinations revealed no TPIB-related effects at any dose. The reproductive and developmental NOAEL, therefore, is 750 mg/kg/day.

A reproductive/developmental toxicity screening test was performed by Eastman Chemical Company under OECD test guideline 421 (Eastman, 2001). Sprague-Dawley rats (12/sex/dose) received dietary doses of 0, 120, 359, or 1135 mg/kg/day (females) or 0, 91, 276, or 905 mg/kg/day (males) for 14 days before mating, during mating (1–8 day), throughout gestation (21–23 days), and through PND 4–5. Significant reductions in mean body weight, body weight gain, and feed consumption/utilization were observed in both sexes of the parental generation at the high-dose level, but were transient in nature. Reductions in mean number of implantation sites were observed in the high-dose group and correlated to the number of corpora lutea.

However, there was no corresponding effect on pre- or post-implantation loss, or litter size on PND 0. Mean litter weights in the high-dose group were statistically lower than those of the control group on PND 0 and 4, an effect attributed to the smaller litter sizes rather than a difference in individual pup size. The mean number of live pups at PND 4 was lower in high dose litters compared to control litters. Mean absolute epididymal sperm counts were statistically lower in all treated groups compared to the control group; however, when counts were normalized for organ weight, values were not statistically different. Males in the high- and low-dose groups had lower mean absolute and/or relative testicular sperm counts. The significance of this was unclear, as there was no effect on relative epididymal sperm counts, fertility, or microscopic lesions in the testes. Authors considered both sperm type changes to be nonadverse. Other reproductive parameters, including reproductive organ weights, gross or microscopic lesions, and mean sperm motility were not affected. Study authors concluded that the NOAEL for reproductive or developmental toxicity was 276 mg/kg bw/day for males and 359 mg/kg bw/day for females, based on decreased total litter weight and litter size on PND4, decreased number of implants and number of corpora lutea (Eastman Chemical 2001).

6.6.1 Consensus NOAEL for TPIB

Although there are data in th**e** Versar report (Versar/SRC, 2010, cited verbatim above), the two studies cited were conducted by Eastman Chemical (2001; 2007) and the data therein have not been published in the peer-reviewed literature. Nonetheless, in neither study is there any indication of any antiandrogenic effects of TXIB® when administered to females at doses as high as 1125 mg/kg/day for 14 days before mating, during mating (1–8 day), throughout gestation (21–23 days), and through PND 4–5. Thus, the developmental NOAEL for TXIB® is greater than 1125 mg/kg/day.

Table A-10 summarizes peer-reviewed developmental toxicity studies on phthalate substitutes.

Table A-10 Developmental toxicity of phthalate substitutes.

STUDY	AGENT	STRAIN/ SPECIES	# DOSE LEVELS	DOSING REGIMEN	# ANIMALS /DOSE	# LITTERS /DOSE	MATERNAL TOXICITY	ENDPOINT	NOAEL
No peer-reviewed studies located	ATBC								
Dalgaard *et al.*, (2003)	DEHA	Wistar	0, 800, 1200 mg/kg/d in dose finding study; 0, 200, 400, 800 mg/kg/d in main study	GD 7-17 in dose finding study; GD 7-PND17	8 in dose finding; 20 in main study	7 in dose finding study; 15-18 in main study	Yes @ 1200 mg/kg/d; length of pregnancy increased, male and female pup birth weights decreased @ 800 mg/kg/d	No effects on male AGD, nipple retention & testosterone levels observed at any dose level	**Authors give 200 mg/kg/d based on dose-dependent increase in postnatal death that almost reached significance @ 400 mg/kg/d**
No peer-reviewed studies located	DINCH®								
Gray *et al.*, (2000)	DOTP/ DEHT	S-D	0, 750 mg/kg/d	GD 14-PND 3	8			No antiandrogenic effects	**NA**
Faber *et al.*, (2007a)	DEHT	S-D	0, 0.3, 0.6, 1.0 % in diet= 0, 226, 458, 747 mg/kg/d	GD 0-20	25	23-24	Yes, decreased maternal body weight & liver weight @ 1.0% (747 mg/kg/d)	No developmental toxicity observed	**747 mg/kg/d for developmental toxicity; 458 mg/kg/d for maternal toxicity**
Faber *et al.*, (2007a)	DEHT	CD1 mice	0, 0.1, 0.3, 0.7% in diet= 0, 197, 592, 1382 mg/kg/d	GD 0-18	25	21-24	Yes, decreased liver weight @ 0.3% (592 mg/kg/d) and above	No developmental toxicity observed	**1382 mg/kg/d for developmental toxicity; 197 mg/kg/d for maternal toxicity**
Faber *et al.*, (2007b)	DEHT	S-D	0, 0.3, 0.6, 1.0% in diet	Two generation study	30	30?	Yes, Increased lethality in F0 and F1 dams @ 1.0%; increased female liver weights @ 0.6% and above	No developmental toxicity observed	**1382 mg/kg/d for developmental toxicity; 226 mg/kg/d for maternal toxicity**
No peer-reviewed studies located	TOTM								

Table A-11 NOAELs for phthalate substitutes.

Phthalate Substitute	NOAEL
ATBC	1000
DEHA	800
DINX	1000
DEHT	750
TOTM	100
TPIB	≥1125

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PEER REVIEW DRAFT

Draft Report to the

U.S. Consumer Product Safety Commission

by the

CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES

March 5, 2013

APPENDIX B

REPRODUCTIVE AND OTHER TOXICOLOGY

TABLE OF CONTENTS

1 Introduction

Dialkyl esters of *o*-phthalic acid (PEs) are a chemical class consisting of a large family of chemicals, about 50 of which are commercial products, many of which are considered high production volume chemicals in the U.S. Toxicology data have accumulated over several decades because of widespread human exposure and concern over additivity of effects. Studies in recent years have shown that certain PEs cause reproductive and developmental health effects in animal models. These effects, in particular, will be the primary focus of this report because of the toxicological significance of the effects and the existence of similar observations in humans that may also be related to exposure to certain PEs.

There are little or no toxicology data on many of members of the large family of PEs. Most of these are chemicals of no commercial importance and do not contribute to human exposures to PEs. The PEs banned by the Consumer Product Safety Improvement Act of 2008 (CPSIA) are as follows.

Phthalate	CAS number
Permanent ban	
Dibutyl phthalate (DBP)	84-74-2
Benzyl butyl phthalate (BBP)	85-68-7
Di(2-ethylhexyl phthalate) (DEHP)	117-81-7
Interim ban	
Di-n-octyl phthalate (DNOP)	117-84-0
Diisononyl phthalate (DINP)	28553-12-0; 68515-48-0
Diisodecyl phthalate (DIDP)	267651-40-0; 68515-49-1

Phthalates not banned by the CPSIA were also reviewed by CHAP:

Dimethyl phthalate (DMP)	131-11-3
Diethyl phthalate (DEP)	84-66-2
Diisobutyl phthalate(DIBP)	84-69-5
Dicyclohexyl phthalate (DCHP)	84-61-7
Diisoheptyl phthalate (DIHEPP)	71888-89-6
Diisooctyl phthalate (DIOP)	27554-26-3
Di(C9-C11 alkyl) phthalate (D911P)	68648-92-0; 68515-43-5
Di(2-propylheptyl) phthalate (DPHP)	53306-54-0

Phthalate alternatives were also reviewed because they are widely used substitutes for phthalates or are solvents or alternative plasticizers:

Acetyl tri-n-butyl citrate (ATBC)	77-90-7
Di(2-ethylhexyl) adipate (DEHA)	103-23-1
Diisononyl 1,2-dicarboxycyclohexane (DINX, DINCH®)[*]	474919-59-0
Di(2-ethylhexyl) terephthalate (DEHT)	6422-86-2
Trioctyl trimellitate (TOTM)	3319-31-1
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (TPIB, TXIB®)[†]	6846-50-0

1.1 Non-reproductive Toxicity

The family of PEs is generally characterized by low acute toxicity and lack of genotoxicity. Thus, the carcinogenicity and reproductive toxicity of certain PEs are likely related to non-genotoxic mechanisms such as peroxisome proliferation, interference with testosterone production in the fetus, or other mechanisms of action.

Absorption of PEs is more efficient from the gastrointestinal tract than it is from other routes. Absorption is less efficient through the respiratory tract and least efficient through the skin. Absorption is enhanced by hydrolysis of the diesters to a monoester. Once absorbed, the monoester continues to be metabolized into substances that are excreted in the urine (Albro and Moore, 1974). Rats are more efficient at hydrolyzing the esters to monoesters than non-human primates (Rhodes *et al.*, 1986; Short *et al.*, 1987). Thus, primates have a lower systemic exposure to the metabolites of PEs than rats exposed to the same amount orally (Rhodes *et al.*, 1986). This probably accounts for the greater sensitivity of rats compared to primates, especially for higher molecular weight esters.

DEHP and DINP cause significant increases in liver tumors in 2-year studies in rats and mice while DEP, DMP, and BBP show no evidence or equivocal evidence of carcinogenicity in the same type of studies (NTP, 1995; NTP, 1997). Because o-DAPs are non-genotoxic, other mechanisms of carcinogenic activity are assumed, specifically peroxisome proliferation. In rodents, peroxisome proliferators stimulate enzyme activities in the liver, causing an increase in endoplasmic reticulum and an increased size and number of peroxisomes. Chronic exposure of rodents results in hypertrophy of the liver and carcinogenesis. Chronic exposure of humans to PEs is much less than levels of exposure used in most animal studies and does not cause the same response in humans as seen in rodents, leading to the conclusion that the mechanism that accounts for carcinogenesis in rodents does not exist in humans (IARC, 2000). As a result, the potential of PEs to cause cancer in humans is not a driving force for regulatory actions compared to concerns about their potential to disturb the hormone-dependent development of young males. Based on this, the primary focus of this report is on the risk from exposure to PEs on the hormone-dependent development of young males.

Among the various types of studies conducted by toxicologists to evaluate and characterize the toxicological properties of chemicals, it has been common to distinguish between effects on

[*] DINCH® is a registered trademark of BASF. The abbreviation DINX is used here to represent the generic chemical.
[†] TXIB® is a registered trademark of Eastman Chemical Co. The abbreviation TPIB is used here to represent the generic chemical.

development (developmental toxicity, teratogenicity) and effects on reproduction (effects on adult male and female reproductive performance). However, reproduction is a total life cycle process with various windows of vulnerability that differ from one species to another or from one chemical to another. In the case of the PEs, the window of greatest vulnerability is during late gestation (days 16-19 in the rat) and permanent damage is evident during the early neonatal period. (Some recovery occurs in non-developmentally altered tissues if exposure is curtailed). The standard protocol for assessment of developmental toxicity in the rat includes exposure from gestation days 6-15. Thus, developmental toxicity studies designed according to international regulatory requirements are usually insensitive to the effects of PEs on the development of male reproductive structures. In this report, the effects of concern of PEs are considered to be developmental effects on reproductive tissues. The relevant literature on the studies that describe these effects are included in Section 2.3.2 on Developmental Effects. The literature on the reproductive toxic effects of PEs is summarized in the next section, Section 2.3.3.

2 Permanently Banned Phthalates

2.1 Di-n-Butyl Phthalate (DBP)

Comments from the NTP-CERHR Monograph of the Potential Human Reproductive and Developmental Effects of Di-n-Butyl Phthalate (DBP), (NTP, 2000)

Summary of NTP-CERHR panel for DBP:
Are people exposed to DBP? Yes
Can DBP affect human development or reproduction? Probably
Are current exposures to DBP high enough to cause concern? Possibly

NTP statements upon review of the report of the NTP-CERHR DBP panel:
The NTP concurs with the CERHR panel that there is minimal concern for developmental effects when pregnant women are exposed to DBP levels estimated by the panel (2-10 µg/kg-day).

Based upon recent estimated DBP exposures among some women of reproductive age, the NTP has some concern for DBP causing adverse effects to human development, particularly of the male reproductive system.

The NTP concurs with the CERHR panel that there is negligible concern for reproductive toxicity in exposed adults.

2.1.1 Human Data

One study reported the effects of exposure to DBP on human reproductive measures (Murature *et al.*, 1987). Total sperm number and concentration of DBP in cellular fractions of ejaculates were measured in semen of college students. There was a negative correlation between DBP concentration and sperm indices but causal relationship was unclear. Confounders were not adequately taken into account.

2.1.2 Animal Data

Over 20 studies were reviewed. All studies showed similar effects at high doses (~ 2g/kg in rats). Representative or key studies include:

In a study reported by Gray *et al.*, (1982), adult rats, mice, guinea pigs, and hamsters were given DBP by gavage for 7 or 9 days at dose levels of 2 or 3 g/kg-day. Testes weights were decreased and histopathologic exams showed reduction in spermatids and spermatogonia with adverse effects in almost all tubules. The effects in rats were > mice > hamsters. The monoester had minimal effect in the hamster (only one of eight animals had more than 90% tubular atrophy of the testes).

Wine *et al.*, (1997) reported the results of a continuous breeding study in Sprague -Dawley rats given doses of 0, 52, 256, or 509 mg/kg-day via the diet. They observed infertility and lighter and fewer pups. A NOAEL was not established.

A multigeneration reproduction study in Long Evans rats was reported by Gray *et al.,* (1999). Females were given 0, 250, or 500 mg/kg/day and males were given 0, 250, 500, or 1000 mg/kg-day orally. They observed a delay in puberty in males, decreased fertility, increased testicular atrophy, decreased sperm counts, mid-term abortions, and malformations among offspring including abdominal testes and hypospadias.

2.1.3 Studies Reported Since the NTP-CERHR Report in 2000

2.1.3.1 Human Data

Duty *et al.,* (2005) studied phthalate metabolites, including monobutyl phthalate (MBP), and reproductive hormones in urine of adult men recruited from Massachusetts General Hospital. The authors admit that changes in hormones did not follow the expected pattern, raising the question of whether the changes were physiologically relevant or were the product of multiple statistical comparisons.

Huang *et al.,* (2007) examined the association between thyroid hormones and phthalate monoesters in serum and urine from pregnant women. There was a significant positive association between estradiol and progesterone, T3 and T4, and T4 and FT4. There was a significant negative association between T4 and MBP, and FT4 and MBP.

Main *et al.,* (2006) studied phthalates, including DBP, in human breast milk and their association with altered endogenous reproductive hormones in three month old infants. There was a significant association between MBP and sex hormone binding globulin.

Jönsson *et al.,* (2005) reported human reproductive effects relative to phthalate exposure in men undergoing military examinations, including sperm concentrations, motility, integrity, semen volume, epididymal and prostate function, and serum reproductive hormones. For those who had urine with DBP, there was no association between DBP and reproductive endpoints.

Zhang *et al.,* (2006) studied the relationship between phthalate levels in semen and semen measures in men from the Shanghai Institute of Planned Parenthood Research. There was no correlation between DBP concentration in semen and sperm concentration or viability. The time for liquefaction of semen increased with increased DBP concentration. Semen quality decreased with increased DBP concentration.

Reddy (2006) studied blood from infertile women with endometriosis and those without but having other causes of infertility. The author concluded that DBP serum concentrations may be associated with increased endometriosis in women.

2.1.3.2 Animal Data

Mahood *et al.,* (2007) evaluated adult and fetal toxicity in Wistar male and female rats given 0, 4, 20, 100 or 500 mg DBP/kg-day on gestation days 13.5 to 20.5 or 21.5. There was a dose dependent decrease in male fertility at 20 mg/kg-day and above, with the decrease being significant at 500. Testicular toxicity was increased while testicular testosterone was decreased at 100 and 500 mg/kg-day. Fetal endpoints were the most sensitive to DBP effects. The NOAEL was 20 mg/kg-day.

The effect of DBP on female reproductive measures was reported in two studies by Gray *et al.,* (2006). Long Evans hooded rats were dosed orally from lactation day 21 to gestation day 13 of a third pregnancy. DBP did not affect maturation, estrus cyclicity, or % mating or pregnant. There was a decrease in live pups from treated females in the first and second pregnancies.

In a second study, 24 day old female rats were dosed orally with 0, 250, 500 or 1000 mg DBP/kg-day 5 days/week for 110 days, then 7 days/week until during the second pregnancy when they were killed. Pregnancies and the number of live pups were decreased at 500 and 1000 mg/kg-day. In the females at the high dose level, serum progesterone was decreased and hemorrhagic corpora lutea were observed on ovaries of females at necropsy.

Ryu *et al.,* (2007) examined DNA changes in male Sprague-Dawley rats dosed orally with 0, 250, 500 or 750 mg DBP/kg-day for 30 days. They saw changes in genes involved in xenobiotic metabolism, testis development, sperm maturation, steroidogenesis and immune response. They also saw upregulation of peroxisome proliferation and lipid homeostasis genes. The authors concluded that DBP can affect gene expression profiles involved in steroidogenesis and spermatogenesis, affecting testicular growth and morphogenesis.

In a publication since the NTP-CERHR review, McKinnell *et al.,* (2009) reported that monobutyl phthalate (MBP) given to marmosets did not measurably affect testis development or function or cause testicular dysgenesis. No effects emerged after adulthood. Effects on germ cell development were inconsistent or of uncertain significance.

Human and animal studies published since the NRP-CERHR review of DBP support the conclusion of the earlier review that DBP probably can affect human development or reproduction.

2.2 Butyl Benzyl Phthalate (BBP)

Comments from the NTP-CERHR Monograph of the Potential Human Reproductive and Developmental Effects of Butyl Benzyl Phthalate (BBP), (NTP, 2003a)

Summary of NTP-CERHR panel for BBP:

Are people exposed to BBP? Yes
Can BBP affect human development or reproduction? Probably
Are current exposures to BBP high enough to cause concern? Probably not.

NTP statements upon review of the report of the NTP-CERHR BBP panel:

The NTP concludes that there is minimal concern for developmental effects in fetuses and children.

The NTP concurs with the CERHR panel that there is negligible concern for adverse reproductive effects in exposed men.

2.2.1 Human Data

No human data on BBP alone were available for review by the panel.

2.2.2 Animal Data

Six studies were reviewed. No study was definitive and no multigeneration study had been published for BBP. Representative or key studies include:

A reproductive screen of BBP was published by Piersma (2000). The study design was that of the standard OECD screen number 421 protocol. Male and female Harlan Cpb-WU rats were gavaged with 0, 250, 500, or 1000 mg/kg-day for 14 days. Males and females were dosed for 14 days during mating. Males were killed at 29 days; dosing of the females continued to postnatal day (PND) 6 after which females were killed and necropsied. Pups were counted and examined on PND 1 and 6.

Low fertility, testicular degeneration and interstitial cell hyperplasia were observed in the high dose males. The NOAEL was of uncertain value because of the screen-design of the study.

A one-generation reproduction study designed according to OECD guideline number 415 protocol was conducted in Wistar rats (TNO, 1993). BBP mixed in the diet provided 0, 106, 217, or 446 mg/kg-day to males and 0, 108, 206, or 418 mg/kg-day to females. All reproductive indices were normal. Liver and reproductive organs were normal upon histopathologic examination.

A 10-week modified mating trial study was conducted by the NTP in male F344 rats (NTP, 1997). BBP mixed in the diet provided 0, 20, 200, or 2,200 mg/kg-day. After 10 weeks of dosing, the treated males were mated 1 male to 2 untreated females. Females were necropsied on GD 13 for examination of uterine contents. There was a decrease in the number of sperm in the epididymis at each dose level. There were no pregnancies at the high dose level of the males. The NOAEL was considered uncertain by the CERHR panel because there was no assessment of reproductive systems in the F1 generation.

2.2.3 Studies Reported Since the NTP-CERHR Report in 2003

2.2.3.1 Human Data

No new studies were reported on BBP. However, see reviews of studies on MBP under the review of DBP.

2.2.3.2 Animal Data

Tyl *et al.*, (2004) reported on a 2 generation reproductive study on BBP given to CD rats in the diet at concentrations to provide 0, 50, 250 or 750 mg/kg-day for 10 weeks prior to mating and through the second generation pups. Systemic effects included reduction in body weights, increased organ weights, and in F0 females, decreased ovarian and uterine weights. There were no significant effects in F0 males.

In the F1 generation, mating and fertility indices were reduced, and weights of testes, epididymis, seminal vesicles, coagulating glands and prostate were reduced. Also, there were reproductive tract malformations—hypospadias, missing organs, and abnormal organ size and shape.

Findings in males included decreased epididymal sperm number, motility, progressive motility and increased histopathologic changes in the testes and epididymis.
In the females, the mating and fertility indices were reduced along with uterine implants, total and live pups, number of live pups and ovarian weight. Uterine weights were increased.

In the F2 generation, findings were similar to those in F1 and also included decreased anogenital distance in males at 250 mg/kg-day and above, increased nipple/areolae retention in males at 750 mg/kg-day.

NOAELs:		adult reproductive toxicity	250 mg/kg-day
	F1, F2	offspring repro toxicity	250 mg/kg-day
NOAEL:	F1, F2	dec anogenital distance in males	50 mg/kg-day

Findings in a 2-generation reproductive study reported by Aso *et al.*, (2005) were in agreement with those of Tyl *et al.*, (2004). The NOEL/NOAEL for the parental animals and for offspring growth and development was less than 100 mg/kg-day.

Animal studies published since the NTP-CERHR review of BBP in 2003 support the conclusions of that review that BBP can probably affect human development or reproduction.

2.3 Di (2-ethylhexyl) Phthalate (DEHP)

Comments from the NTP-CERHR Monograph of the Potential Human Reproductive and Developmental Effects of Di (2-ethylhexyl) Phthalate (DEHP), (NTP, 2006)

Summary of the NTP-CERHR panel for DEHP:

Are people exposed to DEHP? Yes
Can DEHP affect human development or reproduction? Probably
Are current exposures to DEHP high enough to cause concern? Yes

NTP statements upon review of the report of the NTP-CERHR DEHP panel:

The NTP concurs with the CERHR DEHP panel that there is serious concern that certain intensive medical treatments of male infants may result in DEHP levels that affect development of the reproductive tract.

The NTP concurs with the CERHR DEHP panel that there is concern for adverse effects on development of the reproductive tract in male offspring of pregnant and breast-feeding women undergoing certain medical procedures that may result in exposure to high levels of DEHP.

The NTP concurs with the CERHR DEHP panel that there is concern for effects of DEHP exposure on development of the reproductive tract for infants less than one year old.

The NTP concurs with the CERHR DEHP panel that there is some concern for the effects of DEHP exposure on development of the reproductive tract in male children older than one year.

The NTP concurs with the CERHR DEHP panel that there is some concern for adverse effects of DEHP exposure on development of the reproductive tract in male offspring of pregnant women not medically exposed to DEHP.

The NTP concurs with the CERHR DEHP panel that there is minimal concern for reproductive toxicity in adults exposed at 1-30 µg/kg-day. This level of concern is not altered for adults medically exposed to DEHP.

2.3.1 Human Data (Summarized from the November 2006 CERHR Report)

Modigh *et al.,* (2002) evaluated time-to-pregnancy in the partners of men potentially exposed to DEHP occupationally. 326 pregnancies were available for analysis from 234 men. Pregnancies were categorized as unexposed (n=182), low exposure (n=100), or high exposure (n=44) based on measurements of DEHP concentrations in air at the worksite.

Median time-to-pregnancy was 3.0 months in the unexposed group, 2.25 months in the low exposure group, and 2.0 in the high exposure group. The author concluded that there was no evidence of a DEHP-associated prolongation in time-to-pregnancy, although they recognized that there were few highly exposed men in their sample. The mean DEHP exposure level for men in the study was less than 0.5 mg/m^3.

Phthalate esters were measured in seminal plasma of 21 men with unexplained infertility by Rozati *et al.,* (2002). Comparison was made to seminal plasma phthalate concentrations in a control group with evidence of conception and normal semen analysis.
The mean +/- SD seminal plasma phthalate ester concentration in the infertile group was 2.03 +/- 0.214 µg/mL compared to 0.06 +/-0.002 µg/mL in the control group ($p<0.05$). There was a significant inverse correlation between seminal phthalate ester concentration and normal sperm morphology and a positive correlation between seminal phthalate ester concentration and the percent acid-denaturable sperm chromatin. There was no significant correlation between semen phthalate ester concentration and ejaculation volume, sperm concentration, progressive motility, sperm vitality, sperm osmoregulation, or sperm chromatin decondensation. The authors concluded that adverse effects of phthalate esters were consistent with published data on male reproductive toxicity of these compounds.

The CERHR panel concluded that the sample size was small and there was very little information on the selection of controls for infertile cases. There was little assessment of confounders and no evidence that exposure assessment was blind to the case/control status of participants.

The CERHR panel considered this study to be of limited usefulness in the evaluation process.

Papers by Duty *et al.,* (2003a; 2003b) and Hauser *et al.,* (Hauser *et al.,* 2005) report on the results of evaluations of reproductive measures of men being examined in a clinic as part of a fertility evaluation. The study population included 28 men (17%) with low sperm concentration, 74 men (44%) with < 50% motility, 77 men (46%) with more than 4% normal form and 77 men who were normal in all three domains. HPLC/MS methods were used to measure urinary levels of the PE metabolites mono(2-ethylhexyl) phthalate (MEHP) and for monoethyl, monomethyl, mono-n-butyl, monobenzyl, mono-n-octyl, monoisononyl, and monocyclohexyl phthalates. There were no significant associations between abnormal semen parameters and MEHP urine concentration above or below the group median. The authors did not present any conclusions relative to MEHP (Duty *et al.*, 2003a).

Duty *et al.,* (2004) evaluated urinary MEHP levels and sperm motion parameters in males presenting for fertility evaluation without regard to whether the male had a fertility problem. One-hundred eighty-seven of the subjects had measurements of sperm motility and urine phthalate levels. Methods for urinary phthalate measurements were similar to those reported in Duty *et al.,* (2003a). The authors concluded that there was a pattern of decline (non-statistically significant) in motility parameters. Lack of statistical significance may have reflected the relatively small sample size.

Duty *et al.,* (2003b) evaluated a possible association between urinary phthalate monoester concentrations and sperm DNA damage using the neutral comet assay. Subjects were a sub-group (n=141) of Duty *et al.,* (2003a). There were no significant associations between comet assay parameters and MEHP urinary concentrations.

This series of papers by Duty and Hauser were considered by the CERHR panel to be useful in the evaluation process but use of a subfertile population was a weakness of the study design.

2.3.2 Animal Data (Summarized from the November 2006 CERHR Report)

Sixty eight studies were reviewed, predominantly in rodents, building on the original observation that DEHP produced testicular atrophy in a subchronic toxicity study (Gray *et al.*, 1982). Most studies used high dose levels, e.g., 2 gm/kg-day. All report similar effects on the testes. Representative or key studies include:

A key study for quantitative assessment of the reproductive toxicity of DEHP is a study reported by Reel *et al.,* (1984) and Lamb *et al.,* (1987). This was a continuous breeding protocol with cross-over mating trials using CD-1 Swiss mice. DEHP was administered in the feed in concentrations to deliver 0, 14, 141, or 425 mg/kg-day. At 425, no breeding pairs delivered a litter; at 141, fertility was significantly reduced. The cross-over mating trial coupled high dose males with untreated females and untreated males with high dose females. The treated females had no litters; in the matings with treated males, only 4/20 had a litter. When the high dose males were necropsied, testicular and epididymal weights were reduced and there was histologic evidence of seminiferous tubule destruction. The NOAEL was ~14 mg DEHP/kg-day.

Fisher-344 rats (Agarwal *et al.,* 1986), were given DEHP in the diet for 60 days at concentrations to give 0, 18, 69, 284, or 1,156 mg DEHP/kg-day followed by 5 days of mating with untreated females while on control diets. There were testicular lesions at the high dose level but not at lower dose levels. The high dose level was the LOAEL and 284 mg/kg-day was the NOAEL.

Rhoades *et al.,* (1986) reported two studies in marmosets. One involved oral doses of DEHP to 5 males and females for 14 days at a dose level of 2 g/kg-day and an ip study in which five 2-year old males were given 1 g/kg-day for 14 days. There were insufficient data in the published report to support the conclusions. More data on this study were available in an EPA docket but confidence in the data was limited because of the single dose used as well as the procedures used for histological examination of tissues.

Schilling *et al.,* (2001) reported the results of a 2-generation reproduction study in Wistar rats. DEHP was given in the feed at concentrations to provide 0, 113, 340, or 1,088 mg DEHP/kg-day. The authors concluded that reproductive performance and fertility were affected only at the high dose level. Developmental toxicity noted at the top two doses included increased stillbirths and pup mortality, decreased pup body weight, decreased male anogenital distance, and increased retained nipples/areolae in males. There was a delay in sexual maturation of F1 males and female offspring at the high dose.

While the authors concluded that there were significant effects only at the high dose level, the CERHR panel concluded that there were effects at all dose levels.

2.3.3 Studies Reported Since the NTP-CERHR Report in 2006

2.3.3.1 Human Data

Studies since the NTP-CERHR report of 2006 reinforce the conclusion that "DEHP can probably affect human reproduction and development." DEHP-induced reproductive effects are less well described in humans than in animals. Studies associating DEHP exposure to human fertility have been informative. Sperm DNA damage has been associated with urinary MEHP concentrations (Hauser *et al.*, 2007) and a slight increase in odds ratio (OR=1.4; CI=0.7-2.9 adjusted for age, abstinence, and smoking; (Duty *et al.*, 2003a).

Human studies are not uniformly positive when relating DEHP exposures to reproductive deficiencies. While human studies were often limited by small sample sizes, confounders, and sampling methodologies, human studies have shown correlations between certain sperm parameters (morphology, chromatin structure, and mobility) to DEHP or MEHP exposures.

2.3.3.2 Animal Data

Foster *et al.,* (2006) repeated the study of DEHP in rats reported by Reel *et al.*, (1984) using the continuous breeding protocol of the NTP to determine if examination of a larger number of littermates would increase the sensitivity to detect a lower NOAEL. Increasing the cohort examined from breeding males (as done in the previous study) to a larger cohort by including non-breeding males lowered the NOAEL from 50 mg/kg-day to 5 mg/kg-day in this study.

Gray *et al.,* (2009) studied the dose response curve for Phthalate Syndrome effects in Sprague-Dawley rats given DEHP by gavage at dose levels of 0, 11, 33, 100 or 300 mg/kg-day on gestation day 8 to lactation day 17. Exposure for some males continued to age 63-65 days. A significant percent of F1 males displayed one or more of the Phthalate Syndrome lesions at 11 mg/kg-day or greater. This confirms the NTP study (Reel *et al.*, 1984; Lamb *et al.*, 1987) which reported a NOAEL and LOAEL of 5 and 10 mg/kg-day, respectively, via the diet.

While there are many more animal studies on the effects of DEHP and metabolites on reproductive measures than human studies, the experimental design of many of them is not sufficiently robust to assess components of the phthalate syndrome at low levels of exposure. Gray *et al.,* (2009) commented that their study and the NTP study (Reel *et al.*, 1984; Lamb *et al.*, 1987) are the only two studies "that provide a comprehensive assessment of phthalate syndrome in a large enough number of male offspring to detect adverse reproductive effects at low dose levels". Considered overall, animal studies have repeatedly demonstrated that DEHP induces reproductive deficits in males of many species, including many strains of rats and mice. Female reproductive deficits have also been reported in numerous animal studies.

Andrade *et al.*, (2006a) reported an extensive dose-response study following *in utero* and lactational exposure of Wistar rats to DEHP given orally by gavage at a series of dose levels ranging from 0.0015 to 405 mg/kg-day. Phthalate syndrome effects were seen in male offspring of females dosed at 405 mg/kg-day. Delayed preputial separation was seen at 15 mg/kg-day and higher. Testes weight was significantly increased at dose levels of 5, 15, 45, and 135 mg/kg-day but not at 405. The NOAEL was 1.215 mg/kg-day.

In another study, Andrade *et al.,* (2006b) reported on the reproductive effects of *in utero* and lactational exposure to DEHP in adult male rats. The experimental design duplicated Andrade *et al.,* (2006a). Reduced daily sperm production and cryptorchidism were the most frequent effects seen in adult males. The NOAEL for these effects was 1.215 mg/kg-day.

3 Interim Ban Phthalates

3.1 Di-n-Octyl Phthalate

Comments from the NTP-CERHR Monograph of the Potential Human Reproductive and Developmental Effects of Di-n-Octyl Phthalate (DnOP), (NTP, 2003d)

Summary of NTP-CERHR panel for DnOP [DNOP]:
Are people exposed to DnOP? Yes
Can DnOP affect human development or reproduction? Probably not
Are current exposures to DnOP high enough to cause concerns? Probably not

NTP statement upon review of the report of the NTP-CERHR DnOP panel:
The NTP concurs with the CERHR panel that there is negligible concern for effects on adult reproductive systems.

3.1.1 Human Data

No human data on DNOP were available for review by the panel.

3.1.2 Animal Data

One reproductive study in CD-1-Swiss mice was reported by Heindel *et al.*, (1989). DNOP was mixed in the diet to provide 0, 1800, 3600, or 7500 mg DNOP/kg-day. There were no effects on the ability to produce litters, litter size, sex ratio, or pup weight or viability over five successive litters. The last litters were mated to produce the F1 generation. There were no effects on fertility, litter size, or pup weight or viability. Sperm indices and estrus cycles were unchanged.

Poon *et al.*, (1997) reported a subchronic toxicity study in Sprague-Dawley rats given DNOP for 13 weeks at dose levels up to 350 mg/kg-day. Testes weights and histology were normal at all dose levels.

Foster *et al.*, (1980) gavaged male Sprague-Dawley rats with 2800 mg DNOP/kg-day for 4 days. No testicular lesions were observed.

3.1.3 Studies Reported Since the NTP-CERHR Report in 2003

Neither animal nor human studies have been published since the NTP-CERHR review of 2003 that would change the conclusion of that review that DNOP would not be expected to affect human development or reproduction.

3.2 Diisononyl Phthalate (DINP)

Comments from the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-Isononyl Phthalate (DINP), (NTP, 2003c)

Summary of NTP-CERHR panel for DINP:

Are people exposed to DINP? Yes
Can DINP affect human development or reproduction? Probably
Are current exposures to DINP high enough to cause concern? Probably not

NTP statements upon review of the report of the NTP-CERHR DINP panel:

The NTP concurs with the conclusions of the CERHR panel and has minimal concern for DINP causing adverse effects to human reproduction or fetal development.

The NTP has minimal concern for developmental effects in children.

3.2.1 Human Data

No human data on DINP were available for review by the panel.

3.2.2 Animal Data

One study was reviewed which included one- and two-generation feeding studies in Sprague-Dawley rats that were exposed in-utero during the entire duration of gestation (Waterman *et al.*, 2000). In the one-generation dose range finding study, rats were given dietary levels of 0, 0.5, 1.0, or 1.5% DINP. In the two-generation study, rats were given 0, 0.2, 0.4, or 0.8% DINP (up to 665-779 mg DINP/kg-day in males or 555 to 1,229 mg/kg-day in females). In the two-generation study, reproductive parameters including mating, fertility, and testicular histology were unaffected in both generations at the highest dose level.

3.2.3 Studies Reported Since the NTP-CERHR Report in 2003

3.2.3.1 Human Data

No studies were found for review.

3.2.3.2 Animal Data

Patyna *et al.*, (2006) evaluated the reproductive and developmental effects of DINP and DIDP in a three generation study in Japanese medaka fish given 0 or 20 ppm DINP-1 in the diet (flake food). The estimated dose was 1 mg/kg/day. There were no significant effects on survival, fertility or on the number of eggs, and no evidence of endocrine-induced effects such as changes in gonad morphology or weight, sex ratio, intersex conditions, or sex reversal.

Available publications support the NTP conclusion of the CERHR review in 2003 that there is minimal concern for DINP causing adverse effects to human reproduction.

3.3 Diisodecyl Phthalate (DIDP)

Comments from the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-Isodecyl Phthalate (DIDP), (NTP, 2003b)

Summary of the NTP-CERHR Panel for DIDP:

Are people exposed to DIDP? Yes
Can DIDP affect human development or reproduction? Possibly (development but not reproduction)
Are current exposures to DIDP high enough to cause concern? Probably not

NTP statements upon review of the report of the NTP-CERHR panel on DIDP:

The NTP concurs with the CERHR panel that there is minimal concern for developmental effects in fetuses and children.

The NTP concurs with the CERHR panel that there is negligible concern for reproductive toxicity to exposed adults.

3.3.1 Human Data

No human data on DIDP were available for review by the panel.

3.3.2 Animal Data

Onereport was reviewed which consisted of two 2-generation reproduction studies (ExxonMobil, 2000). Dose levels for the first study were selected on the basis of range finding studies. Dose levels for the second 2-generation study were selected on the basis of the results of the first 2-generation study. All studies were in Crl:CDBR VAF rats given DIDP in the diet. Based on standard measures and procedures, no adverse reproductive effects were observed in either 2-generation study at dose levels that caused decreased weight gain and increased liver and kidney weights in the adults. The highest dose level, 0.8% DIDP in the diet, administered the following doses of DIDP in mg/kg-day: males, F0—427-781; F1—494-929, during premating; females, F0—641-1,582; F1—637-1,424 during gestation and lactation.

3.3.3 Studies Reported Since the NTP-CERHR Report in 2003

Neither human nor animal studies have been published since the NTP-CERHR review in 2003 that would change the conclusion of that review that DIDP would not be expected to affect human reproduction.

4 Phthalates not Banned by the CPSIA

4.1 Dimethyl Phthalate (DMP)

4.1.1 Human Data

No human studies were available for review.

4.1.2 Animal Data

No single or multiple generation reproductive studies in animals were available for review.

4.2 Diethyl Phthalate (DEP)

4.2.1 Human Data

Jönsson *et al.,* (2005) examined urine, serum, and semen samples from 234 young Swedish men. The highest quartile for urinary MEP had 8.8% fewer sperm, 8.9% more immotile sperm, and lower LH values compared to subjects in the lowest quartile.

Hauser *et al.,* (2007) and Duty *et al.,* (2003b) reported that sperm DNA damage correlated with urinary MEP levels in men who presented to a health facility for semen analyses as part of an infertility investigation.

Pant *et al.,* (2008) found a significant inverse relationship between sperm concentration and level of DEP in semen in a group of 300 males 20-40 years of age.

4.2.2 Animal Data

Lamb *et al.,* (1987), NTP (1984) reported on a two-phase study in which mice were first given DEP in the diet at concentrations that provided 451, 2,255 and 4,509 mg/kg-day to males and 488, 2,439, and 4,878 mg/kg-day to females for seven days prior to mating and for 98 days of cohabitation plus 21 days after separation. Following exposure, there were no effects on reproductive indices--number fertile pairs, pups/litter, live pups/ litter, live pups/litter, or the live pup birth weight. Offspring of these mice were subsequently given DEP in their diets (4,509, 4,878 mg/kg-day) from weaning through seven weeks premating plus the continuous breeding period. F1 parental males had 32% increased prostate weight, 30% decreased sperm concentration, increased rates of abnormal sperm (excluding tailless sperm), 25% decreased body weight, and 14% decreased total number of live F2 pups(male and female combined) per litter at birth versus controls. F1 parental females had a non-significant decrease in absolute and relative uterine weight (LOAEL = 4,878 mg/kg-day).

Fugii *et al.,* (2005) reported on a two generation reproductive study in rats given DEP in the diet at concentrations to provide 1,016 mg/kg-day to males and 1,375 mg/kg-day to females for ten weeks prior to mating, throughout mating, and during gestation and lactation. There were no effects on fertility or fecundity. Decreased serum testosterone levels in FO males and increased tailless sperm in F1 males were considered nonsignificant.

A dose-related decrease in the absolute and relative uterine weight (F1 and F2 weanlings; LOAEL = 1,297-1,375; NOAEL = 255-267 mg/kg-day) and a decrease in the number of gestation days (F0, F1 adults; LOAEL = 1,297-1,375; NOAEL = 255-267 mg/kg-day) were reported for female rats.

Oishi and Hiraga (1980) also reported significantly decreased serum testosterone, serum dihydrotestosterone, and testicular testosterone in JCL:Wistar rats following dietary exposure. These results are questionable, however, when taken in context of other results of the study where increases in testosterone levels were seen after exposure to DBP, DiBP and DEHP.

4.3 Diisobutyl Phthalate (DIBP)

4.3.1 Human Data

No studies were reported in humans.

4.3.2 Animal Data

No single or multiple generation reproductive toxicology studies were reported.

Zhu *et al.,* (2010) reported on testicular effects in male adolescent rats given DIBP orally once or for seven days at dose levels of 0, 100, 300, 500, 800 and 1,000 mg/kg-day and higher. In rats dosed for seven days, there was a significant decrease in testes weights, increase in apoptotic spermatogenic cells, disorganization or reduced vimentin filaments in Sertoli cells at doses of 500 mg/kg-day and higher.

Hodge *et al.*, (1954) report the effects of DIBP in a four-month subchronic study in albino rats. DIBP was mixed in the diet at concentrations of 0, 0.01, 1.0, and 5%. The estimated mg/kg-day by the authors were 0, 67, 738, and 5,960.

Absolute and relative testis weights were significantly decreased at the high dose. Thus, the NOAEL was 1.0% or 738 mg/kg-day.

4.4 Dicyclohexyl phthalate (DCHP)

4.4.1 Human Data

No human studies were available for review.

4.4.2 Animal Data

Hoshino *et al.,* (2005) reported on a study in Sprague Dawley rats given DCHP in the diet at concentrations of 0, 240, 1,200, and 6,000 ppm.

The estrus cycle length was increased in F0 females at 6,000ppm (500-534 mg/kg-day). However, this effect is the opposite of what is reported for other phthalates and is therefore of questionable toxicological significance.

Atrophy of seminiferous tubules was increased at 1,200 and 6,000 ppm.

There was a significant decrease in spermatid head count in F1 males at 1,200 and 6,000 ppm. However, the relevance is uncertain because other sperm parameters are normal and this finding was not reported with other phthalates. Prostate weight was significantly decreased at all dose levels; relative prostate weight was decreased at 6,000ppm. However, the relevance of these findings is uncertain because other sperm parameters were normal and these findings were not reported with other phthalates.

The NOAELs stated by the authors:

--reproductive toxicity in F1 males—240ppm or 18 /mg/kg-day,

--reproductive toxicity in females—6,000ppm or 511-534 mg/kg-day.

4.5 Diisoheptyl Phthalate (DIHEPP)

4.5.1 Human Data

No human studies were available for review.

4.5.2 Animal Data

McKee *et al.*, (2006); ExxonMobil Chemical Co. (2003) reported a two-generation reproductive toxicity study in Sprague Dawley rats given DIHEPP in the diet at concentrations of 0, 1,000, 4,500, and 8,000ppm

Fertility was decreased at 4,500 and 8,000 ppm. Sperm concentration and sperm production were decreased at all dose levels. Weights of testes, epididymis, cauda epididymis, and ovary were decreased at 8,000 ppm. There was degeneration of seminiferous tubules in F1 males at 4,500 and 8,000 ppm. The authors concluded that some of the effects seen in F1 males could be related to clinical signs of toxicity associated with changes in the external genitalia (hypospadias, absent or undescended testes) observed in the F1 males.

Concentrations of DIHEPP in the diet of males after breeding were 4,500 ppm (227 mg/kg-day) and 1,000 ppm (50 mg/kg-day). Thus, the NOAEL in this study is 50 mg/kg-day.

4.6 Diisooctyl Phthalate (DIOP)

4.6.1 Human Data

No human studies were available for review.

4.6.2 Animal Data

No animal studies were available for review.

4.6.3 Mode of Action

While activation of PPAR-α is involved in carcinogenesis in rodents, it probably does not play a significant role in the induction of developmental toxicity and testicular toxicity. Genetically modified mice (PPAR-alpha knockout mice) are susceptible to phthalate induced developmental and testicular effects. Also, PPAR-α null mice have less frequent and less severe testicular lesions following exposure to DEHP (Ward *et al.*, 1998). This mouse does express PPAR-γ in the testes (Maloney and Waxman, 1999). The roles of PPAR-beta and gamma activation in reproductive toxicity has not been thoroughly studied.

Guinea pigs, a non-responding species to peroxisome proliferating effects of DBP, is susceptible to the testicular effects of this phthalate (Gray *et al.*, 1982).

Gray *et al.,* (1982) investigated the reason for the lack of testicular lesions in hamsters administered DBP and the monobutyl ester (MBP) orally at doses higher than those that cause testicular lesions in rats. The levels of MBuP in urine were 3-4 fold higher in the rat than in the hamster. A significantly higher level of testicular beta-glucuronidase in the rat compared to the hamster caused the authors to speculate that damage in the rat may be related to higher levels of unconjugated MBP, the putative toxicant. In addition, MEHP and DPENP did cause testicular effects in the hamster (Gray *et al.*, 1982).

All phthalates that cause testicular toxicity produce a common lesion characterized by alterations in Sertoli cell ultrastructure and function (Gray and Butterworth, 1980; Creasy *et al.*, 1983; Creasy *et al.*, 1987). More recent studies have concluded that testicular toxicity caused by some phthalates during development are related to decreased testosterone production (Mylchreest *et al.*, 1998; Parks *et al.*, 2000; 2002; Barlow and Foster, 2003).

Hannas *et al.,* (2011) reported that dipentyl phthalate (DPENP) is much more potent than other phthalates in disrupting fetal testis function and postnatal development of the male Sprague-Dawley rat. Compared to the effect of DEHP under similar conditions of dosing, dipentyl phthalate was eight fold more potent in reducing testosterone production and two to threefold more potent in inducing development of early postnatal male reproductive malformations.

4.7 Di(2-propylheptyl) Phthalate (DPHP)

4.7.1 Human Data

No human studies were available for review.

4.7.2 Animal Data

No published animal studies were available for review. A summary of a preliminary report of a 90-day dietary subchronic study in rats was available from Union Carbide Corp (1997).

There was a significant reduction in sperm velocity indices (n=6 rats/group). Other factors associated with sperm function and concentration (total sperm, static count, percent motile, motile count, total sperm concentration, and concentration of sperm /gm of tissue) were not affected, nor was this endpoint reported in other studies. Further, males had a 23% decrease in body weight. Spermatic endpoints, therefore are of questionable value.

5 Phthalate Substitutes

5.1 Non-reproductive Toxicity

The phthalate substitute chemicals reviewed here are generally low in acute toxicity by several routes of exposure. They are also generally negative in tests for genotoxic potential.

These substitutes have a different carcinogenic profile than the phthalates they have replaced. Phthalates, to varying degrees, activate PPAR-α receptors in rodent tissues that result in peroxisome proliferation in the liver and cancer of the liver. That is not a general property of the substitutes.

A carcinogenesis study conducted on ATBC in rats did not have an increase in tumors but the study had low group sizes and low power to detect an effect. Two year studies on DEHA in rats were negative but an increased number of liver tumors were seen in both male and female mice. The increase in tumors may have been related to peroxisome proliferation. There was a significant increase in thyroid tumors in rats given DINX in the diet for two years. A carcinogenesis study of DEHT in rats was negative. No cancer studies have been done on TOTM.

(Likewise, none of the substitutes caused the same kind of developmental abnormalities of male offspring caused by certain phthalates. The only substitute that caused damage to spermatogenesis in adult male rodents was TOTM which caused a decrease in the number of spermatocytes and spermatids in rats upon histopathologic examination of the testes of rats. Reproductive studies on other substitutes did not show the types of testicular toxicity or developmental abnormalities that are characteristic of certain phthalates).

5.2 Reproductive Toxicity

5.2.1 2,2,4-Trimethyl-1,3-pentanediol-diisobutyrate (TPIB)

5.2.1.1 Human Data

No published data were available for review.

5.2.1.2 Animal Data

Eastman Chemical (2007) reported the results of a combined repeated dose and reproductive/developmental toxicity screening test in Sprague-Dawley rats given TPIB by gavage at dose levels of 0, 30, 150 or 750 mg/kg-day from 14 days before mating to 30 days after mating (males) or day three of lactation (females). The authors reported that TPIB had no significant effect on mating, fertility, the estrus cycle, or delivery or lactation period. Measures were limited to body weights on postnatal day 0 and 4 and necropsy results on day 4. No TPIB-related effects were reported at any dose level. The NOAEL for reproduction and development was 750 mg/kg-day.

Another study by Eastman Company (2001) was conducted according to OECD test guideline 421. Sprague-Dawley rats (12/sex/dose level) were given TPIB in the diet at concentrations to give 0, 120, 359, or 1,135 mg/kg-day to females and 0, 91, 276, or 905 mg/kg-day to males for 14 days before mating, during mating (1-8 days), through gestation (21-23 days), and through postnatal day 4 or 5. Transient decreased body weight gains were noted in parents at high dose levels. There were decreases in the number of implantation sites and numbers of corpora lutea. Changes in epididymal and testicular sperm counts were not considered adverse by the authors. Other reproductive measures were not affected. The authors concluded that the NOAEL for reproduction was 276 mg/kg-day for males and 359 mg/kg-day for females based on total litter weight and size on postnatal day 4 and the decreased number of implants and corpora lutea.

5.2.2 Di(2-ethylhexyl) Adipate (DEHA)

5.2.2.1 Human Data

There were no published data to review.

5.2.2.2 Animal Data

DEHA was administered in the diet of F344 rats and B6C3F1 mice in subchronic and chronic studies reported by the NTP (1982). No histopathologic effects were observed in reproductive organs (testes, seminal vesicles, prostate, ovary or uterus) at ~2,500 mg/kg-day in rats and 4,700 mg/kg-day in mice.

Nabae *et al.*, (2006) and Kang (2006) reported on the testicular toxicity of DEHA given to F344 rats in their diet at concentrations that gave 0, 318, or 1,570 mg/kg-day. There were no changes in body weight, spermatogenesis, relative weight and histology of testes, epididymis, prostate, or seminal vesicles. Kang *et al.*, (2006) found that DEHA caused no testicular toxicity in rats pretreated with thioacetamide to induce liver damage or folic acid to induce chronic renal dysfunction; the testicular toxicity of DEHP was enhanced with the same pretreatments.

Miyata *et al.*, (2006) reported a study in Crj:CD(SD) rats given DEHA by gavage at dose levels of 0, 40, 200, or 1,000 mg/kg-day for at least 28 days. Reproductive endpoints in both sexes were measured but there was no mating trial. The estrus cycle was prolonged in females at the high dose level. No reproductive toxicity was observed in males at any of the dose levels.

Dalgaard (2002; 2003) reported on perinatal exposure of Wistar rats by gavage at dose levels of 0, 800 or 1,200 mg/kg-day on gestation day 7 through postnatal day 17. This was a dose range finding study to examine pups for evidence of antiandrogenic effects—none were observed. Decreased pup weights were seen at both dose levels. In the main study, DEHA was given by gavage at dose levels of 0, 200, 400 and 800 mg/kg-day on gestation day 7 through postnatal day 17. No antiandrogenic effects were seen; a NOAEL of 200 mg/kg-day was based on postnatal deaths.

5.2.3 Di(2-ethylhexyl)terephthalate (DEHT)

5.2.3.1 Human Data

No published data were available for review.

5.2.3.2 Animal Data

Faber *et al.*, (2007) reported the results of a two-generation reproduction study in Sprague-Dawley rats given DEHT in the diet. The dietary admix was given to males and females for 70 days prior to mating plus during pregnancy and lactation. Concentrations in the diet gave O, 158, 316, or 530 mg/kg-day to males and 0, 273, 545, or 868 mg/kg-day to females. No adverse effects on reproduction were observed in either generation at any dose level. Weight gain was decreased in F0 high dose males. Weight gain was decreased in F1 and F2 males at the top two dose levels. The NOAEL for reproductive effects was 530 mg/kg-day; the NOAEL for parental and pup systemic toxicity was 158 mg/kg-day.

Gray *et al.*, (2000) reported a study to look for antiandrogenic effects of DEHT. Pregnant Sprague-Dawley rats were dosed by gavage with 0 or 750 mg/kg-day on gestation day 14 through postnatal day 3. No antiandrogenic effects were observed.

5.2.4 Acetyl Tri-n-Butyl Citrate (ATBC)

5.2.4.1 Human Data

There were no published data to review.

5.2.4.2 Animal Data

A two-generation reproduction study in Sprague-Dawley rats was reported by Robbins (1994). ATBC was mixed in the diet at concentrations to give 0, 100, 300, 1,000 mg/kg-day. Males were exposed for 11 weeks, females for 3 weeks before mating, during mating, and through gestation and lactation. Male and female pups were given diets with ATBC for 10 weeks after weaning. There were no reproductive or developmental effects attributable to ATBC at any dose level.

Chase and Willoughby (2002) reported a one-generation reproduction study (summary only) in Wistar rats given ATBC in the diet at concentrations to provide 0, 100, 300, or 1,000 mg/kg-day four weeks prior to and during mating plus during gestation and lactation. The F0 parents produced an F1 generation of litters. No systemic or reproductive effects were seen at any dose level.

5.2.5 Cyclohexanedicarboxylic Acid, Dinonyl Ester (DINX)

5.2.5.1 Human Data

No published data were available for review.

5.2.5.2 Animal Data

A two-generation reproduction study was reported by SCENIHR (2007) in summary form only. Because the study used OECD TG 416, it was likely conducted in rats. Dose levels by diet were 0, 100, 300, or 1,000 mg/kg-day. The authors reported that there were no effects on fertility or reproductive performance in F0 and F1 parents and no developmental toxicity in F1 or F2 pups. A substudy designed to look for antiandrogenic effects reportedly showed no developmental toxicity at any dose level.

5.2.6 Trioctyltrimellitate (TOTM)

5.2.6.1 Human Data

No published human data were available for review.

5.2.6.2 Animal Data

A one-generation reproduction study was reported in Sprague-Dawley rats given TOTM by gavage at dose levels of 0, 100, 300, or 1,000 mg/kg-day (JMHW, 1998). Males were dosed for 46 days, females for 14 days prior to mating and during mating through lactation day 3. Histologic examination showed a decrease in spermatocytes and spermatids at the top two dose levels. No other reproductive toxicity was seen. The NOAEL was 100 mg/kg-day.

Pre and postnatal effects of TOTM in Sprague-Dawley rats were reported from Huntington Life Sciences (2002). Rats were given 0, 100, 500, or 1,050 mg/kg-day by gavage on days 6-19 of pregnancy or day 3 through day 20 of lactation. There were no significant effects on developmental measures but there was a slight delay in the retention of areolar regions on postnatal day 13 but not day 18 (not considered to be toxicologically significant).

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PEER REVIEW DRAFT

Draft Report to the

U.S. Consumer Product Safety Commission

by the

CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES

AND PHTHALATE ALTERNATIVES

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APPENDIX C

EPIDEMIOLOGY

TABLE OF CONTENTS

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1 Phthalates and Male Reproductive Tract Development

The association of gestational exposure to phthalates and reproductive tract development was explored in three study cohorts. Swan and colleagues (Swan *et al.*, 2005; Swan, 2008) published two papers on the association of urinary phthalate metabolite concentrations and anogenital distance (AGD) in male infants from the same multi-center pregnancy cohort study. In Swan's first paper (2005), there were 85 mother-son pairs with prenatal urinary phthalate concentrations (mean 28.6 weeks of gestation) and AGD measures (mean age at examination was 12.6 months). To account for differences in body size, they defined anogenital index (AGI) as AGD/body weight, a weight–normalized index of AGD. For short AGI, the OR (95% confidence interval) for high compared with medium and low concentrations of MBP were 3.8 (1.2, 12.3) and 10.2 (2.5, 42.2), respectively. The corresponding OR (95% CI) for short AGI for high compared with medium and low concentrations of MBZP, MEP and MIBP were 3.1 (1.002, 9.8) and 3.8 (1.03, 13.9), 2.6 (0.9, 7.8) and 4.7 (1.2, 17.4), 3.4 (1.1, 10.5) and 9.1 (2.3, 35.7), respectively. There were no associations of AGI with MMP and MCPP (metabolites of DMP and DNOP, respectively).

In addition to exploring associations with individual phthalate metabolites, they calculated a summary phthalate score to explore associations with joint exposure to more than one phthalate. The summary phthalate score was strongly associated with short AGI. It is important to note that the summary scores were defined using the results from the analyses for the individual phthalates with AGI. Therefore, it is expected that the summary measure would have a stronger association with AGI. As a group, boys with incompletely descended testicles or a scrotum categorized as small and/or not distinct from surrounding tissue had a shorter AGI.

In 2008, Swan *et al.*, published an update (Swan, 2008) extending their analyses on maternal phthalate exposure and genital development to 106 mother-son pairs, 68 of the sons had AGD measured at two visits. This updated analysis included the original 85 mother-son pairs (Swan *et al.*, 2005). To further reduce confounding by the babies weight, they calculated weight percentile, defined as the expected weight for age using sex-specific estimates of weight percentiles in the U.S. population. Statistical methods accounting for the repeated measures were used, controlling for age and weight percentile. There were significant associations of five phthalate metabolites (MEP, MBP, MEHP, MEHHP, MEOHP) with shortened AGD. This differs from the earlier analysis in which DEHP metabolites were not significantly (MEHP) or marginally (MEOHP, MEHHP) associated with AGD. However, the direction of the associations for the DEHP metabolites with AGD were consistent in the original (Swan *et al.*, 2005) and updated analysis (Swan, 2008). MBZP, of borderline significance with AGD in the original analysis, was not associated with AGD in the updated analysis. MMP and MIBP were of borderline significance with reduced AGD. MCPP was not associated with AGD. As in the earlier paper, the summary phthalate score was more strongly associated with shorter AGD than were individual phthalate measures.

In a small study on 33 male and 32 female infants, researchers from Taiwan (Huang *et al.*, 2009) explored associations of prenatal urine and amniotic fluid levels of MEHP, MBP, MBZP, MMP and MEP with AGD measured at birth. AGD for female infants, after adjusting for birth weight or length, were significantly shorter among those above the median for amniotic fluid MBP or MEHP concentrations, as compared to those below the median. In female infants, urine concentrations of MBP had suggestive negative associations with AGD after adjustment for birth weight or length. Among male infants, birth weight, length, and AGD were not associated with amniotic fluid levels of MBP or MEHP.

A study from Japan, Suzuki *et al.*, (2012), explored associations of urinary phthalate metabolite concentrations with AGI (AGD normalized for body weight) among 111 mother-son pairs. Urine was collected between the 9th and 40th week of gestation (mean (SD) was 29 (9) weeks) and AGD was measured at birth. There were significant associations of MEHP with reduced AGI and suggestive associations with sum of DEHP metabolites. There was no association of MMP, MEP, MNBP, MBZP, MEHHP or MEOHP with AGI. One primary limitation of this study was that 23 examiners performed the AGD measures on the newborns, contributing to possible measurement error and potential attenuation of associations.

1.1 Supporting Evidence for Anti-androgenic Effects of Phthalates

A Danish-Finnish study on 130 three month old male infants, 62 cases with cryptorchidism and 68 controls, explored the association of phthalate concentrations in breast milk with serum reproductive hormones (Main *et al.*, 2006). Breast milk phthalate concentrations were not associated with cryptorchidism but there were associations with hormones related to Leydig cell function. MMP, MEP and MBP were positively associated with LH:free testosterone ratio (a 10 fold increase in MMP, MEP and MBP concentrations raised the LH:free testosterone ratio 18% to 26%) There were suggestive positive associations of MEHP and MINP with LH:free testosterone ratio and suggestive positive associations of MMP, MEP, MBP, and MEHP with LH:testosterone ratio. MINP was associated with increased LH (a 10 fold increase in MINP was associated with a 97% increase in LH) and there was a suggestive association with increased testosterone. MBP was inversely associated with free testosterone, whereas MEP and MEHP showed similar directions of association but were non-significant. For Sertoli cell makers (i.e., FSH and inhibin B), positive non-significant associations were found for MBzP and MEHP with inhibin B. All monoesters were negatively associated with the FSH:inhibin B ratio, which was significant for MEHP. Finally, MEP and MBP were positively associated with SHBG and there were suggestive non-significant positive associations of MBZP and MINP with SHBG.

The Main *et al.*, results for MEP, MBP and MEHP suggest that human Leydig cell development and function is affected following perinatal exposure. The reduced free testosterone and increased LH: free testosterone ratio support the associations of phthalates with reduced AGD reported in the Swan *et al.*,*(Swan et al., 2005)*. Although the changes in hormones related to

Leydig cell function may or may not pose a significant health effect in a single individual, such a shift on a population basis could presumably lead to potential adverse health outcomes.

1.2 Maternal Occupational Exposure and Male Reproductive Tract Anomalies

Several epidemiological studies investigated the association of maternal occupational exposure to phthalates with male reproductive tract anomalies, including cryptorchidism and hypospadias (Van Tongeren *et al.*, 2002; Vrijheid *et al.*, 2003; Ormond *et al.*, 2009; Morales-Suarez-Varela *et al.*, 2011). None of these studies used biological markers to assess phthalate exposure, but instead assigned potential exposure to phthalates based on job titles or self-reported occupational histories. Therefore, these studies are only briefly described because their relevance to the report is limited by the non-specific assessment of phthalate exposure and the lack of data for specific phthalates.

Analyzing data from the Danish National Birth Cohort, Morales-Suarez-Varela *et al.*, (2011) reported an association between hypospadias and exposure to phthalates using a job exposure matrix for endocrine disruptors. In Southeast England, Ormond and coworkers (2009) reported an association between phthalate exposure, defined using job exposure matrices, and increased odds of hypospadias. Using data from the National Congenital Anomaly System in England and Wales, Vrijheid *et al.*, (2003) did not find an association of phthalates with hypospadias. Overall these studies provide limited evidence of an association of hypospadias with jobs that may have phthalate exposure. Critical study design limitations include: 1) non-specific assessment of phthalate exposure based on job title or occupational histories, 2) lack of information on exposure to specific phthalates while at work and their potential level of exposure, and 3) inability to adjust for important co-exposures at work that may confound these associations.

2 Phthalates and Neurodevelopmental Outcomes

Swan and colleagues (2010) assessed the association of prenatal exposure to phthalates with play behavior of children from their multi-center prospective pregnancy cohort study. The child's mother completed a pre-school activities inventory questionnaire that assessed their child's sexually dimorphic play behavior. The association of urinary phthalate metabolite concentrations with play behavior scores (masculine and feminine composite) was assessed separately for boys (n=74, mean age 5 years, range 3.6 to 6.4 years) and girls (n=71, mean age 4.9 years, range 3.6 to 6.0 years). Multivariate regression analyses controlling for child's age, mother's age and education, and parental attitude towards atypical play choices were adjusted for. Among boys, there was an inverse association of urinary concentrations of MBP, MIBP and their sum with decreased (less masculine) composite scores. Additionally, DEHP metabolites, MEOHP, MEHHP, and the sum of these two metabolites with MEHP were associated with a decreased masculine score. Among boys for the other phthalate metabolites measured, they did not find associations with play behavior. Among girls there were no associations of play behavior with any of the phthalate metabolites. Study limitations include the use of a single urine sample during pregnancy to assess exposure to phthalates and self-reported play behavior by the mother. However, it is unlikely that these limitations would introduce bias away from the null, but rather attenuate associations.

Three publications utilizing data from the Mount Sinai School of Medicine Children's Environmental Health Cohort reported on children's neurodevelopmental outcomes in relation to prenatal urinary phthalate concentrations (Engel *et al.*, 2009; Engel *et al.*, 2010; Miodovnik *et al.*, 2011). The Mount Sinai study was a prospective multiethnic birth cohort of 404 primiparous women with singleton pregnancies recruited in New York City between 1998 and 2002. In their first publication, Engel *et al.*, (2009) analyzed the association of prenatal urinary phthalate concentrations with scores on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) measured in 295 children within the first 5 days after delivery. Maternal urine was collected during the third trimester between 25 and 40 weeks' gestation (mean, 31.2 weeks). The exposure assessment approach summed 10 phthalate urinary metabolites based on a molar basis into low (MMP, MEP, MBP, MIBP) and high (MBZP, MECPP, MEHHP, MEOHP, MEHP, MCPP) molecular weight phthalates. Of note is that MEP was the largest contributor, by a wide margin, to the LMW phthalate sum, while the DEHP metabolites were the largest contributors to the HMW sum. This should be taken into account when interpreting the MW sums since the contribution of the individual metabolites is not equivalent within the sum. There were few associations of individual phthalate metabolites (data not shown) and their molar sums with most BNBAS scores. However, there were significant sex-phthalate interactions ($p<0.10$) for the Orientation and Motor domains and the overall Quality of Alertness score. Among girls, there was a significant decline in adjusted mean Orientation score and Quality of Alertness score with increasing urinary concentrations of HMW phthalates. Boys and girls showed opposite patterns of association between low and high MW phthalates and motor performance, with suggestion of improved motor performance in boys with increasing LMW concentrations. Although BNBAS domains represent general CNS organization, the authors hypothesized that there may be sex-specific effects of phthalates.

The second publication from the Mount Sinai study by Engel *et al.*, (2010) reported on the association of prenatal urinary phthalate concentrations with behavior and executive functioning among 188 children assessed up to three times between age 4 and 9 years. Mother's completed the parent-report forms of the Behavioral Rating Inventory of Executive Function (BRIEF) and the Behavior Assessment System for Children Parent Rating Scales (BASC-PRS). Higher urinary concentrations of LMW phthalates were associated with poorer BASC scores for aggression, conduct problems, attention problems, and depression clinical scales, as well externalizing problems and behavioral symptoms index (BSI, the apical summary score that assessed overall level of behavioral functioning). LMW phthalates were also associated with poorer scores on the global executive composite index and the emotional control scale of the BRIEF. Although urinary MBP concentrations were significantly associated with only aggression and externalizing problems, the magnitude of the MBP associations were very similar to LMW phthalates for attention problems, adaptability and the BSI. MBP was also associated with poorer scores on working memory, and the associations for other domains were similar to the LMW associations.

The authors concluded that the profile of the parent reported behaviors were suggestive of the behavioral profiles of children clinically diagnosed with disruptive behavior disorders, conduct disorder, or ADHD. Furthermore, although few children in the study met the standard at risk or clinically significant criteria on the BASC, the patterns across scales and the consistency of the findings across instruments suggest associations of prenatal LWM phthalate exposure with the emergence of disruptive behavior problems in children. Limitations in the Mount Sinai publications include the use of a single spot urine sample late in pregnancy to assess exposure and the use of parent self-report of behavioral and executive function. However, it is unlikely that these limitations would introduce bias away from the null, but rather attenuate associations.

The third publication from the Mount Sinai study by Miodovnik (2011) investigated relationships between prenatal urinary phthalate concentrations and Social Responsiveness Scale (SRS) among 137 children assessed between age 7 and 9 years. The SRS is a quantitative scale for measuring the severity of social impairment related to Autistic Spectrum Disorders (ASD). Higher urinary concentrations of LMW phthalates were associated with higher SRS scores, positively with poorer scores on Social Cognition, Social Communication, and Social Awareness, but not with Social Motivation or Autistic Mannerisms. These associations were statistically significant for MEP and in the same direction for MBP and MMP but not significant. HMW phthalates and sum of DEHP metabolites were non-significantly associated with poorer SRS scores, though of a smaller magnitude. Limitations discussed above for the Mount Sinai study also apply to this report and include the use of a single spot urine sample late in pregnancy to assess exposure and the use of a parent rating survey. It is important to note that the study did not include clinical diagnoses of ASD but rather symptoms common to the disorder. Finally, the associations reported were modest on an individual level.

In a cross-sectional study on 621 Korean school-age children (mean age of 9.05 years, range 8 to 11 years old), Cho *et al.*, (2010) explored associations of urinary MEHP, MEOHP and MBP concentrations with intelligence scores. These were the only phthalate metabolites measured in the spot urine samples. In multivariate models, there were significant associations of the DEHP metabolites with decrements in Full Scale IQ, Verbal IQ, Vocabulary and Block design scores measured using the abbreviated form of the Korean Educational Development Institute-Wechsler Intelligence Scale for Children (KEDI-WISC). Urinary concentrations of MBP were significantly associated with decrements in Vocabulary and block design scores. However, after adjusting for maternal IQ, only the association of DEHP metabolites with Vocabulary score remained significant. A second Korean study (Kim *et al.*, 2009) explored cross-sectional associations of urine phthalate concentrations with ADHD symptoms and neuropsychological dysfunction among 261 children 8 to 11 years of age. Urine DEHP metabolites (MEHP, MEOHP), but not MBP, were associated with teacher assessed ADHD scores. Conclusions based on these two cross-sectional studies are limited because the spot urine samples were collected concurrently with the outcome assessments.

In a third Korean study, Kim *et al.*, (2011) conducted a multi-center prospective cohort study on 460 mother infant pairs, recruited during their first trimester of pregnancy. Spot urine samples, collected during weeks 35 to 41 of gestation, were analyzed for MEHHP, MEOHP and MBP. They reported negative associations between MEHHP, MEOHP and MBP with mental development indices (MDI) of the Bayley Scales of Infant Development assessed at 6 months of age. The psychomotor development indices (PDI) were negatively associated with MEHHP. In a subset analysis adjusted for maternal intelligence, there were negative associations of MEHHP with MDI, and MEHHP, MEOHP and MBP with PDI. They reported sex specific differences whereby in boys, MDI and PDI was negatively associated with MEHHP, MEOHP, andMBP. Coefficients were negative in girls for these associations but were not statistically significant.

Whyatt and colleagues (2011) explored the association of mental, motor and behavioral development at age 3 years with urinary phthalate concentrations measured during the third trimester of pregnancy. In their prospective cohort study on 319 women-child pairs from New York (U.S.), they reported negative associations between urinary concentrations of MIBP and MBPP and PDI and among girls they found a negative association of MBP with MDI. MBP and MIBP were also associated with increased odds of psychomotor delay on BSID-II, with no differences based on child gender. However, there were child sex differences in the relationship between MBP and mental delay. They did not find associations between the sum of DEHP metabolites and measures of neurodevelopment. In the total cohort, MNBP was associated with increased somatic complaints, withdrawn behavior and internalizing behaviors on the Child Behavior Check List (CBCL); there were no associations with child sleep problems or scales in the externalizing domains. MIBP was associated with increased emotionally reactive behavior, whereas MBZP was associated with increased withdrawn behavior and internalizing behavior. There were several differences based on child's gender. Among boys only, MBP was associated with emotionally reactive behavior, somatic complaints, withdrawn behavior, and internalizing behaviors. Among girls only, MBZP was associated with anxious/depressed behavior, somatic complaints, withdrawn behavior and internalizing behaviors. When scores on borderline and clinical ranges of CBCL were used, they found increased odds for MBP and MBZP with scores in clinical range for withdrawn behavior and scoring in the borderline range for internalizing behavior in association with MIBP and MBZP and clinical range on internalizing behaviors for MBZP.

In the seventh prospective pregnancy cohort study, Yolton *et al.*, (2011) reported on the association of early infant neurobehavior, assessed with the NICU Network Neurobehavioral Scale (NNNS), measured at five weeks after delivery in 350 mother-child pairs. The NNNS evaluates neurological functioning, provides a behavioral profile, and measures signs of stress in young infants. They measured maternal urinary phthalate metabolites at 16 and 26 weeks of gestation. Higher total DBP/DIBP metabolites (MBP and MIBP) at 26 weeks (but not at 16 weeks) gestation were associated with improved behavioral organization as evidenced by lower levels of arousal, higher self-regulation, less handling required and improved movement quality, as well as a borderline association with movement quality. There was no sex by DBP interactions. In males, higher total DEHP metabolites at 26 weeks were associated with more non-optimal reflexes.

3 Pubertal Development and Gynecomastia

Several epidemiologic studies reporte*d* on the association of measures of phthalate exposure with pubertal development or gynecomastia (Colon *et al.*, 2000; Lomenick *et al.*, 2009; Durmaz *et al.*, 2010). In a small study on pubertal gynecomastia in boys, Durmaz and colleagues (2010) measured plasma phthalate concentrations of DEHP and MEHP in 40 newly diagnosed pubertal gynecomastia cases and 21 age-matched control children without gynecomastia or other endocrinologic disorders. They reported higher concentrations of serum DEHP and MEHP in the children with pubertal gynecomastia compared to the control group. In an earlier study, Colon *et al.*, (2000) reported associations between serum concentrations of DEHP with premature thelarche in a case (n= 41) control (n=35) study. In a small case control study (Lomenick *et al.*, 2009) on 28 girls with central precocious puberty and 28 age- and race-matched prepubertal girls, there were no differences in urinary phthalate metabolite concentrations between the cases and controls.

These three studies were very small, limiting power to detect associations, and each used a single spot sample (i.e., blood or urine) to measure phthalate concentrations which only represents recent exposure and may not reflect exposure during the relevant window of susceptibility, such as gestational or early childhood. Furthermore, two studies had important limitations in methods used to assess phthalate exposure (Colon *et al.*, 2000; Durmaz *et al.*, 2010). They measured the diester in serum, raising concern with contamination which may occur at the collection or analysis phase. Therefore, these two studies need to be interpreted very cautiously due to critical limitations.

Another study with a very limited sample size was conducted by Rais-Bahrami *et al.*, (2004) on 19 children who presumably had high DEHP exposure as neonates from extracorporeal membrane oxygenation (ECMO) while in the intensive care unit. They examined and collected blood from 13 boys and 6 girls at ages 14 to 16 years old. All the children (except for one with Marfan syndrome) had normal growth percentiles for age and sex and normal values for thyroid, liver, and renal functions. Reproductive hormones (LH, FSH, and testosterone for males and estradiol of girls) were appropriate for Tanner stage of pubertal development. Although comprehensive assessments were performed on the children at age 14 to 16 years of age, the very limited sample size makes comparisons with population distributions non-informative since the power to detect subtle shifts in distributions is minimal. However, the design of the study is a strength since children receiving ECMO, or other medical treatments, in neonatal intensive care units represent a population with potentially high DEHP exposure (Calafat *et al.*, 2009). Larger studies on NICU populations would be informative and should be conducted.

Table C-1 Phthalates and pubertal measures.

Author, yr	Design	Exposure Metric	Outcome	Results	Comments
Durmaz *et al.*, (2010),	Case (n=40) control (n=21)	Serum concentrations of DEHP and MEHP	Pubertal gynecomastia in boys	Higher serum concentrations of DEHP and MEHP among cases	Small sample size and concern with contamination of blood
Lomenick *et al.*, (2009)	Case (n=28) control (n=28)	Urine concentrations of 9 phthalate metabolites	Central precocious puberty in girls	No difference in cases of controls for any of the phthalate metabolites	Small sample size
Colon *et al.*, (2000)	Case (41) control (35)	Serum concentrations of DEHP (MEHP), DBP, BBzP, DMP, DOP	Premature Thelarche in girls	Higher serum concentrations of DEHP among the cases	Small sample size and concern with contamination of blood
Rais-Bahrami *et al.*, (2004)	Follow-up of 19 children who underwent ECMO as neonates	Presumed high DEHP exposure from ECMO as a neonate in the intensive care unit	Pubertal assessment, physical growth, reproductive hormones in boys and girls 14 to 16 years old	As compared to population norms, no differences in hormones or growth percentiles	Small sample size

4 Adult Exposure and Semen Quality

In addition to epidemiologic studies that investigated health outcomes in relation to gestational, infant and/or childhood exposure to phthalates, there is a growing literature on adult exposure to phthalates and semen quality, an outcome relevant to the hypothesized testicular dysgenesis syndrome. All of the semen quality studies were cross-sectional, during adulthood they measured urinary concentrations of phthalate metabolites and semen quality (Liu *et al.*; Murature *et al.*, 1987; Rozati *et al.*, 2002; Duty *et al.*, 2003; Duty *et al.*, 2004; Hauser *et al.*, 2006; Zhang *et al.*, 2006; Hauser *et al.*, 2007; Lily and al., 2007; Pant *et al.*, 2008; Wirth *et al.*, 2008; Herr *et al.*, 2009; Won Han *et al.*, 2009). The evidence was inconsistent across studies, with several publications from an infertility clinic suggesting associations of reduced semen quality with urinary concentrations of MBP and MEHP, whereas other studies did not confirm these associations. These studies are less relevant to this report since exposure was measured during adulthood and cannot be used to infer childhood or early life exposure since phthalates have short biological half-lives and exposure patterns change with life stage. Therefore, they are not discussed further.

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PEER REVIEW DRAFT

Draft Report to the
U.S. Consumer Product Safety Commission
by the
CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES
AND PHTHALATE ALTERNATIVES

May 15, 2013

APPENDIX D

HAZARD INDEX

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1 Estimated Exposure of Phthalates using Biomonitoring Data and Risk Evaluation Using the Hazard Index

Biomonitoring data have provided evidence of complex human exposures to mixtures of phthalates and other anti-androgens. In the case of phthalates, urinary concentrations of phthalates monoesters (metabolites of the parent diesters) are measured through biomonitoring. These monoesters demonstrate exposure to multiple phthalates. Through calculations based on human metabolism studies, estimates of daily intake from the parent phthalate diesters can be estimated. However, the source(s) and route(s) of the exposure are impossible to determine from biomonitoring data alone.

The first objective of this appendix is to use biomonitoring data to estimate daily intake values for multiple phthalates in adult men and women of reproductive age (15-45 yrs). These are produced for comparison to the estimates from data from pregnant women and infants to estimate daily exposure to phthalates and compare these estimates to those determined through exposure assessment modeling (CHAP report, section 2.6). Two data sources were used to evaluate exposures in adults and pregnant women:

(1) the National Health and Nutrition Examination Surveys (NHANES, 2005-6, CDC, 2012b), and

(2) the Study for Future Families (SFF; Sathyanarayana *et al.*, 2008a; 2008b) with pre-natal and post-natal measurements in women.

The SFF data also include concentrations from infants (age: 2-36 months).

We included in our analyses the six phthalates under consideration by the Consumer Product Safety Improvement Act (CPSIA):

- DEHP, DBP, and BBP: banned chemicals; and
- DINP, DIDP, and DNOP: chemicals with interim prohibition on their use.

Since diisobutyl phthalate (DIBP) is also known to be anti-androgenic (comparable to DBP), we included it in the analysis. However, exposure estimates for DNOP were not available in the SFF data and were generally not detectable in NHANES. Thus, DNOP was dropped from further consideration.

Although pregnant women and infants are exposed to DIDP, DEP and DMP as evidenced from biomonitoring studies, evidence of endocrine disruption in experimental animal studies has not been found for these three chemicals. Thus, these three phthalates were not considered in the cumulative risk evaluation.

We used a novel approach for cumulative risk evaluation of these phthalates by calculating the Hazard Index (HI) per individual (i.e., pregnant woman and infant) based on their urinary concentrations of mixtures of phthalates. This is in contrast to the standard HI method of using population percentiles from exposure studies on a per chemical basis. The HI is used in cumulative risk assessment of chemical mixtures based on the concept of dose-addition (Teuschler and Hertzberg, 1995; Kortenkamp and Faust, 2010). It is the sum of hazard quotients (HQs) defined as the ratio of exposure (e.g., estimate of daily intake, DI) to an acceptable level for a specific chemical for the same period of time (e.g., daily). Here, we define the acceptable level by the reference dose (RfD) defined by *in vivo* evidence of anti-androgenic effects (AA):

$$\text{Hazard Index (HI)} = \sum_{j=1}^{c} \frac{DI_{\text{j}}\ (\mu\text{g/kg/day})}{\text{RfD}_{\text{j}}\ (\text{AA};\ \mu\text{g/kg/day})} \tag{1}$$

where c is the number of chemicals in the index. The RfDs were generally selected using NOAELs as points of departure (PODs) and adjusted with uncertainty factors.

We include three cases for comparison of the impact of assumptions in calculating the HI:

Case 1: using RfD AA values as published in Kortenkamp and Faust (2010).

Case 2: using RfD AA values derived from data provided by Hannas *et al.*, (2011a; 2011b).

Case 3: using RfD AA values from de novo analysis of individual phthalates conducted by CHAP (Section 2.3.2).

The RfD values in these cases were derived from *in vivo* evidence of reproductive or developmental effects in pregnant animals. Less is known about the PODs for infants. However, there is evidence that the most sensitive time of exposure is *in utero*, so RfDs associated with reproductive or developmental effects in pregnant women should be protective for infants.

2 Estimating Exposure from Biomonitoring Data in Pregnant Women and Infants

2.1 Methods

2.1.1 Calculation of Daily Intake

Following Koch *et al.*, (2007), we calculated the daily intake of each parent chemical separately per adult and child. The model for daily intake (DI) includes the creatinine-related metabolite concentrations together with reference values for the creatinine excretion (David, 2000) in the following form:

$$DI(\mu g/kg_{bw}/day) = \frac{UE_{sum}(\mu mole/g_{crt}) \times CE(mg_{crt}/kg/day)}{F_{UE} \times (1000 mg_{crt}/g_{crt})} \times MW_{parent}(g/mole) \qquad (3)$$

where

- UE_{sum} is the molar urinary excretion of the respective metabolite(s) as described for (2).

- CE is the creatinine excretion rate normalized by bodyweight which was calculated based on equations using gender, age, height and race (Mage et al, 2008).[1] In the SFF data, height was not measured for prenatal and postnatal women; for these women, a fixed value of CE was used based on the following logic:

  - A rate of 18 mg/kg/day for women is used in the general population (Harper *et al.*, 1977; Kohn *et al.*, 2000).
  - Wilson (2005) noted that creatinine excretion on average increases by 30% during pregnancy. Thus we set CE to 23 mg/kg/day for these SFF women, a 30% increase from 18.

- The molar fraction F_{ue} describes the molar ratio between the amount of metabolite(s) excreted in urine and the amount of parent compound taken up. Values for these fractions are given in Table D-1.

- The molecular weights for each parent compound and metabolite(s) are given in Table D-1.

2.1.2 Inference from NHANES Data to U.S. Population: Use of Survey Sampling Weights (CDC, 2012a; CDC, 2012b)

NHANES data are NOT obtained using a simple random sample. Rather, a complex, multistage,

[1] When height was outside the tabulated range for gender and age categories or when weight was missing, CE was considered missing.

probability sampling design is used to select participants representative of the civilian, non-institutionalized US population. The sample does not include persons residing in nursing homes, members of the armed forces, institutionalized persons, or U.S. nationals living abroad.

The NHANES sampling procedure consists of 4 stages.

- Stage 1: Primary sampling units (PSUs) are selected (e.g., 15 PSUs per year) from a sampling frame that includes all counties in the United States. These are mostly single counties or, in a few cases, groups of contiguous counties with probability proportional to a measure of size (PPS).
- Stage 2: The PSUs are divided up into segments (generally city blocks or their equivalent). As with each PSU, sample segments are selected with PPS.
- Stage 3: Households within each segment are listed, and a sample is randomly drawn. In geographic areas where the proportion of age, ethnic, or income groups selected for oversampling is high, the probability of selection for those groups is greater than in other areas.
- Stage 4: Individuals are chosen to participate in NHANES from a list of all persons residing in selected households. Individuals are drawn at random within designated age-sex-race/ethnicity screening subdomains. On average, 1.6 persons are selected per household.

Based on this complex sampling design, a sample weight is assigned to each sample person. It is a measure of the number of people in the population represented by that sample person in NHANES, reflecting the unequal probability of selection, nonresponse adjustment, and adjustment to independent population controls.

The recommended and most reliable approach for estimating summary statistics for resulting data from NHANES is to use survey procedures that account for the strata (i.e., PSUs) and the clusters (i.e., households selected within each strata) in addition to the weight on each subject (e.g., Proc SurveyMeans in SAS). Alternative approaches that only weight individuals based on their sample weight provide rough approximate estimates of summary statistics but not their standard errors. Based on software constraints, the population percentiles presented herein in tabular form have been generated using survey procedures that account for the complex design. Summary statistics included as insets, box plots and histograms provide rough approximations to the percentiles and distributions.

Table D-1 Molecular weights for parent compounds and metabolites. Excretion fractions (F_{ue}) of parent metabolite(s) in human urine related to the ingested amount of the parent compound determined 24h after oral application (Adapted from Wittassek *et al.*, 2007; Anderson *et al.*, 2011).

Phthalate Diesters	Abbreviation (as denoted in NHANES when different)	Molecular weight	Comment	
a) Dimethyl phthalate	DMP	194		
b) Diethyl phthalate	DEP	222		
c) Diisobutyl phthalate	DIBP	278		
d) Di-n-butyl phthalate	DnBP	278	BANNED	
e) Butyl benzyl phthalate	BBP	312		
f) Di (2-ethylhexyl) phthalate	DEHP	391		
g) Di-n-octyl phthalate	DNOP	391	INTERIM BANNED	
h) Diisononyl phthalate	DINP	419		
i) Diisodecyl phthalate	DIDP	447		
Phthalate Monoesters (%>LOD in U.S. population; NHANES, 2005-06)	**Abbreviation (as denoted in NHANES when different)**	**Molecular weight**	**Excretion Factor (F_{ue})**	
a) Mono n-methyl phthalate (41%)	MNM	180	69%[a]	
b) Mono ethyl phthalate (>99%)	MEP	194	69%[a]	
c) Mono-iso-butyl phthalate (98%)	MiBP (MIB)	222	69%	
d) Mono-n-butyl phthalate (>99%)	MBP	222	69%	
e) Mono-benzyl phthalate (98%)	MBzP (MZP)	256	73%	
f) Mono(2-ethylhexyl) phthalate (67%)	MEHP (MHP)	278	6.2%	45.2%
Mono(2-ethyl-5-hydroxyhexyl) phthalate (>99%)	MEHHP (MHH)	294	14.9%	
Mono(2-ethyl-5-oxohexyl) phthalate (99%)	MEOHP (MOH)	292	10.9%	
Mono(2-ethyl-5-carboxypentyl) phthalate (>99%)	MECPP (ECP)	308	13.2%	

g) Mono-n-octyl phthalate (1%)	MOP	278	omitted
h) Mono-(carboxyisooctyl) phthalate (95%)	cx-MiNP (COP)	322	9.9%
i) Mono-(carboxyisononyl) phthalate (90%)	cx-MiDP (CNP)	336	4%

[a] Set to 69% to be similar to DBP and MBP.

2.1.3 Analysis of Biomonitoring Data from Adults (NHANES, 2005-06)

There were 1181 men and women of reproductive age (i.e., 15-45 years) in NHANES 2005-06 in which urinary phthalate monoesters were measured with non-missing values for height, weight, urinary creatinine, and the sampling weight variable (i.e., wtsb2yr). Using the sampling weights corresponding to this subset of participants, these adults represent 124M non-institutionalized Americans with roughly equal representation for men (50%) and women (50%). Sixty-four percent are non-Hispanic white; 13% are non-Hispanic black; 12% are Mexican American; 4% are 'other' Hispanic; and 7% 'other race – including multiracial.

Daily intake was estimated for the eight phthalate diesters for men and women of reproductive age (Figure D-1; approximately adjusted by survey sampling weights). Using the survey sampling weights, these percentiles are generalizable to the adult U.S. population of reproductive age (Table D-2). The median exposure estimate for DEHP was the highest followed by DEP (Table D-2). DMP has the lowest median daily intake estimate.

Figure D-1 Box plots for daily intake for age 15-45 yrs (NHANES, 2005-06).

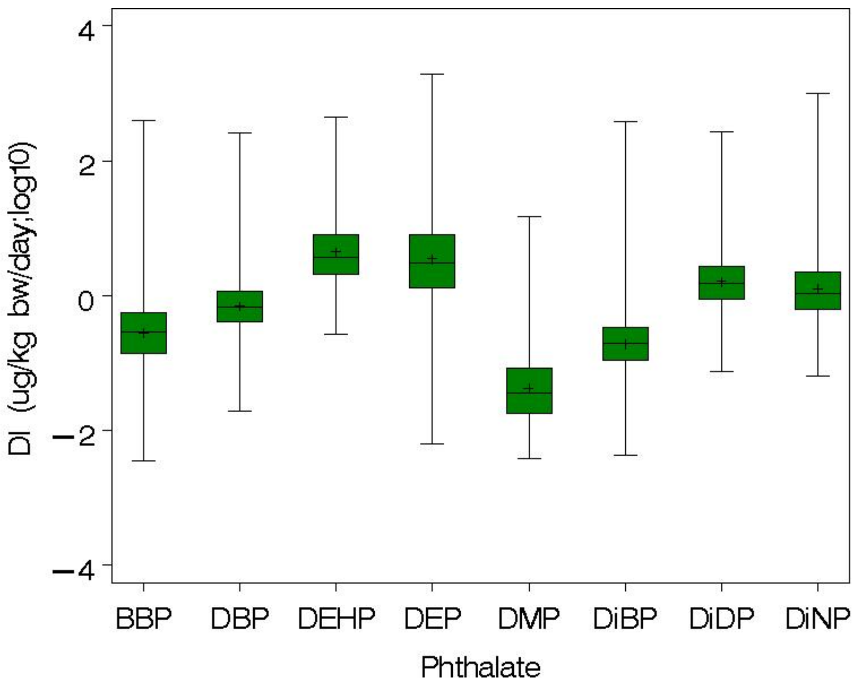


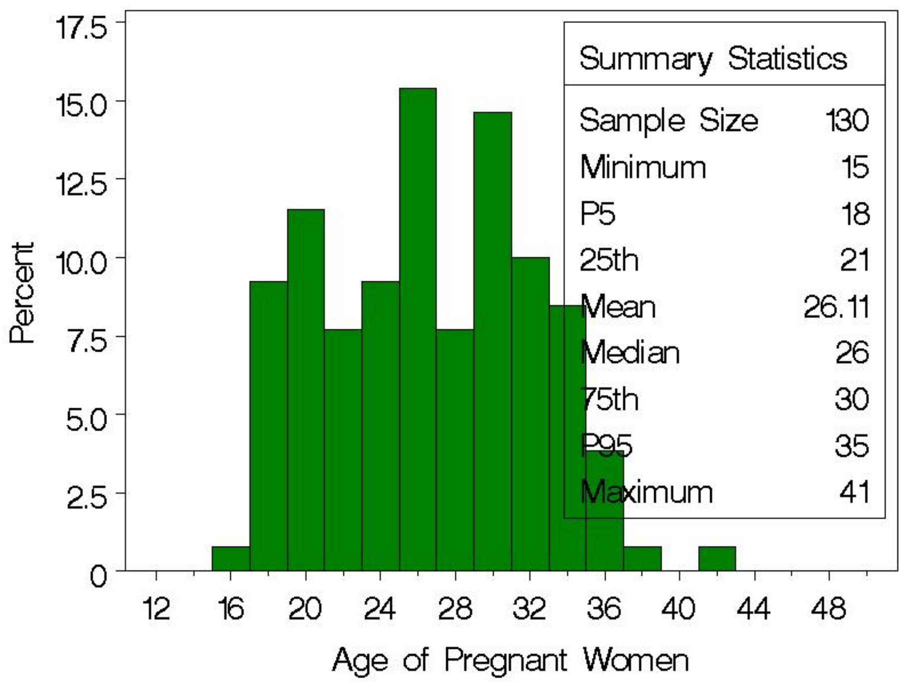
Table D-2 Summary statistics for estimated daily intake of phthalate diesters in adults of reproductive age (age:15-45 yrs) from NHANES (2005-06) and SFF (pre-natal, post-natal, and infants) biomonitoring data, estimated from exposure modeling (Wormuth *et al.*, 2006), and as given in Kortenkamp and Faust, (2010).

Daily Intake Estimates (µg/kg bw/ day)	BBP[a]	DBP	DEHP	DEP[b]	DMP	DiBP	DiDP	DiNP
Median Estimates from biomonitoring data (NHANES, 2005-06; 15<=Age<=45) (CDC, 2012b)								
Adults (represents 123M)	0.29	0.66	3.8	3.3	0.03	0.19	1.5	1.1
Pregnant Women (represents 5M)	0.30	0.63	3.5	3.4	0.05	0.17	1.5	1.0
99th Percentile Estimates from biomonitoring data (NHANES, 2005-06; 16<=Age<=45) (CDC, 2012b)								
Adults	2.5	5.5	203	118	0.80	1.9	19	35
Pregnant Women	2.7	6.4	366	357	0.68	2.0	11	27
Median Estimates from biomonitoring data (Sathyanarayana *et al.*, 2008a)								
Pre-natal	0.51	0.88	2.9	6.6	0.06	0.15	2.3	1.1
Post-natal	0.44	0.62	2.7	3.7	0.06	0.14	1.7	0.63
Infants	1.2	1.7	5.5	4.8	0.12	0.31	6.0	3.5
99th Percentile Estimates from biomonitoring data (Sathyanarayana *et al.*, 2008a)								
Pre-natal	4.2	5.1	69	307	0.67	1.7	28	7.6
Post-natal	4.1	4.7	45	171	0.60	1.8	68	8.1
Infants	22	13	110	217	2.1	2.9	70	24
Average Estimates from Exposure Modeling (Wormuth *et al.*, 2006)								
Adults	0.31	3.5	1.28	1.28		0.44		0.00
Women	0.28	3.5	1.40	1.40		0.42		0.004
Upper bound Estimates from Exposure Modeling (Wormuth *et al.*, 2006)								
Adults	1.8	28	58	58		1.5		0.28
Women	1.7	38	66	66		1.5		0.28
Median Intake Estimates from Kortenkamp and Faust, (2010)								
German population	0.3	2	2.7			1.5		0.6
High Intake Estimates from Kortenkamp and Faust, (2010)								
US population	4	6	3.6			1.5		1.7

2.1.4 Analysis of Biomonitoring Data from Pregnant Women (NHANES, 2005-06)

Pregnancy status was evaluated in females 8-59 years of age in the NHANES study. Menstruating girls 8–11 years of age and all females 12 years and over received a urine pregnancy test. If the respondent reported they were pregnant at the time of the exam, they were assumed to be pregnant regardless of the result of the urine pregnancy test. Three-hundred-eighty-two women were coded as pregnant at the time of the exam. Of these, 130 women were included in the subsample in which phthalates were evaluated with non-missing values for height, weight, urinary creatinine and the sampling weight. The age distribution for these women is presented in Figure D-2.

Figure D-2 Age distribution for pregnant women evaluated for phthalate exposure (NHANES 2005-06).



Using survey-sampling weights, these 130 pregnant women are representative of 5M pregnant women in the non-institutionalized U.S. population. These are estimated to have the following characteristics:

- Marital status: 71% married, 1% divorced, 2% separated, 15% never married, 11% living with partner;
- Ethnicity/race: 27% Mexican American, 2% other Hispanic, 53% non-Hispanic white, 13% non-Hispanic black, 5% other plus multi-race;
- Education: 5% <9th grade, 17% 9-12th grades, 15% high school graduate, 25% some college, and 38% college graduate or above.

The internal exposure for the eight phthalate diesters was estimated and the percent from each diester per pregnant woman was calculated. The median exposure estimates for DEP and DEHP were the largest of the phthalate diesters evaluated. The mixture of phthalate diesters is different in each subject; box plots for the distributions of percentages of the mixture for each diester (calculated from the sum) per subject are provided in Figure D-3. DEP and DEHP have the largest median percentage of the mixtures. The estimated daily intakes have a complex bivariate correlation structure (Table D-3). Two clusters with significant positive correlations are (1) low molecular weight phthalates: DBP, DIBP, BBP; and (2) high molecular weight phthalates: DEHP, DINP, AND DIDP.

Figure D-3 Summary statistics for the distributions of the percentage of each diester in the sum of diesters per pregnant woman (NHANES, 2005-06).

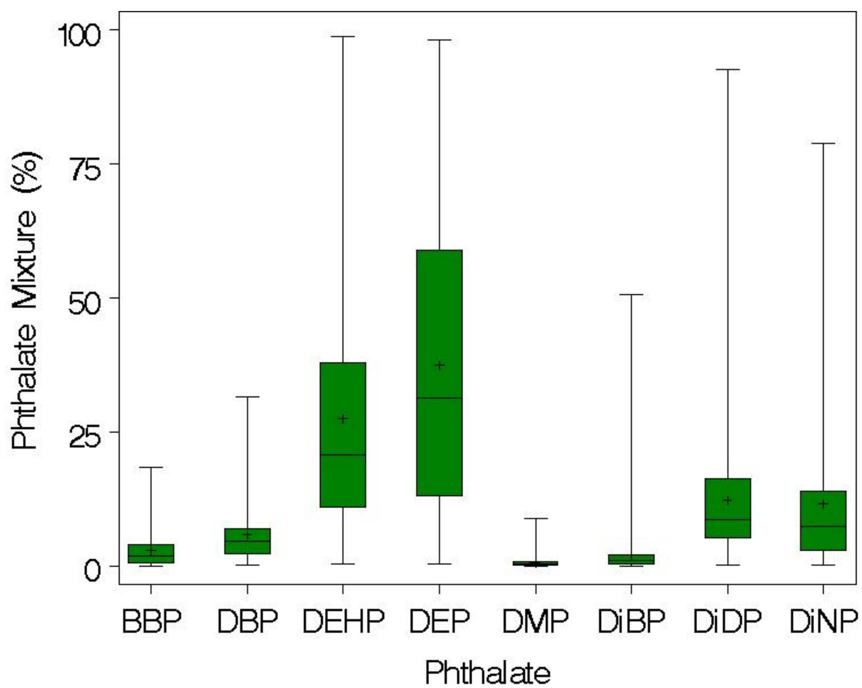


Table D-3 Pearson correlation coefficient estimates between estimated daily intakes of the eight phthalate diesters (log10 scale) for pregnant women in NHANES (2005-06, representing 5.3M pregnant women).

Estimate	DMP	DEP	DIBP	DBP	BBP	DEHP	DINP	DIDP
DMP	1	0.20	-0.02	-0.19	-0.05	-0.11	0.03	0.09
DEP	0.20*	1	0.12	0.12	0.04	-0.17	-0.06	0.14
DIBP	-0.02	0.12	1	0.59*	0.38*	-0.13	-0.04	0.12
DBP	-0.19	0.12	0.59*	1	0.59*	-0.05	0.17	0.15
BBP	-0.05	-0.04	0.38*	0.59*	1	-0.06	0.17	0.23*
DEHP	-0.11	-0.17	-0.13	-0.05	-0.06	1	0.40*	0.26*
DINP	0.03	-0.06	-0.04	0.17	0.17	0.40*	1	0.52*
DIDP	0.09	0.14	0.12	0.15	0.23*	0.26*	0.52*	1

* $p<0.01$; highlighted.

3 Analysis of SFF Data

Exposure data from the SFF in young children and their mothers were provided to the CHAP by Dr. Shanna Swan and are published in Sathyanarayana *et al.*, (2008a). The study included prenatal and postnatal evaluation of phthalates in pregnant women and their babies. Measurements were available in four centers across the US including in California (n=61), Missouri (n=84), Minnesota (n=112) and Iowa (n=34). Urinary concentrations from twelve monoesters were evaluated (Table D-4) that are generally specific to eight phthalate diesters. Although mono-3-carboxyprobyl phthalate was measured, it was considered not specific to a single phthalate; thus, a monoester specific for DNOP was not available.

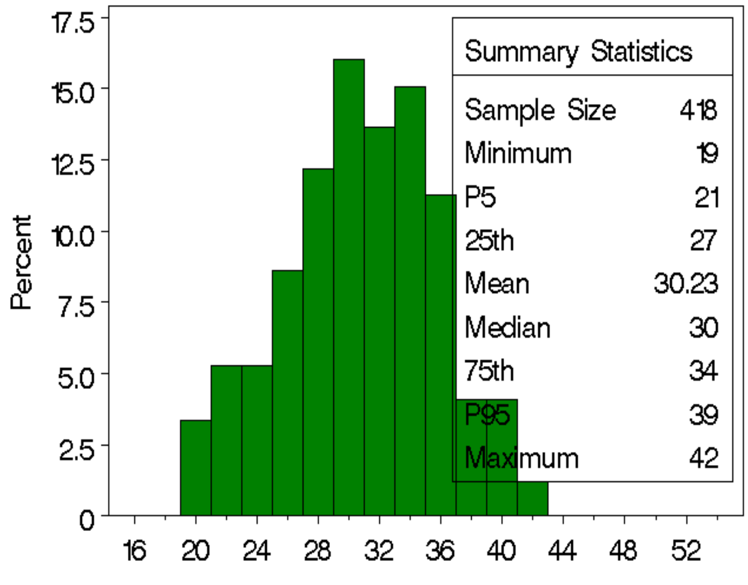
Table D-4 Phthalate monoesters evaluated by Sathyanarayana *et al.*, (2008a).

Abbreviation	NHANES Variable	Monoester	Phthalate Diester(s)
mBP	urxmbp	Mono-n-butyl phthalate	DBP
mBzP	urxmzp	Mono-benzyl phthalate	BBP
mCPP	urxmc1	Mono-3-carboxypropyl phthalate	DNOP and others
mEHHP	urxmhh	Mono-(2-ethyl-5-hydroxyhexyl) phthalate	DEHP
mEHP	urxmhp	Mono-(2-ethylhexyl) phthalate	DEHP
mEOHP	urxmoh	Mono-(2-ethyl-5-oxohexyl) phthalate	DEHP
mECPP	urxecp	Mono-2-ethyl-5-carboxypentyl phthalate	DEHP
mEP	urxmep	Mono-ethyl phthalate	DEP
mMP	urxmnm	Mono-methyl phthalate	DMP
miBP	urxmib	Mono-iso-butyl phthalate	DIBP
mCNP	urxcnp	Mono(2 7-dimethyl-7-carboxyheptyl) phthalate	DIDP
mCOP	urxcop	(2 6-dimethyl-6-carboxyhexyl) phthalate	DINP

3.1 Analysis of Prenatal and Postnatal Measurements in Women

Either or both prenatal and postnatal measurements were made in 418 pregnant women; 340 women had prenatal measurements and 335 had postnatal measurements. The median age for the moms was 30 years and their age ranged between 19 and 42 (Figure D-4).

Figure D-4 Histogram for age of pregnant women with either prenatal or postnatal measurements (Sathyanarayana *et al.*, 2008a).



From the phthalate monoester measurements, diester values were calculated using the method of David (2000) and Koch *et al.*, (Koch *et al.*, 2007). Box plots across the phthalates for pre-natal and post-natal estimates are provided in Figure D-5. DEP and DEHP have the highest median estimates for both cases. Table D-2 provides 50th and 99th percentiles for each diester across the three measurements (i.e., NHANES; SFF pre-natal; SFF post-natal). The exposure distributions are generally quite similar. The SFF pre-natal estimates for DEHP is slightly lower than the other two; and the distribution for DIDP in NHANES is slightly lower compared to the SFF data. However, these possible shifts are within the interquartile ranges of the comparison groups. Bivariate correlations for these estimates are provided in Table D-5. Significant correlations between prenatal and postnatal measurements of the estimated daily intake were detected for DBP, DIBP, BBP and DIDP.

Figure D-5 Box plots across estimates of daily intake for (A) pre-natal and (B) post-natal estimates.

(A) Pre-natal **(B) Post-natal**

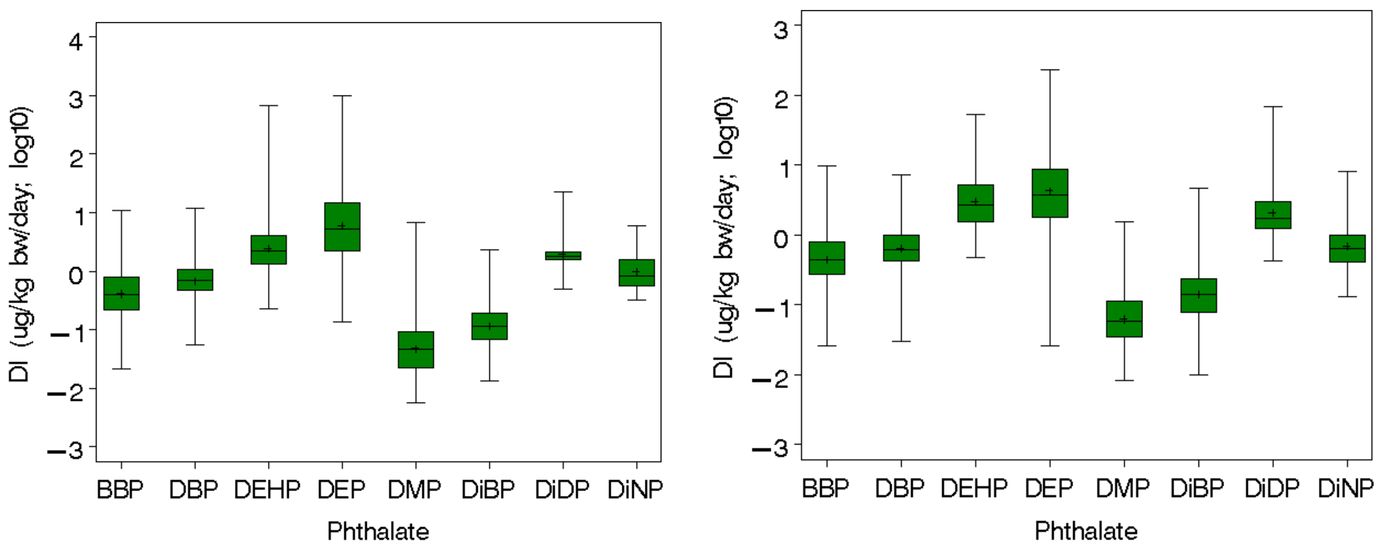


Table D-5 Pearson correlation estimates (*p<0.05 and highlighted) for estimated daily intake values (log10 scale) for prenatal and postnatal values from N=258 women except for DINP and DIDP where N=18. There were no post-natal DMP or DEP estimates with pre-natal values.

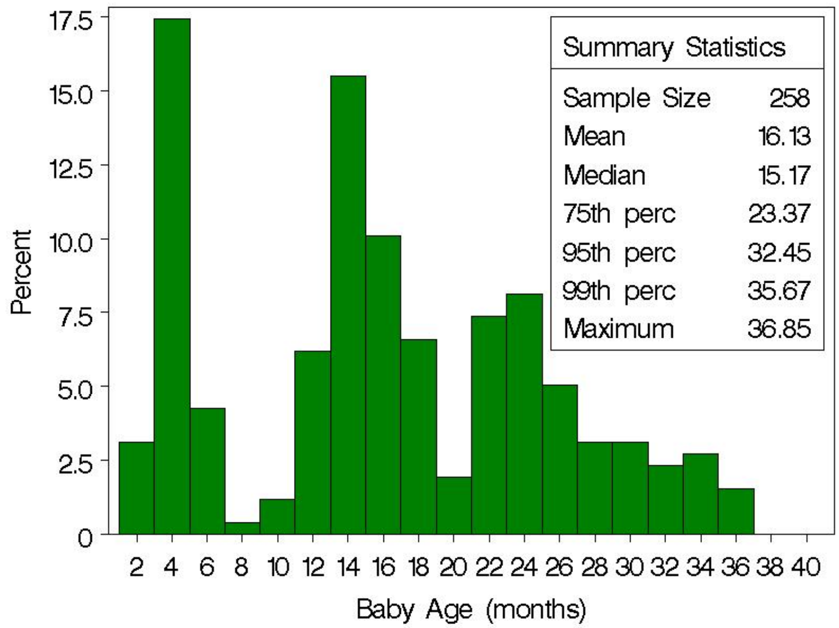
Pre\ Post	DMP	DEP	DIBP	DBP	BBP	DEHP	DINP*	DIDP*
DMP			0.12	0.09	0.06	0.04		
DEP			0.02	0.05	0.03	-0.06	0.51*	0.22
DIBP			0.15	0.06	0.05	0.06	0.28	0.13
DBP			0.07	0.13*	0.13*	0.00	0.31	0.06
BBP			-0.10	-0.05	0.29*	0.08	0.23	-0.08
DEHP			-0.03	0.01	0.02	0.11	0.40	0.51*
DINP*			0.41	0.31	0.07	0.08	0.11	0.42
DIDP*			0.44	0.40	0.11	0.02	0.13	0.66*

Significant associations are highlighted in yellow.

3.2 Analysis of Infant Data

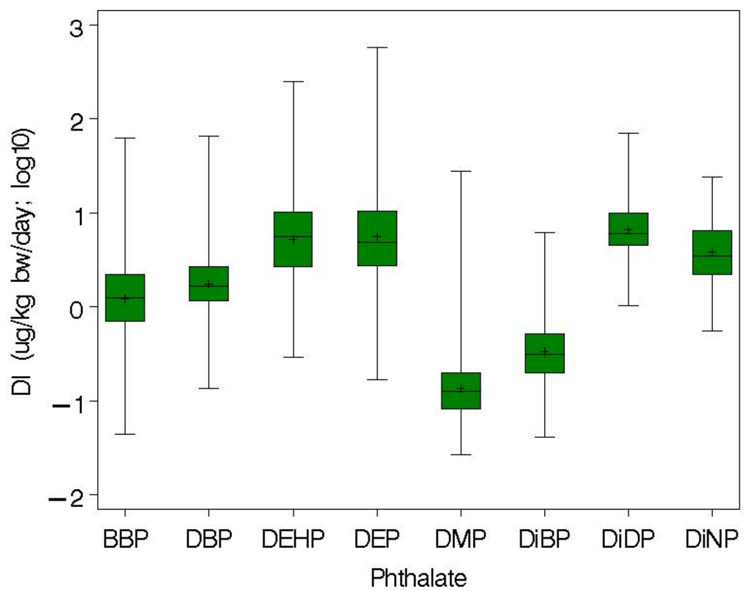
Phthalate monoesters were evaluated in 258 infants, age 0-37 months (Figure D-6) where daily intake can be estimated; 49% (n=127) of the babies were boys. At least one of the monoesters was detected in all babies and seven monoesters were detected in at least 95% of the babies (Table D-6). To estimate the internal exposure for the phthalate diesters, the creatinine excretion rate was calculated using equations from Mage *et al*. (2008) based on age, gender, height and race.

Figure D-6 Age distribution for infants evaluated by Sathyanarayana *et al.*, (2008a).



Using the urinary concentrations from the 11 monoesters, the internal exposure to DBP, BBP, DEHP, DIBP, DIDP, DINP, DEP, and DMP were estimated in these infants (Table D-2). The median estimate for DEP was the highest of the eight evaluated followed by DEHP (Figure D-7).

Figure D-7 Box plots for daily intake estimates for infants from the SFF study.



Pearson correlation estimates between baby estimates for daily intake and those from the prenatal and postnatal estimates in the moms are provided in Table D-7. The prenatal estimates for daily intake of BBP and DEP are positively correlated with that measured in the babies with a correlation estimate of 0.31 (p<0.001) and 0.15 (p=0.044), respectively. The correlations between postnatal and baby daily intake estimates are positive and significant for DEP (0.35; p=0.005), DIBP (0.43; p<0.001), BBP (0.35; p<0.001), DEHP (0.35; p<0.001), DINP (0.26; p=0.043), and DIDP (0.43; p<0.001).

Table D-6 Percent above the limit of detection (LOD) in samples from the babies.

Abbreviation	% >LOD
mBP	99%
mBzP	96%
mEHHP	94%
mEHP	67%
mEOHP	96%
mECPP	100%
mEP	99%
mMP	64%
miBP	88%
mCNP	96%
mCOP	96%

Table D-7 Pearson correlation estimates (* p<0.05; highlighted) for estimated daily intake values (log10 scale) for prenatal and postnatal values with daily intake values estimated in their babies. In the prenatal values N=191 except for DINP and DIDP where N=0; in the postnatal values N=251 except for DINP and DIDP where N=62, DEP where N=62, and DMP where N=181.

	DMP (p value)	DEP (p value)	DIBP (p value)	DBP (p value)	BBP (p value)	DEHP (p value)	DINP (p value)	DIDP (p value)
PRE \ BABY								
DMP	-0.09	-0.10	-0.11	-0.01	-0.05	0.14*		
DEP	0.03	0.15*	0.01	-0.09	-0.04	-0.10		
DIBP	-0.15*	-0.06	0.06	-0.10	0.00	0.03		
DBP	-0.04	0.05	0.07	-0.05	0.01	-0.02		
BBP	-0.06	0.05	-0.02	-0.03	0.31*	0.07		
DEHP	-0.09	-0.07	-0.09	-0.15*	-0.04	-0.03		
DINP								
DIDP								
POST \ BABY								
DMP								
DEP		0.35*	-0.05	0.00	-0.08	-0.04	-0.10	-0.15
DIBP	-0.06	0.06	0.43*	0.06	-0.09	0.08	0.02	0.02
DBP	-0.06	0.17*	0.10	0.12	-0.03	0.09	0.19	0.22
BBP	0.03	0.13*	-0.03	0.01	0.35*	-0.06	0.16	0.13
DEHP	-0.03	0.06	0.02	0.03	0.05	0.35*	0.18	0.27*
DINP		0.02	0.01	0.06	0.03	0.15	0.26*	0.26*
DIDP		-0.13	0.00	0.02	-0.09	0.15	0.28*	0.43*

4 Risk Evaluation Using the Hazard Index

Evaluation of risk using the HI is a comparison of human exposure estimates to points of departure (POD) estimates using toxicology data. The PODs are changed to so-called reference doses (RfDs) with adjustments due to extrapolations using uncertainty factors. The selection of RfDs is based on *in vivo* data with relevant endpoints. Here, the RfDs for pregnant women are based on reproductive and developmental endpoints in animal studies. Our selection of RfDs for infants was based the following logic. Rodents are most sensitive to the anti-androgenic effects of phthalates *in utero*. However, exposure at higher doses also induces testicular effects in adolescent and adult males, with adolescents being more sensitive than adults (Sjöberg *et al.*, 1986; Higuchi *et al.*, 2003). Thus, the RfDs determined for *in utero* exposures should be protective for juvenile males.

Although pregnant women and infants are exposed to DIDP, DEP and DMP as evidenced from biomonitoring studies, evidence of endocrine disruption in experimental animal studies has not been found for these three chemicals. Thus, these three diesters were not considered in the calculation of the hazard index.

4.1 Selection of Reference Dose (RfD) for Each Chemical

Case 1: Following Kortenkamp and Faust (2010), reference doses were determined using anti-androgenicity *in vivo* data to estimate the points of departure (POD: doses where the effect levels could not be discriminated from untreated control animals). These are typically either NOAELs or the lower limits of benchmark doses (BMDL), as indicated in Table D-8. Uncertainty factors (UFs) were used to adjust the PODs to arrive at RfD AA to be used to calculate the HI.

Case 2: A second case for evaluating the HI was undertaken so that the sensitivity of the results to some of the underlying assumptions could be assessed. The RfD values were alternatively estimated using the following assumptions:

- DIBP, DBP, DEHP, and BBP are approximately equipotent in terms of testosterone modulated effects (Hannas *et al.*, 2011b).
- The NOAEL is 5 mg/kg/day for DEHP; the other three phthalates were assumed to have equivalent values. An uncertainty factor of 100 was used – which sets the RfD for the four chemicals at 50 µg/kg/day.
- Assuming DINP is 2.3 times less potent compared to DEHP, the RfD is 115 µg/kg/day for DINP (Hannas *et al.*, 2011b).

Case 3: NOAELs associated with reproductive and developmental endpoints (and specifically, phthalate syndrome when available) were summarized in Section 2.3 based on *de novo* review by the CHAP.

The calculation of RfD values from all three cases is illustrated in Table D-8.

Table D-8 Established *in vivo* anti-androgenic chemicals and chemicals showing limited evidence of anti-androgenicity. (Table and Case 1 are altered from Kortenkamp and Faust, (2010); assumptions for Case 2 are from Hannas *et al.*, (2011a); Case 3 are from NOAELs for developmental endpoints (Section 2.3, Table 2.1).

CASE 1					CASE 2				CASE 3			
Chemical	**Effect**	**Point of Departure (POD) (mg/kg/day)**	**Uncertainty Factor (UF)**	**RfD AA[a] (µg/kg/day)**	**Effect**	**POD (mg/kg/day)**	**UF**	**RfD AA (µg/kg/day)**	**Effect**	**POD (mg/kg/day)**	**UF**	**RfD AA (µg/kg/day)**
Established *in vivo* anti-androgenic chemicals												
DBP	Suppression of fetal testosterone synthesis	20	200[b]	100	Disruption of testicular function and/or malformations in male rat offspring	5	100	50	NOAELs for Develop-mental Endpoints	50	100	500
BBP		66		330		5	100	50		50	100	500
DINP		750	500[c]	1500		11.5[g]	100	115		50	100	500
DIBP		40	200	200		5	100	50		125	100	1250
DEHP	Retained nipples in male offspring	3	100[d]	30		5	100	50		5	100	50
Chemicals with limited evidence of anti-androgenic activity												
BPA	Decreased testosterone levels in male offspring[e]	1.25	100[e]	12.5								
BPB	Suppression of testosterone levels, decreased epididymis weights, decreases in sperm production[f]	10	100	100								
PPB		100	100	1000								

[a] $RfD(\mu g/kg/day) = \frac{POD(mg/kg/day)}{UF} \times 1000 \cdot$

[b] PODs are BMDLs estimated by NRC (2008) based on Howdeshell *et al.*, (2008) data; the study was of limited size, therefore an UF of 200 was applied by Kortenkamp and Faust (2010).

[c] POD is from LOAELs from Gray *et al.*, (2000), Borch *et al.*, (2004), NOAELs are not available and therefore an UF of 500 was applied by Kortenkamp and Faust (2010).

[d] POD is from NOAEL from Christiansen *et al.*, (2009); standard UF applied by Kortenkamp and Faust (2010).

[e] from (Tanaka *et al.*, 2006) as applied by Kortenkamp and Faust (2010).

[f] after oral administration to post-weanling male Wistar rats (Oishi, 2001; 2002)as applied by Kortenkamp and Faust (2010).

[g] DINP is 2.3 less potent than DEHP, (Hannas *et al.*, 2011b)

5 Results of Hazard Index Evaluations

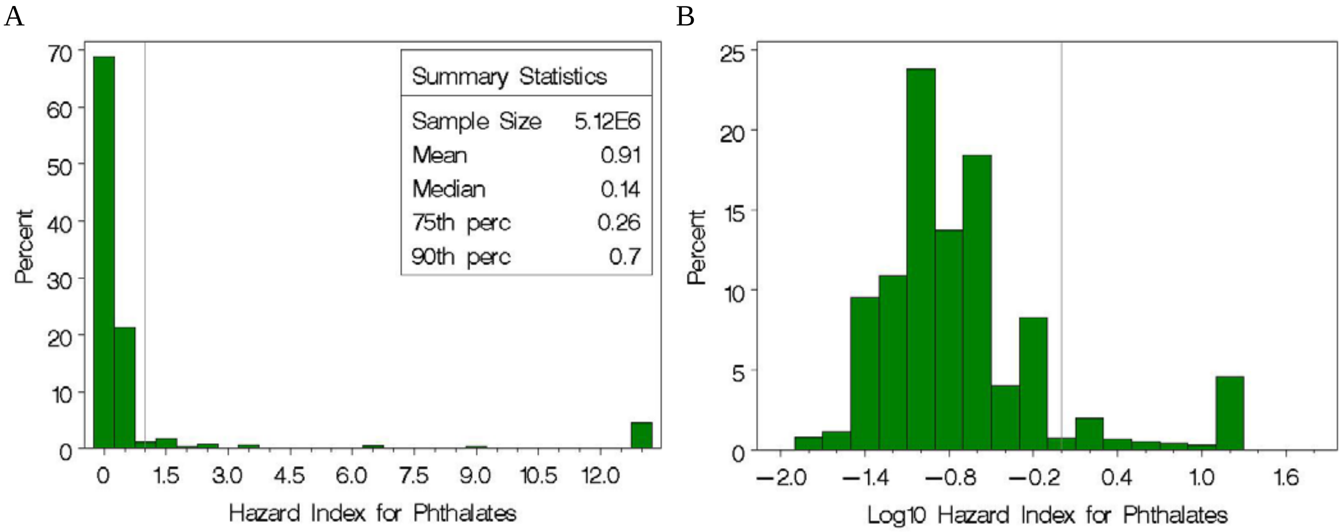
5.1 Calculation of the Hazard Index Using Case 1 RfDs.

The Hazard Index was calculated per woman using the daily intake estimates for the five phthalate diesters and RfD values as published by Kortenkamp and Faust, (2010). Figure D-8A provides a histogram for the distribution of HI for the 130 pregnant women with the sampling weights applied so that roughly 5M pregnant women from the U.S. population are represented.[2]

The distribution is highly skewed with a median value of 0.14 and estimated mean of 0.91. The reference value of 1 is depicted in Figure D-8A. Linearly interpolating between the 95th percentile and the 90th percentile, roughly 10% of pregnant women in the U.S. population have estimated HIs exceeding 1.0 with RfD values as specified in Case 1. Figure D-8B demonstrates the general bell-shaped distribution of the log of the Hazard Index with the exception of the upper tail; here, the reference value of 0 is shown.

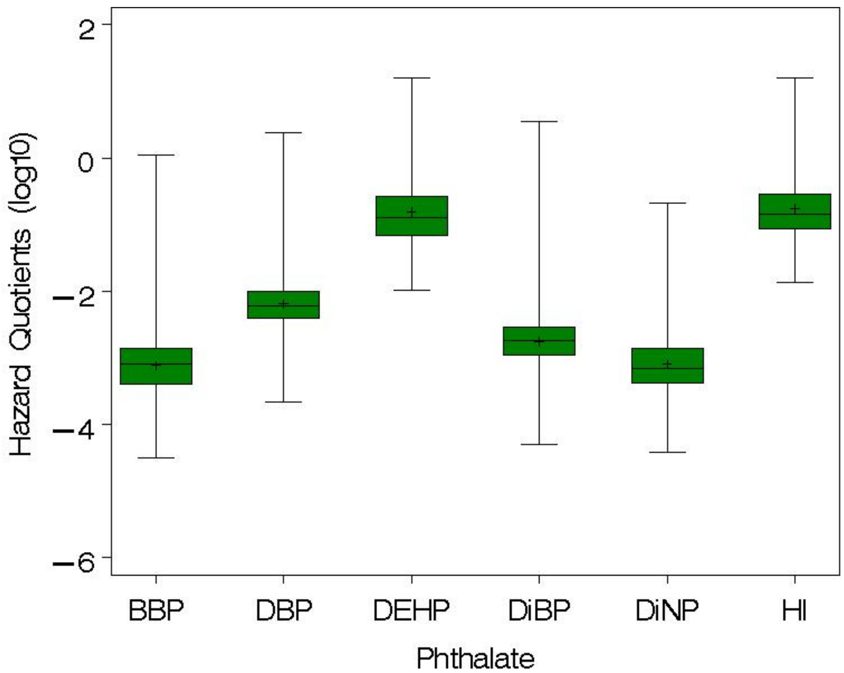
[2] Percentile estimates presented in insets of histograms in this and all similar figures use positive survey sampling weights as weights in the calculations from Proc Univariate in SAS v9.2 using a ‘weight’ statement. This is only a rough approximation to the percentile estimates more accurately calculated using Proc Survey Means with ‘strata’, ‘cluster’, and ‘weight’ statements.

Figure D-8 Distribution of the Hazard Index (A,B) for five phthalates as estimated in pregnant women using daily intake estimates from urinary metabolite concentrations and Case 1 values for RfDs. Data are from NHANES (2005-06) for the 5 phthalates.



Box plots for the hazard quotients for each of the 5 phthalates that comprise the HI are presented in Figure D-9. DEHP has the highest contribution to the HI followed by DBP, DIBP and BBP. As expected, DEHP has the highest contribution to the HI with high exposure levels and the lowest RfD in Case 1.

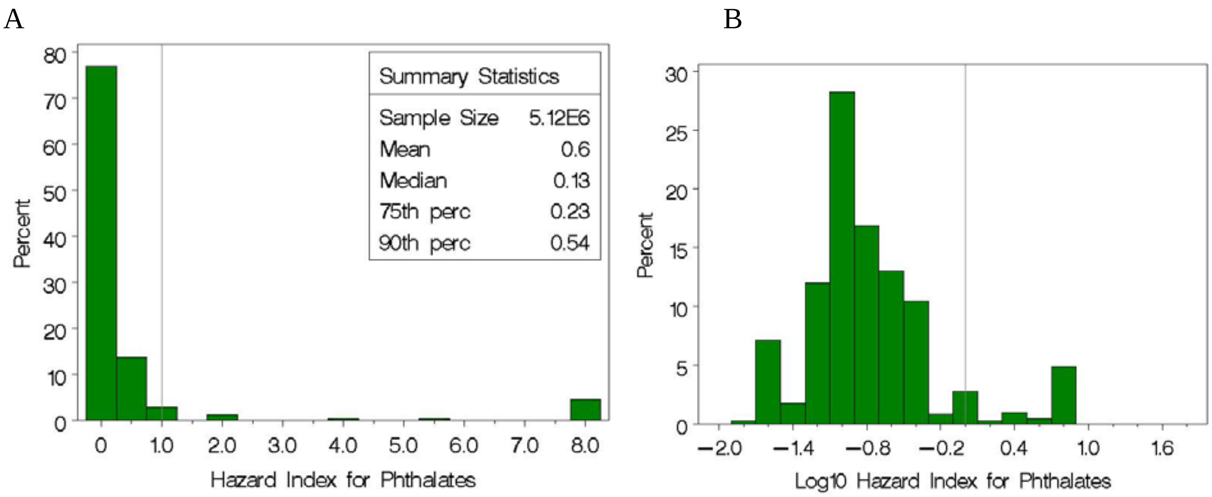
Figure D-9 Box plots for the Hazard Quotients that comprise the Hazard Index for five phthalates as estimated in pregnant women using daily intake estimates from urinary metabolite concentrations and Case 1 values for RfDs. Data are from NHANES (2005-06).



5.2 Calculation of the Hazard Index in Pregnant Women Using Case 2 RfDs.

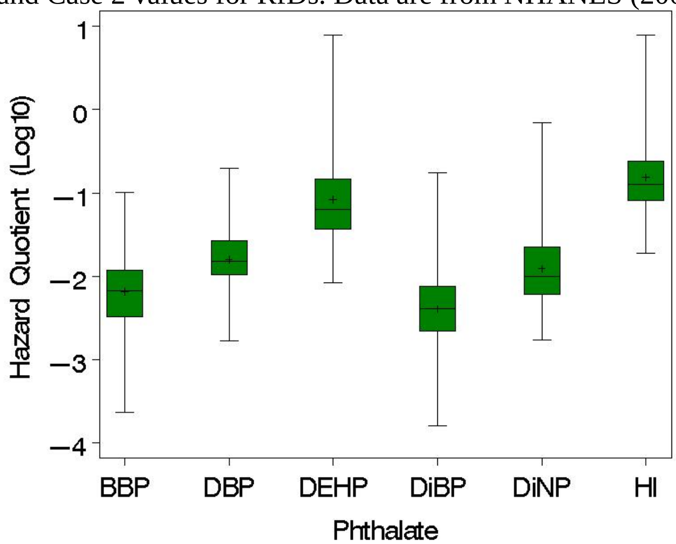
The Hazard Index was calculated per woman using the daily intake estimates for the five phthalate diesters and Case 2 estimates for RfDs (Table D-8). Figure D-10A provides a histogram for the distribution of HI for the 130 pregnant women adjusted with sampling weights to represent roughly 5.1M pregnant women in the U.S. population. The distribution is highly skewed with a median value of 0.13 and estimated mean of 0.6. The reference value of 1 is depicted in the figure. Linearly interpolating between the 95th and 90th percentiles, roughly 9% of pregnant women in the U.S. population have HI values exceeding 1.0 using Case 2 RfDs. Figure D-10B demonstrates the general bell-shaped distribution of the log of the Hazard Index except with a heavy upper tail; here, the reference value of 0 is shown.

Figure D-10 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women using daily intake estimates from urinary metabolite concentrations and Case 2 values for RfDs. Data are from NHANES (2005-06).



The contribution of each of the five phthalate diesters to the HI is presented in Figure D-11 for Case 2 RfD values. DEHP is again the heaviest contributor to HI due to its higher exposure values. However, in this case, the RfD values for DBP, BBP and DIBP are the same as for DEHP, and the RfD for DINP is about 10% of its value in Case 1. These changes in the RfDs result in the relative contribution to HI of these four phthalates increases compared to Case 1 (Figure D-9). However, the estimate for the percent of pregnant women with values of HI exceeding 1.0 is roughly similar.

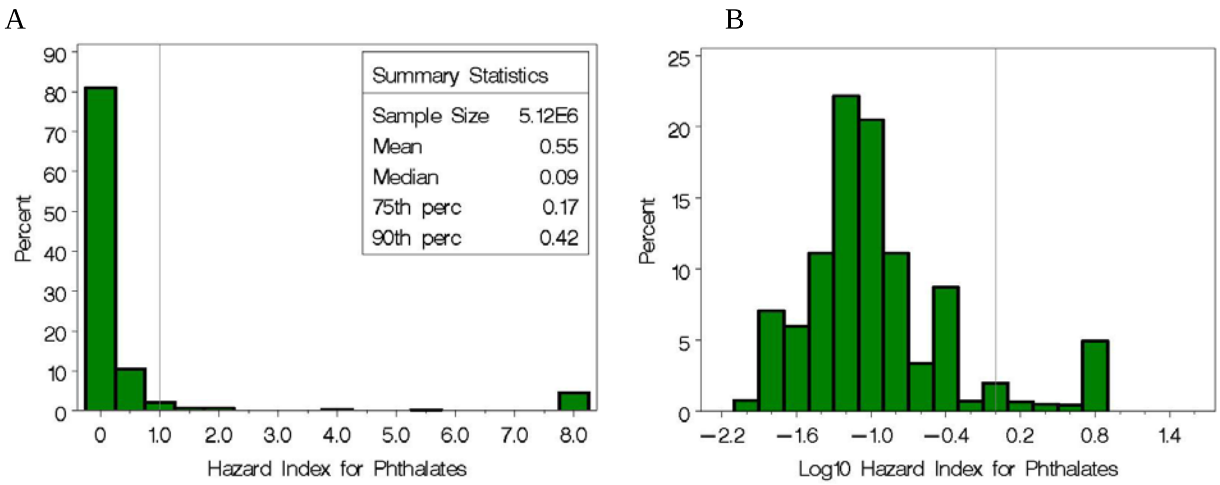
Figure D-11 Box plots for the Hazard Quotients that comprise the Hazard Index for five phthalates as estimated in 130 pregnant women using daily intake estimates from urinary metabolite concentrations and Case 2 values for RfDs. Data are from NHANES (2005-06).



5.3 Calculation of the Hazard Index in Pregnant Women Using Case 3 RfDs.

The Hazard Index was calculated per woman using the daily intake estimates for the five phthalate diesters and Case 3 estimates for RfDs (Table D-8). Figure D-12A provides a histogram for the distribution of HI for the 130 pregnant women with sampling weights generalizing the analysis to 5.1M pregnant women in the U.S. population. The distribution is highly skewed with a median value of 0.09 and estimated mean of 0.55. The reference value of 1 is depicted in the figure. Interpolating between the estimate for the 95th percentile and the 90th percentile, roughly 9% of pregnant women in the U.S. population have HI values exceeding 1.0 using Case 3 RfDs. Figure D-12B demonstrates the general bell-shaped distribution of the log of the Hazard Index except in the upper tail; here, the reference value of 0 is shown.

Figure D-12 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women using daily intake estimates from urinary metabolite concentrations and Case 3 values for RfDs. Data are from NHANES (2005-06).



The contribution of each of the five phthalate diesters to the HI is presented in Figure D-13 for Case 3 RfD values. DEHP is again the heaviest contributor to HI due to its higher exposure values and, in this case, the lowest RfD.

The distribution of the HI is somewhat robust to the choice of RfD values (Table D-9). In all three cases, the HI value is largely driven by the distribution of the hazard quotient for DEHP. The median and 75th percentiles are similar in cases 1, 2 and 3; and the distributions of HI based on the median, 75th, 95th and 99th percentiles are ordered from highest to lowest with Case 1 > Case 2 > Case 3. However, the percentage of pregnant women exceeding 1.0 is similar, i.e., roughly 9-10%.

Figure D-13 Box plots for the Hazard Quotients that comprise the Hazard Index for five phthalates as estimated in pregnant women using daily intake estimates from urinary metabolite concentrations and Case 3 values for RfDs. Data are from NHANES (2005-06).

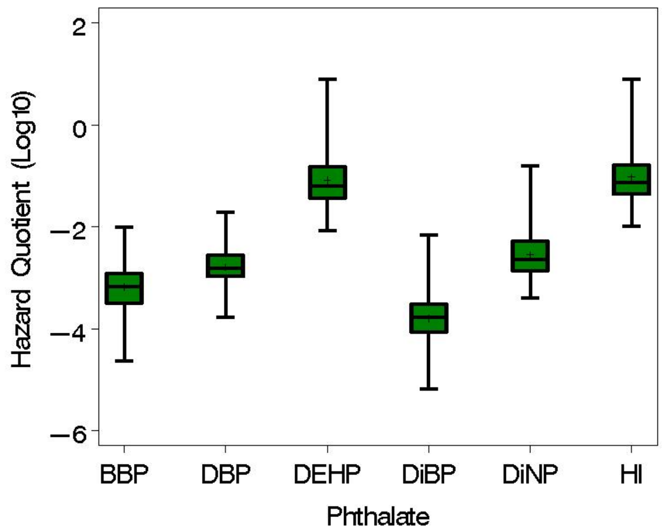


Table D-9 Summary percentiles from the Hazard Index distributions using five phthalates for pregnant women and children from NHANES (2005-06) and from SFF (Sathyanarayana et al., 2008a). The NHANES estimates infer to 5.1M pregnant women in the U.S.

Hazard Index	AA set		RfD Case	Percentiles: Median	75th	95th	99th
Pregnant Women	NHANES		**1**	0.14	0.26	6.1	12.2
			2	0.13	0.23	3.7	7.4
			3	0.08	0.15	3.6	7.3
	SFF	Prenatal	**1**	0.11	0.19	0.57	2.39
		Postnatal		0.10	0.19	0.73	1.51
		Prenatal	**2**	0.10	0.16	0.41	1.54
		Postnatal		0.09	0.16	0.46	0.92
		Prenatal	**3**	0.06	0.11	0.33	1.40
		Postnatal		0.06	0.11	0.43	0.91
Infants	SFF Infants		**1**	0.22	0.40	0.95	3.71
			2	0.20	0.34	0.81	2.32
			3	0.12	0.22	0.54	2.21

6 Adjusting the Hazard Index for Additional Anti-Androgenic Chemicals

To focus too narrowly on phthalates when pregnant women are also exposed to other chemicals with anti-androgenicity activity may underestimate risk. We consider three other AA chemicals available in the 2005-06 NHANES biomonitoring. These are BPA, BPB and PPB. Adding these to the hazard index shifts its distribution only slightly to the right. For example using Case 1 RfDs, the median changes from 0.14 to 0.19. Accounting for the 5 phthalates and these 3 other AAs, 9.8% of pregnant women have HI values that exceed 1.0.

Two more extreme cases were also considered. Kortenkamp and Faust (2010) provide median and high intake values for the phthalates and other anti-androgens including vinclozolin, prochloraz, procymidone, linuron, fenitrothion, p,p'-DDE and BDE99. Their daily intake estimates were from German (Wittassek and Angerer, 2008), French (Menard *et al.*, 2008), and Polish (Galassi *et al.*, 2008)studies. As described in Kortenkamp and Faust (2010), estimates for the RfDs were based on NOAELs for retained nipples for vinclozolin, prochloraz, procymidone, linuron, p,p'-DDE; and for anogenital distance for fenitrothion and BDE99. An uncertainty factor of 100 was used for six of the seven chemicals; a value of 500 was used for linuron as a NOAEL was not available – a dose of 50 mg/kg induced nipple retention in male rats exposed *in utero*.

Using the median estimates for daily intake for the seven AAs (Kortenkamp and Faust, 2010) in addition to the estimated HI using biomonitoring data for the five phthalates and three AAs (BPA, PPB, and BPB) increases the HI 0.176 units (Table D-10); conservatively, the increase in the HI using the high intake estimates increases the HI 0.593 units. The most conservative case (using high intake estimates for the seven AAs) increases the distribution of HI for the 15 chemicals such that the 75th percentile is 0.88 and 21% of pregnant women have estimated HI values that exceed 1.0 (Table D-10; calculated by linearly interpolating).

Table D-10 Summary percentiles from the Hazard Index distributions for pregnant women with sampling weights from NHANES (2005-06) using Case 1 RfD values.

AA Set	Percentile				
	Median	**75th**	**90th**	**95th**	**99th**
5 phthalates	0.14	0.26	0.70	6.73	13.1
5 phthalates + 3 AAs	0.19	0.29	0.73	6.75	13.2
5 phthalates + 3 AAs + median intake of 7 other AAs	0.37	0.46	0.91	6.92	13.3
5 phthalates + 3 AAs + high intake of 7 other AAs	0.78	0.88	1.33	7.34	13.8

7 Analysis of SFF Data

7.1 Calculation of the Hazard Index in Pregnant Women Using Case 1 RfDs.

The Hazard Index was calculated per woman from prenatal and postnatal values using the daily intake estimates for the five phthalate diesters. Figure D-14A provides a histogram for the distribution of HI for the 340 prenatal estimates. The distribution is highly skewed with a median HI value of 0.11 and the estimated mean was 0.30. Interpolating between the 99^{th} and 95^{th} percentiles, roughly 4% of the prenatal women have HI values that exceed 1.0, with one woman with an extremely high value of 29.3. Figure D-14B demonstrates the general bell-shaped distribution of the log of the Hazard Index.

Figure D-14 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women from **prenatal** values from the SFF data using daily intake estimates from urinary metabolite concentrations and Case 1 values for RfDs.

A B

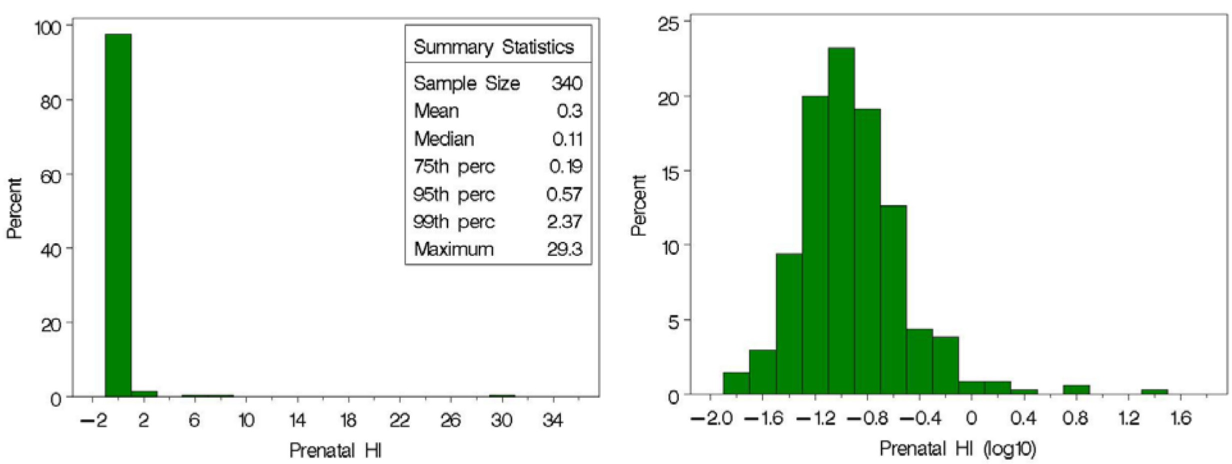
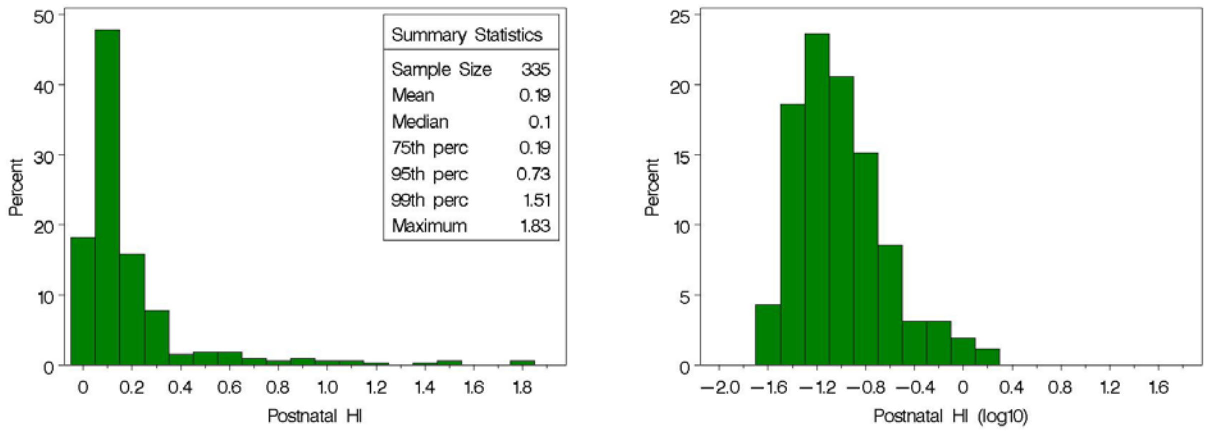


Figure D-15A provides a histogram for the distribution of HI for the postnatal estimates. The distribution is highly skewed with a median HI value of 0.10 and the estimated mean was 0.19. Interpolating between the 99^{th} and 95^{th} percentiles, roughly 4% of the post-natal women have values exceeding 1.0. Figure D-15B demonstrates the general bell-shaped distribution of the log of the Hazard Index.

Figure D-15 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women from **postnatal** values from the SFF data using daily intake estimates from urinary metabolite concentrations and Case 1 values for RfDs.

A B



Box plots for the hazard quotients for each of the five phthalates that comprise the HI are presented in Figure D-16. DEHP is the primary contributor to the HI for both prenatal and postnatal values using Case 1 RfDs.

Figure D-16 Box plots for the Hazard Quotients for (A) prenatal and (B) postnatal Hazard Indices using Case 1 RfDs.

A B

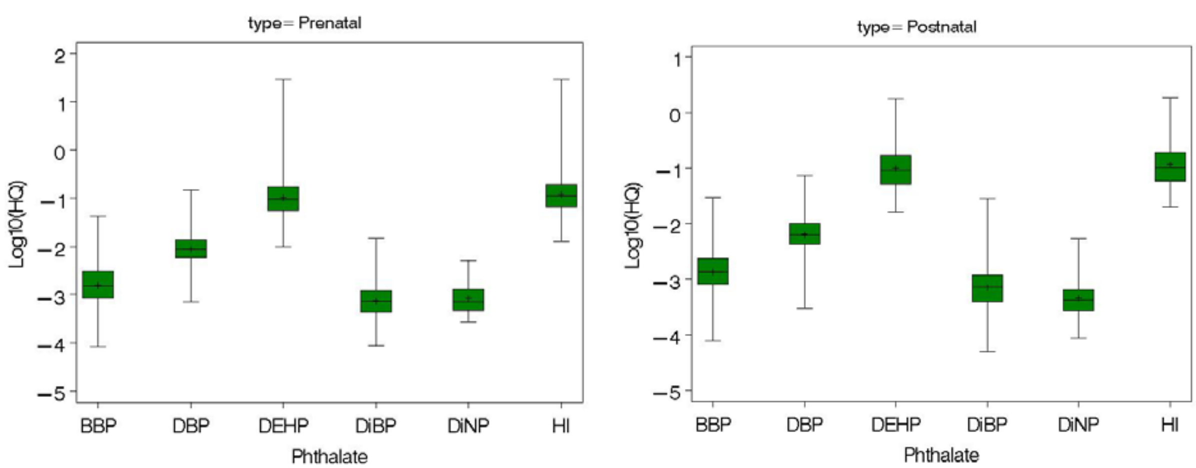
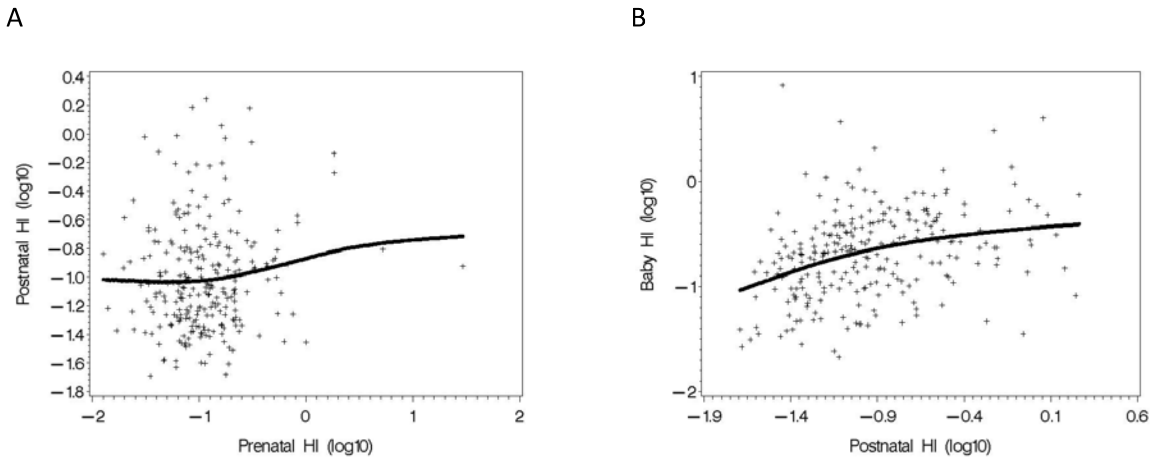


Figure D-17 Bivariate plot of (A) prenatal and postnatal and (B) postnatal and baby Hazard Index values from Case 1.



Although the distribution of HI from prenatal and postnatal measurements are quite similar (Table D-9), the bivariate correlation (on the log10 scale) is not significant (p=0.120; N=258) and is estimated to be 0.10 (Figure D-17A). There is not a strong systematic relationship between prenatal and postnatal values of HI. However, there is a significant relationship between postnatal HI values and baby HI values (Figure D17B) from Case 1; the correlation estimate is 0.32 (p<0.001; N=251).

7.2 Calculation of the Hazard Index in Pregnant Women Using Case 2 RfDs.

The Hazard Index was calculated per woman from prenatal and postnatal values using the daily intake estimates for the five phthalate diesters – or the number of non-missing diesters. Figure D-18A provides a histogram for the distribution of HI for the 340 prenatal estimates. The distribution is highly skewed with a median HI value of 0.10 and the estimated mean was 0.22. Interpolating between the 95th and 99th percentiles, roughly 3% of the prenatal estimates for HI exceed 1.0. Figure D-18B demonstrates the general bell-shaped distribution of the log of the Hazard Index for prenatal values.

Figure D-18 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women from prenatal values from the SFF data using daily intake estimates from urinary metabolite concentrations and Case 2 values for RfDs.

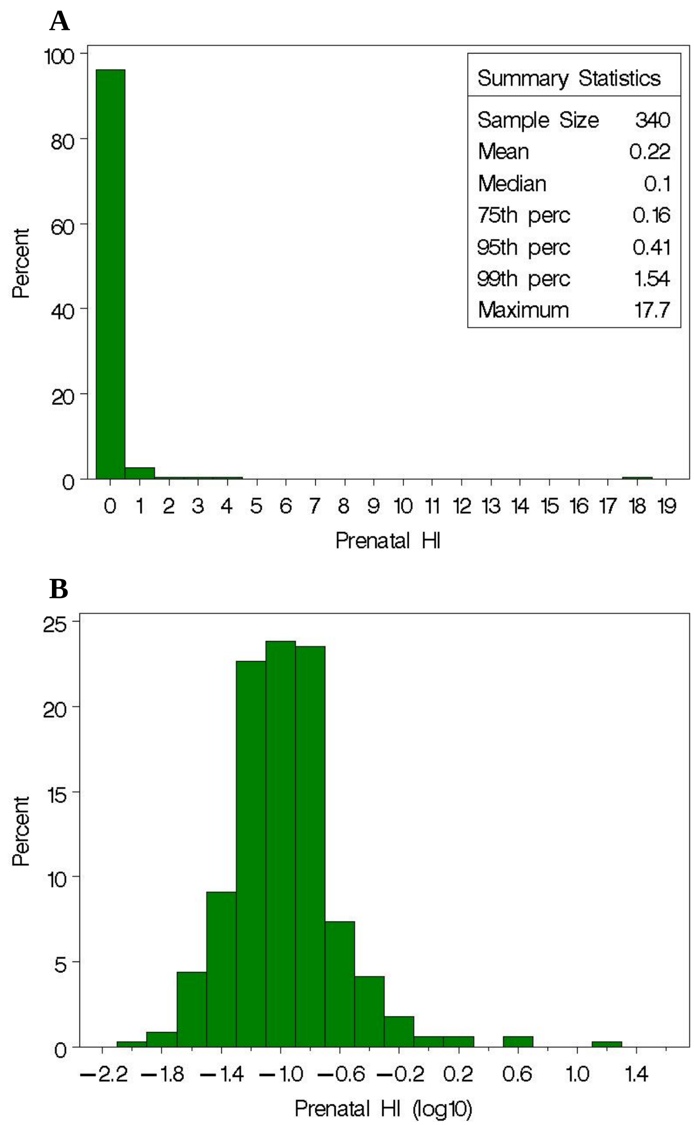
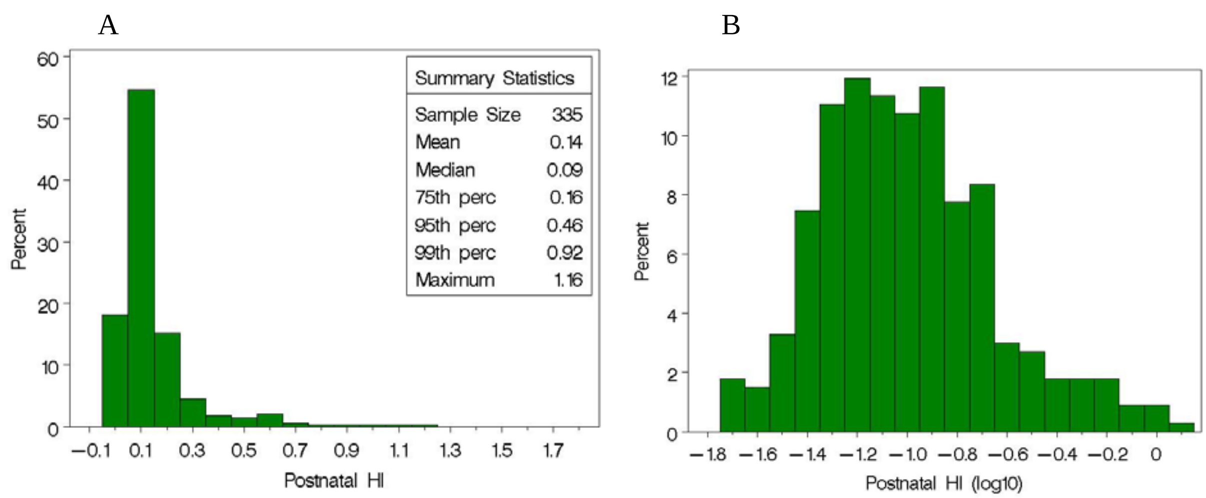


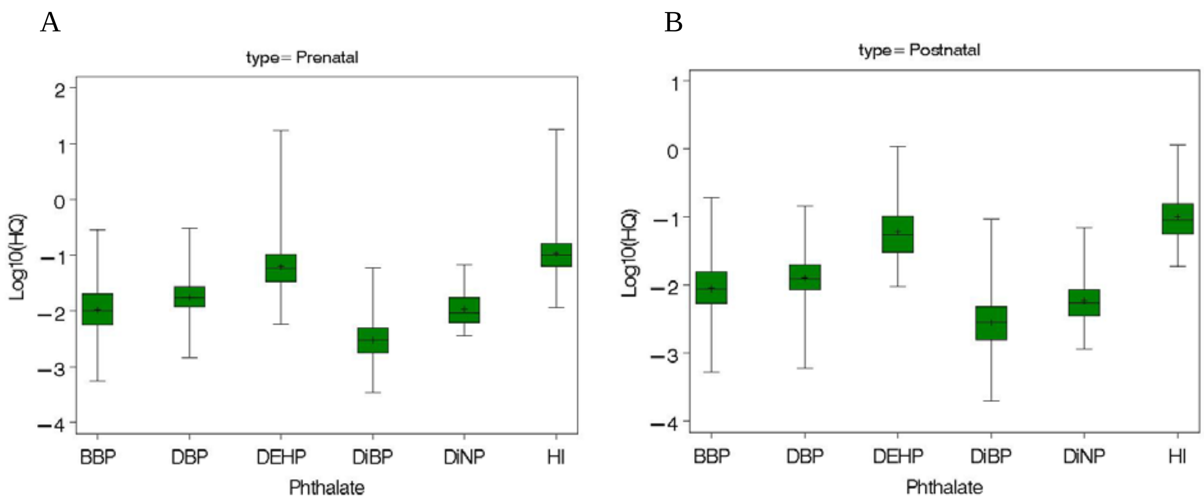
Figure D-19A provides a histogram for the distribution of HI for the 335 postnatal estimates. The distribution is highly skewed with a median HI value of 0.09 and the estimated mean was 0.14. Less than 1% of the estimates exceed 1.0. Figure D-19B demonstrates the distribution of the log of the Hazard Index has a heavy upper tail.

Figure D-19 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women from **postnatal** values from the SFF data using daily intake estimates from urinary metabolite concentrations and Case 2 values for RfDs.



Box plots for the hazard quotients for each of the five phthalates that comprise the HI are presented in Figure D-20 for Case 2 RfDs. DEHP is the primary contributor to the HI for both prenatal and postnatal values using Case 2 RfDs.

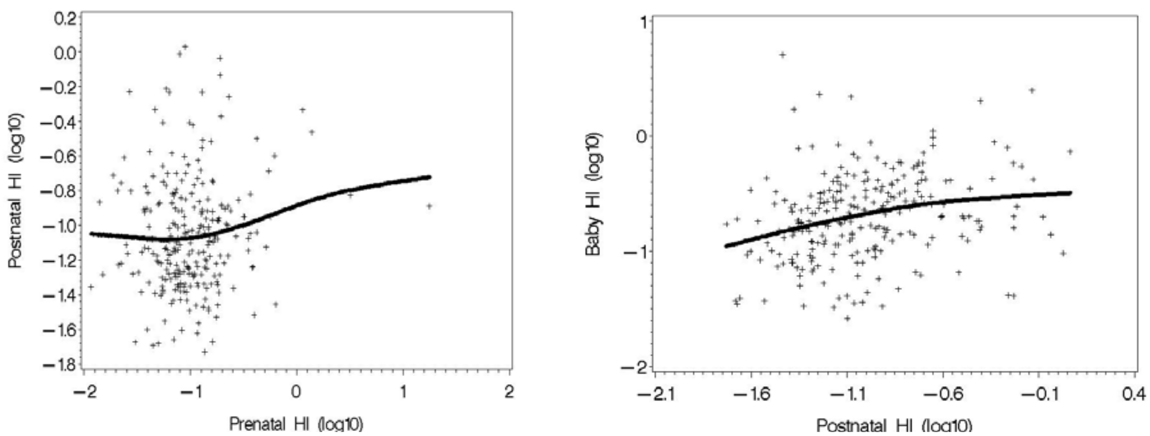
Figure D-20 Box plots for the Hazard Quotients that comprise the Hazard Index for five phthalates in (A) prenatal and (B) postnatal measurements from SFF data for Case 2.



The bivariate association between the prenatal and postnatal estimates for HI is borderline significant (p=0.082; N=258) with a Pearson correlation coefficient estimate of 0.11 (Figure D-21A). Omitting the two highest prenatal HI values, the correlation estimate is 0.09 (p=0.132; N=256). However, there is a significant relationship between postnatal HI values and baby HI values with a correlation estimate of 0.26 (p<0.001; N=251; Figure D-21B).

Figure D-21 Bivariate plot of (A) prenatal and postnatal (N=258); and (B) postnatal and baby (N=251) Hazard Index values for Case 2.

A B



7.3 Calculation of the Hazard Index in Pregnant Women Using Case 3 RfDs.

The Hazard Index was calculated per woman from prenatal and postnatal values using the daily intake estimates for the five phthalate diesters – or the number of non-missing diesters. Figure D-22A provides a histogram for the distribution of HI for the 340 prenatal estimates. The distribution is highly skewed with a median HI value of 0.06 and the estimated mean was 0.17. Roughly 2% of the prenatal estimates exceed 1.0, with one woman with an extremely high value of 17.6. Figure D-22B demonstrates the general bell-shaped distribution of the log of the Hazard Index.

Figure D-22 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women from prenatal values from the SFF using daily intake estimates from urinary metabolite concentrations and Case 3 values for RfDs.

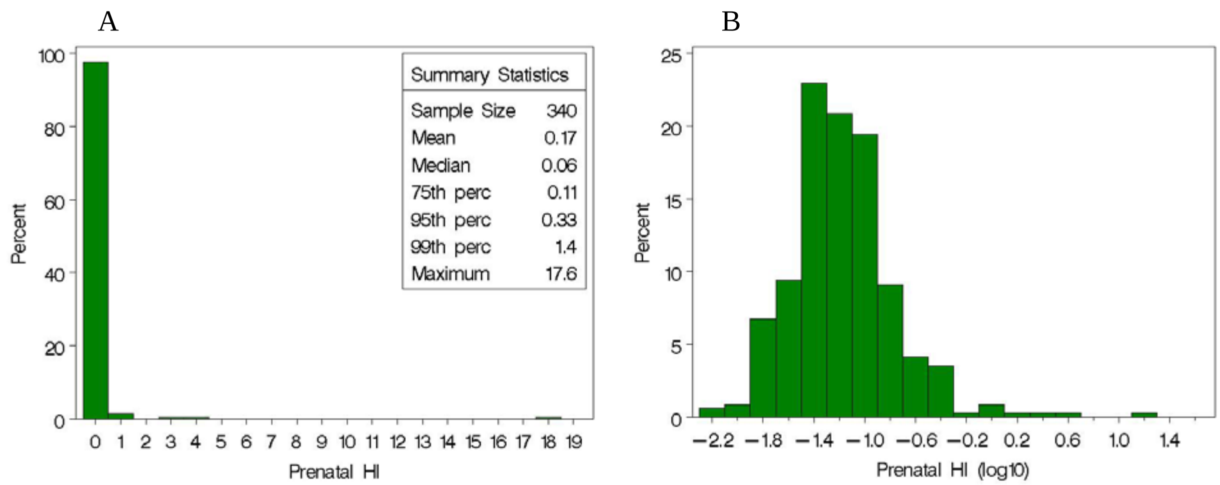


Figure D-23A provides a histogram for the distribution of HI for the 335 postnatal estimates. The distribution is highly skewed with a median HI value of 0.06 and the estimated mean was 0.11. The maximum observed value was 1.09. Figure D-23B demonstrates the general bell-shaped distribution of the log HI.

Figure D-23 Distribution of the Hazard Index (A,B) for five phthalates, as estimated in pregnant women from **postnatal** values from the SFF data using daily intake estimates from urinary metabolite concentrations and Case 3 values for RfDs.

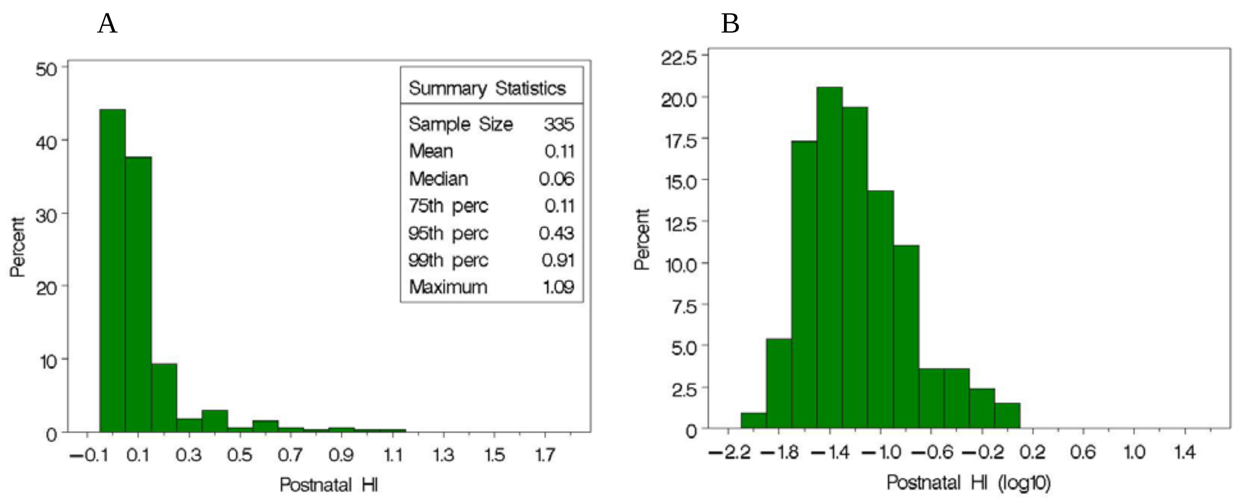
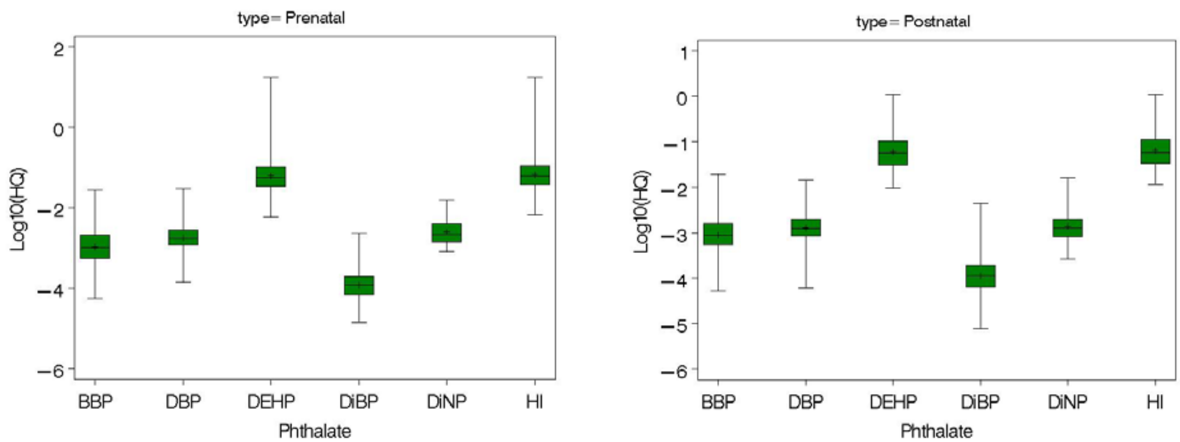


Figure D-24 provides box plots for the hazard quotients for the HI for Case 3 across the five phthalates. Again, the hazard quotient for DEHP dominates the sum for the HI.

Figure D-24 Box plots for the Hazard Quotients that comprise the Hazard Index for five phthalates in (A) prenatal and (B) postnatal measurements from SFF data for Case 3.

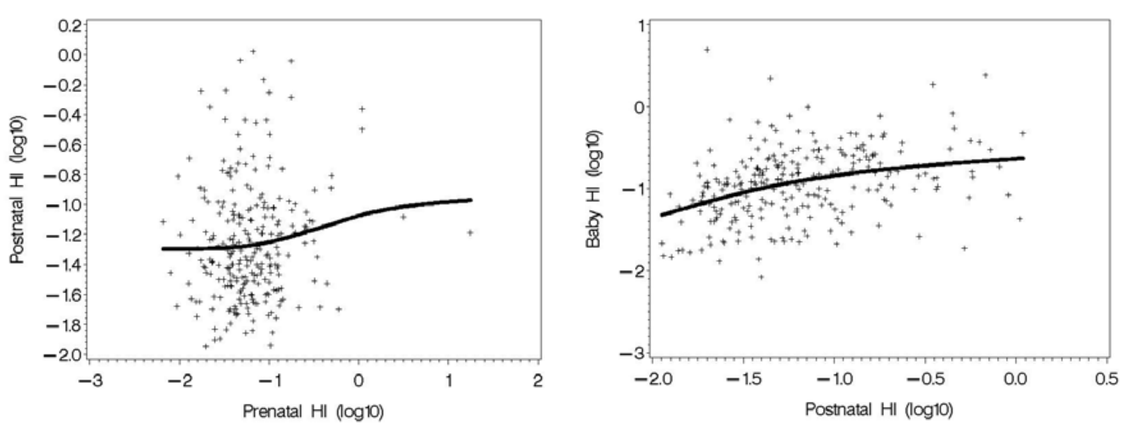
A B



The bivariate association (Figure D-25) between the prenatal and postnatal HI values using Case 3 is not significant ($p=0.076$; $N=258$) with a Pearson correlation estimate of 0.11. However, there is a significant relationship between postnatal HI values and baby HI values with a correlation estimate of 0.34 ($p<0.001$; $N=251$; Figure D-25B)

Figure D-25 Bivariate plot of (A) prenatal and postnatal (N=258); and (B) postnatal and baby (N=251) Hazard Index values for Case 3.

A B



8 Analysis of Infant Data

8.1 Calculation of the Hazard Index in Infants Using Case 1 RfDs.

The Hazard Index was calculated per baby using the daily intake estimates for the five phthalate diesters – or the number of non-missing diesters. Figure D-26A provides a histogram for the distribution of HI for the 258 babies. The distribution is highly skewed with a median HI value of 0.22 and the estimated mean was 0.36. Approximately 5% of the HI values from infants exceed 1.0. Figure D-26B demonstrates the general bell-shaped distribution of the log of the Hazard Index.

Figure D-25 Bivariate plot of (A) prenatal and postnatal (N=258); and (B) postnatal and baby (N=251) Hazard Index values for Case 3.

A B

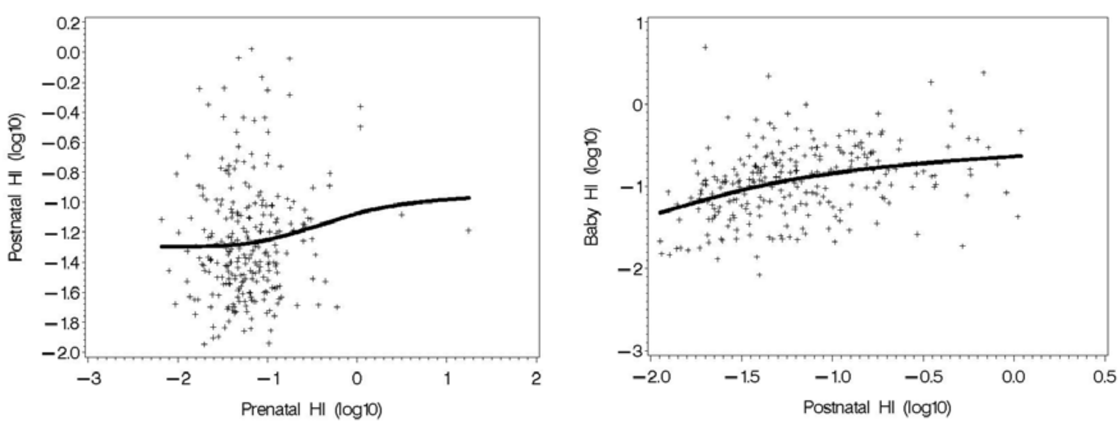
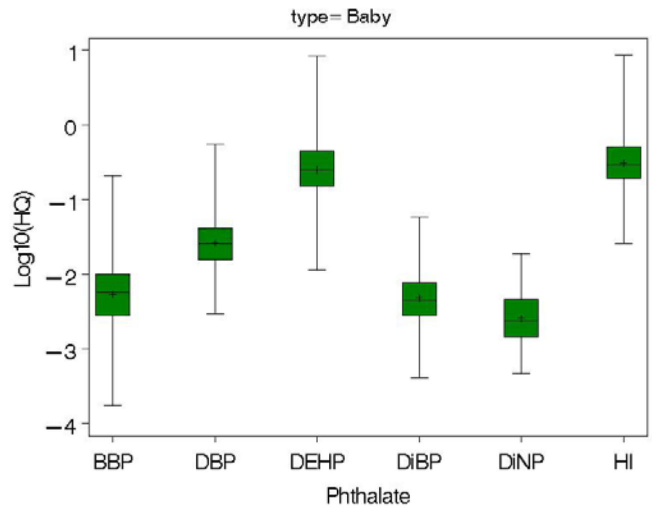


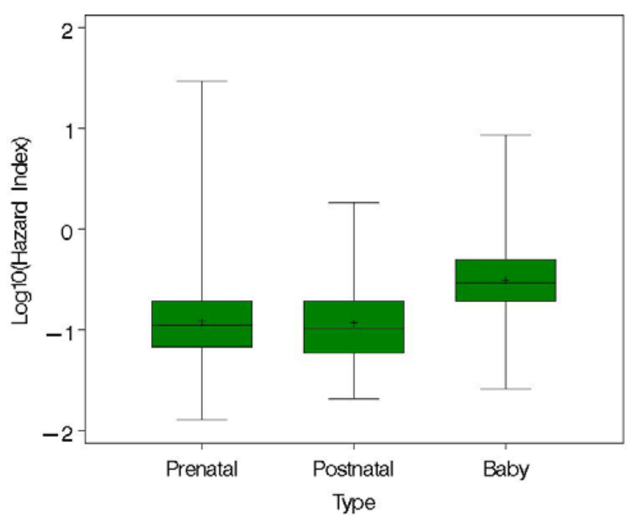
Figure D-27 provides box plots for the distributions of the hazard quotients for infants using Case 1 RfDs. The DEHP Hazard Quotient dominates the HI sum.

Figure D-27 Box plots for the Hazard Quotients for the Hazard Index for infants from the SFF.



Using Case 1 values for RfDs in calculating the HI, the distribution of the hazard index is most extreme in the infants. The median value for the infants exceeds the 75th percentiles from the prenatal and postnatal values (Figure D-28).

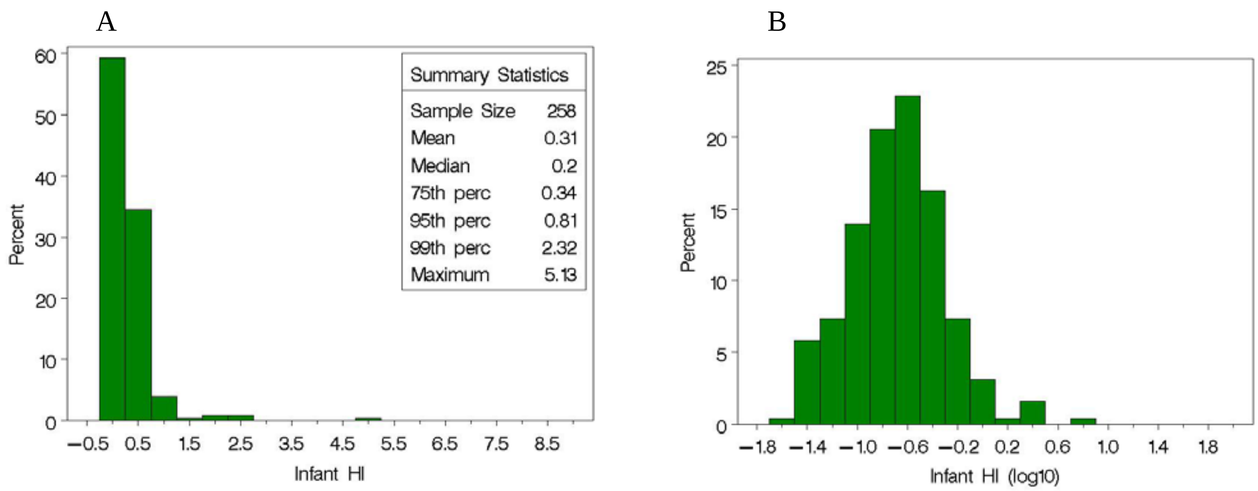
Figure D-28 Box plots comparing the distributions of the Hazard Index values using Case 1 RfD values for prenatal, postnatal measurements and from babies from the SFF.



8.2 Calculation of the Hazard Index in Infants Using Case 2 RfDs.

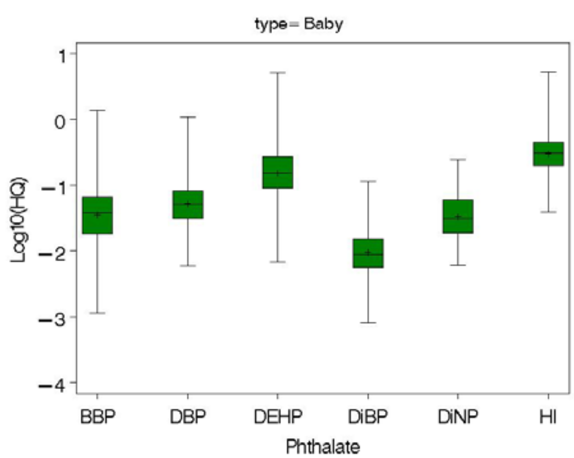
The Hazard Index was calculated per baby using the daily intake estimates for the five phthalate diesters – or the number of non-missing diesters using Case 2 RfDs. Figure D-29A provides a histogram for the distribution of HI for the 291 babies. The distribution is highly skewed with a median HI value of 0.31 and the estimated mean of 0.41. Approximately 5% of the infants have estimated HI values that exceeded 1.0. Figure D-29B demonstrates the general bell-shaped distribution of the log of the Hazard Index.

Figure D-29 Distribution of the (A) Hazard Index, and (B) log10 Hazard Index using Case 2 RfD values, as estimated in babies (0-37 months) using daily intake estimates from urinary metabolite concentrations. Data are from the SFF.



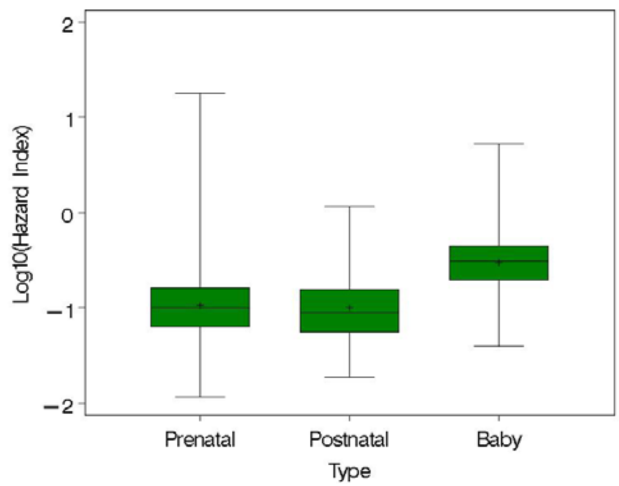
The hazard quotient for DEHP is again the dominant contributor to the HI sum (Figure D-30).

Figure D-30 Box plots for the Hazard Quotients for the Hazard Index for infants from the SFF using Case 2 RfDs.



Using Case 2 values for RfDs in calculating the HI, the distribution of the hazard index is most extreme in the infants. The median of HI for the infants exceeds the 75th percentiles from the prenatal and postnatal values using Case 2 RfD values (Figure D-31).

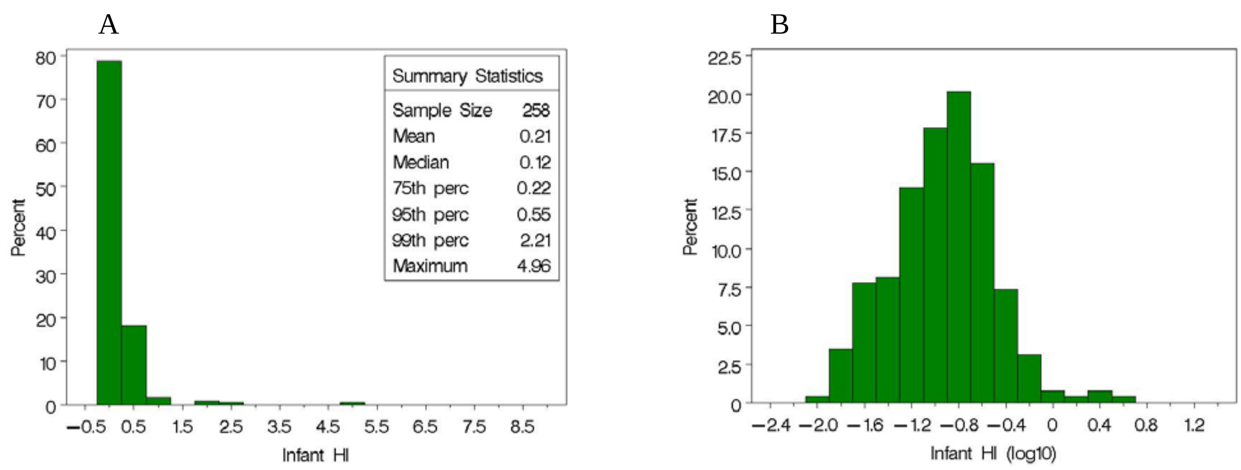
Figure D-31 Box plots comparing the distributions of the Hazard Index values using Case 2 RfD values for prenatal, postnatal measurements and from babies from the SFF data.



8.3 Calculation of the Hazard Index in Infants Using Case 3 RfDs.

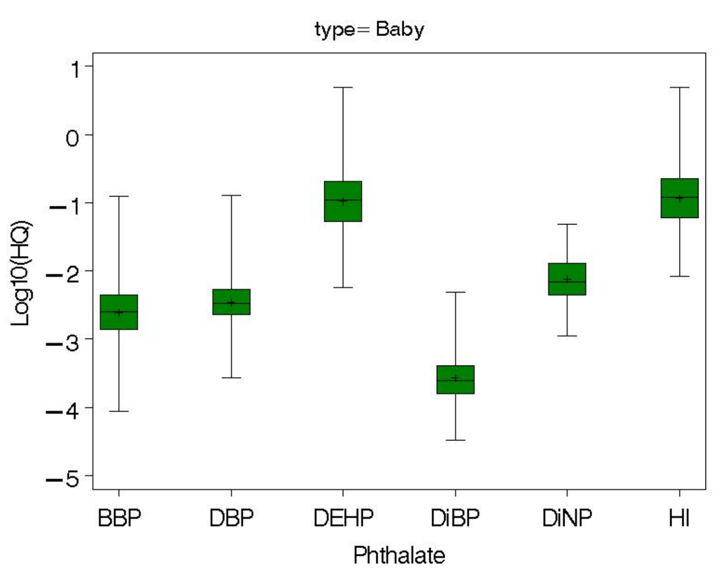
The Hazard Index was calculated per baby using the daily intake estimates for the five phthalate diesters – or the number of non-missing diesters using Case 3 RfDs. Figure D-32A provides a histogram for the distribution of HI for the 258 babies. The distribution is skewed with a median HI value of 0.12 and the estimated mean of 0.21. Roughly 4% of infants have HI estimates that exceed 1.0. Figure D-32B demonstrates the general bell-shaped distribution of the log of the Hazard Index.

Figure D-32 Distribution of the (A) Hazard Index, and (B) log10 Hazard Index using Case 3 RfD values, as estimated in babies (0-37 months) using daily intake estimates from urinary metabolite concentrations. Data are from SFF.



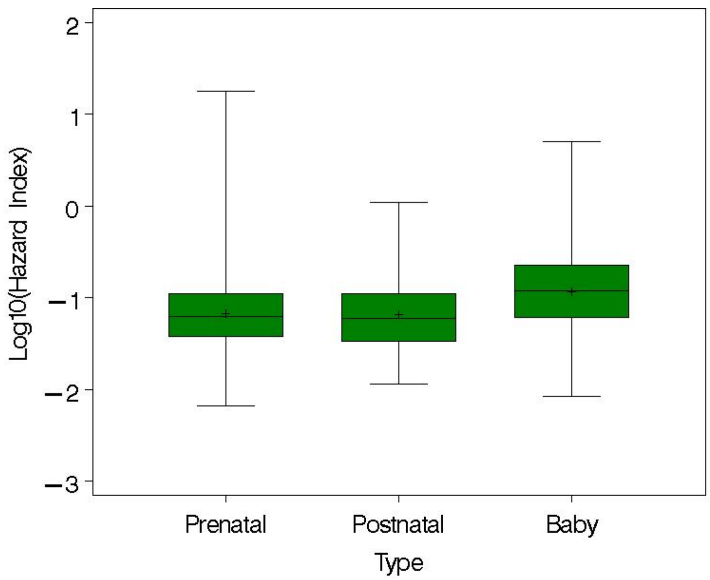
Again, the hazard quotient for DEHP dominates the HI sum using Case 3 RfDs (Figure D-33).

Figure D-33 Box plots for the Hazard Quotients for the Hazard Index for infants from the SFF using Case 3 RfDs.



Using Case 3 values for RfDs in calculating the HI, the distribution of the hazard index is most extreme in the infants. As for Cases 1 and 2, the median value of HI for the infants exceeds the 75th percentiles from the prenatal and postnatal values (Figure D-34) using Case 3 RfD values.

Figure D-34 Box plots comparing the distributions of the Hazard Index values using Case 3 RfD values for prenatal, postnatal measurements and from babies from SFF data.



9 Summary of Results

The CHAP considered 3 cases in calculating the HI based on different sets of RfDs. Cases 1 and 3 were largely based on points of departures (i.e., NOAELs or BMDLs) for individual chemicals. Case 2 is based on the dose-response curves and the assumptions of potencies. Four of the five phthalates (i.e., DEHP, DBP, BBP, and DIBP) were assumed to be equipotent in terms of testosterone modulated effects (Hannas *et al.*, 2011b). The potency of DINP was assumed to be 2.3 times less potent from the same set of studies.

Hazard indices for these five anti-androgens were calculated for individual pregnant women from NHANES data (2005-06) and in prenatal and postnatal maternal concentrations from the SFF. From the NHANES data, the HI exceeds 1.0 in about 10% of pregnant women in the U.S. population. The rate was about 4-5% in the SFF data for both maternal and infant measurements.

In all three cases studied, the HI value was dominated by DEHP since it had both high exposure and a low RfD. The smallest contributor to the HI was generally DIBP in all three cases, which was due to low exposure.

A limitation of the analyses presented here is the use of exposure data from 2005-06 for NHANES and 1999-2005 for the SFF. Since these data were collected, the Consumer Product Safety Improvement Act restricted some of the uses of the five phthalates evaluated. The impact on exposure is unknown and not accounted for in the calculation of the HI.

10 Supplement

Table S-1 Comparison of estimated percentiles for Hazard Quotients and Hazard Indices from pregnant women using survey sampling weights in NHANES 2005-6.

	Approximated as a weight (PROC UNIVARIATE)			Estimated using survey design features (strata, clusters) (PROC SURVEYMEANS)		
CASE 1	**Median**	**95th**	**99th**	**Median**	**95th**	**99th**
BBP	0.001	0.004	0.01	<0.001	0.004	0.01
DBP	0.006	0.04	0.10	0.01	0.03	0.06
DEHP	0.12	6.7	13.1	0.12	6.0	12.2
DIBP	0.001	0.005	0.01	0.001	0.005	0.01
DINP	0.001	0.01	0.02	0.001	0.01	0.02
HI	0.14	6.7	13.1	0.14	6.1	12.2
CASE 2	**Median**	**95th**	**99th**	**Median**	**95th**	**99th**
BBP	0.01	0.03	0.05	0.01	0.03	0.05
DBP	0.01	0.08	0.20	0.01	0.07	0.13
DEHP	0.07	4.0	7.9	0.07	3.6	7.3
DIBP	0.003	0.02	0.04	0.003	0.02	0.04
DINP	0.01	0.10	0.30	0.01	0.10	0.24
HI	0.13	4.1	7.9	0.13	3.7	7.4
CASE 3	**Median**	**95th**	**99th**	**Median**	**95th**	**99th**
BBP	0.001	0.003	0.005	0.001	0.003	0.005
DBP	0.001	0.008	0.02	0.001	0.007	0.01
DEHP	0.07	4.0	7.9	0.07	3.6	7.3
DIBP	<0.001	0.001	0.002	<0.001	0.001	0.002
DINP	0.002	0.02	0.07	0.002	0.02	0.05
HI	0.09	4.0	7.9	0.08	3.6	7.3

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PEER REVIEW DRAFT

Draft Report to the
U.S. Consumer Product Safety Commission
by the
CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES
AND PHTHALATE ALTERNATIVES

March 7, 2013

APPENDIX E1

MODELING CONSUMER EXPOSURE TO PHTHALATE ESTERS

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

Memorandum

Date: May 17, 2012

TO : Mary Ann Danello, Ph.D., Associate Executive Director for Health Sciences

THROUGH : Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Michael A. Babich, Ph.D., Chemist, Division of Health Sciences
Kent R. Carlson, Ph.D., Toxicologist
Leslie E. Patton, Ph.D., Toxicologist

SUBJECT : Modeling consumer exposure to phthalate esters (PEs)—DRAFT *

The attached report provides the U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences' staff assessment of consumer exposures to phthalate esters from all sources and routes of exposure, including diet, teethers and toys, child care articles, and cosmetics. This work was performed at the request of the Chronic Hazard Advisory Panel (CHAP) on phthalates and phthalate substitutes.

* These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

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1 Introduction

The Consumer Product Safety Improvement Act (CPSIA)[*] of 2008 (CPSC, 2008) was enacted on August 14, 2008. Section 108 of the CPSIA permanently prohibits the sale of any "children's toy or child care article" individually containing concentrations of more than 0.1 percent of dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), or di(2-ethylhexyl) phthalate (DEHP). Section 108 prohibits on an interim basis the sale of "any children's toy that can be placed in a child's mouth" or "child care article" containing concentrations of more than 0.1 percent of di-*n*-octyl phthalate (DNOP), diisononyl phthalate (DINP), or diisodecyl phthalate (DIDP). In addition, section 108 of the CPSIA directs the CPSC to convene a Chronic Hazard Advisory Panel (CHAP) "to study the effects on children's health of all phthalates and phthalate alternatives as used in children's toys and child care articles." The CHAP will recommend to the Commission whether any phthalates or phthalate alternatives other than those permanently banned should be declared banned hazardous substances.

In support of the CHAP, CPSC staff contracted with Versar, Inc., Springfield, VA, to review the published literature on human exposure to phthalate esters (PEs) (Versar/SRC, 2010) and to estimate human exposure to eight selected PEs (Table E1-1) (Versar, 2011). These phthalates were selected because they are subject to the CPSIA, are found in human tissue, and/or exposure data are available. Following the completion of the Versar exposure assessment, the CHAP requested additional analyses, including:

- Incorporating new concentration data that were not available to Versar;
- Emphasizing the most recent concentration data, rather than the entire historical data base;
- Including mouthing exposure to phthalate alternatives; and
- Performing additional sensitivity analyses.

This report describes the additional analyses on phthalates, which were performed by CPSC staff under the direction of the CHAP. We estimated exposures of four subpopulations (women of reproductive age; infants; toddlers; and children) to eight PEs selected by the CHAP. Exposure to phthalate alternatives is described in a separate report.

[*] Public Law 110-314.

Table E1-1 Phthalate esters in this report.

Name	Abbr. [a]	CAS	MF	MW (range) [b]
Diethyl phthalate	DEP	84-66-2	C12H14O4	222.2
Di-n-butyl phthalate [c]	DBP	84-74-2	C16H22O4	278.4
Diisobutyl phthalate	DIBP	84-69-5	C16H22O4	278.4
Butylbenzyl phthalate [c]	BBP	85-68-7	C19H20O4	312.4
Di-n-octyl phthalate [d]	DNOP	117-84-0	C24H38O4	390.6
Di(2-ethylhexyl) phthalate [c]	DEHP	117-81-7	C24H38O4	390.6
Diisononyl phthalate [d]	DINP	28553-12-0	C26H42O4	418.6
		68515-48-0		(390.6 - 446.7)
Diisodecyl phthalate [d]	DIDP	26761-40-0	C28H46O4	446.7
		68515-49-1		(418.6 - 474.7)

[a] Abbr., abbreviation; CAS, Chemical Abstracts Service number, MF, molecular formula; MW, molecular weight.

[b] DINP includes isomers with C8 – C10 ester groups; DIDP includes isomers with C9 – C11 ester groups.

[c] Subject to a permanent ban in child care articles and children’s toys.

[d] Subject to an interim ban in child care articles and toys that can be placed in a child’s mouth.

2 Methodology

In this report, we estimated human exposure to selected PEs by identifying and evaluating relevant exposure scenarios. This approach required knowledge of all relevant sources of PE exposure, data on concentrations of PEs in environmental media and products, physiological parameters, and consumer use information. The scenario-based (indirect) approach is complementary to the biomonitoring approach, which is also employed by the CHAP. The biomonitoring (direct) approach provides robust estimates of total human exposure to PEs, but does not provide information regarding the sources of exposure. The scenario-based approach, employed for this report, estimates the relative contributions of various sources of PE exposure.

2.1 Sources and Scenarios

Humans are exposed to PEs from many sources and through multiple pathways and scenarios (Wormuth *et al.*, 2006; Versar/SRC, 2010; Clark *et al.*, 2011). PEs are ubiquitous environmental contaminants that are present in air, water, soil, food, cosmetics, drugs and medical devices, automobiles, and consumer products.[*] PEs were also commonly used in toys and child care articles before their use was restricted by the European Commission and the United States. The sources and scenarios that may contribute significantly to human exposure were identified by CPSC staff and are listed in Table E1-2.

Table E1-2 Sources of exposure to phthalate esters (PEs) included by exposure route.

Source	Target Population (age range)			
	Women (15 to 44)[a]	Infants (0 to <2)	Toddlers (2 to <3)	Children (3 to 12)
Children's Products				
Teethers & toys	D[b]	O, D	O, D	D
Changing pad	--	D	D	--
Play pen	--	D	D	--
Household Products				
Air freshener, aerosol	I (direct)[c]	I (indirect)[d]	I (indirect)	I (indirect)
Air freshener, liquid	I (indirect)	I (indirect)	I (indirect)	I (indirect)

[*] In this report, "consumer product" refers to products under the jurisdiction of the CPSC. This includes products used in and around the home, recreational settings, and schools that are not regulated by other federal agencies, for example, food, drugs, cosmetics, and medical devices.

Source	Target Population (age range)			
	Women (15 to 44) [a]	Infants (0 to <2)	Toddlers (2 to <3)	Children (3 to 12)
Vinyl upholstery	D	--	D	D
Gloves, vinyl	D	--	--	--
Adhesive, general purpose	D	--	--	--
Paint, aerosol	I, D	--	I (indirect) [d]	I (indirect) [d]
Adult toys	Internal	--	--	--
Cosmetic Products				
Soap/body wash	D	D	D	D
Shampoo	D	D	D	D
Skin lotion/cream	D	D	D	D
Deodorant, aerosol	D, I (direct)	I (indirect)	I (indirect)	D, I (direct) [e]
Perfume, aerosol	D, I (direct)	I (indirect)	I (indirect)	D, I (direct) [e]
Hair spray, aerosol	D, I (direct)	I (indirect)	I (indirect)	D, I (direct) [e]
Nail polish	D	--	--	D
Environmental Media				
Outdoor air	I	I	I	I
Indoor air	I	I	I	I
Dust	O	O	O	O
Soil	O	O	O	O
Diet				
Food	O	O	O	O
Water	O	O	O	O
Beverages	O	O	O	O
Prescription drugs	O	--	O	O

[a] Age range, years.
[b] D, dermal; O, oral; I, inhalation.
[c] Includes direct exposure from product use.
[d] Indirect exposure from product use by others in the home.
[e] Females only.

2.2 Calculations

Exposures were calculated with equations specific to the exposure route and the physico-chemical processes by which exposure may occur. Exposure from direct ingestion was estimated by:

$$E_{O.1} = C \times M \times N \times B \times F / W \qquad (1)$$

where: $E_{O.1}$, estimated oral exposure by ingestion, μg/kg-d; C, concentration in product or environmental medium, μg/g; M, mass ingested per event, g; N, frequency of exposure, events per day, d^{-1}; B, fraction absorbed by the gastrointestinal tract, unitless; F, fraction of population exposed by this scenario, unitless; W, body weight, kg.

Exposure from mouthing soft plastic teethers and toys was estimated by:

$$E_{O.2} = R \times T \times N \times B \times F / W \qquad (2)$$

where: $E_{O.2}$, estimated oral exposure from mouthing, μg/kg-d; R, migration rate, μg/10 cm^2-h; T, exposure duration, h; N, frequency of exposure, d^{-1}; B, fraction absorbed, unitless; F, fraction of population exposed by this scenario, unitless; W, body weight, kg.

Inhalation exposure was calculated by:

$$E_I = C \times I \times T \times N \times B \times F / W \qquad (3)$$

where: E_I, estimated inhalation exposure, μg/kg-d; C, concentration in air, μg/m^3; I, inhalation rate, m^3/h; T, exposure duration, h; N, frequency of exposure, d^{-1}; B, fraction absorbed, unitless; F, fraction of population exposed by this scenario, unitless; W, body weight, kg.

Percutaneous exposure[*] from non-PVC products was estimated by:

$$E_{D.1} = C \times M \times D \times T \times N \times F / W \qquad (4)$$

where: $E_{D.1}$, estimated dermal exposure, μg/kg-d; C, concentration in the medium of interest, μg/g; M, mass of medium in contact with the skin; D, dermal absorption rate, h^{-1}; T, exposure duration, h; N, frequency of exposure, events per day, d^{-1}; F, fraction of population exposed, unitless; W, body weight, kg.

For dermal contact with polyvinyl chloride (PVC) films or solid products, exposure was estimated by (Deisinger *et al.*, 1998; Wormuth *et al.*, 2006):

[*] Strictly speaking, equations (4) and (5) calculate absorbed doses, rather than exposures.

$$E_{D.2} = DT \times S \times \left(\frac{D_{PE}}{D_{DEHP}}\right) \times T \times N \times F/W \qquad (5)$$

where: $E_{D.2}$, estimated dermal exposure from contact with PVC, µg/kg-d; DT, rate of dermal transfer and absorption for DEHP, 0.24 µg/cm^2-h (Deisinger *et al.*, 1998); S, surface area of exposed skin, cm^2; D_{PE}, dermal absorption rate of the PE of interest, h^{-1}; D_{DEHP}, dermal absorption rate of DEHP, h^{-1}; T, exposure duration per event, h; N, frequency of exposure, d^{-1}; F, exposed fraction of the population, unitless; W, body weight, kg.

Internal exposure from PVC adult toys was estimated by:

$$E_A = R \times A \times T \times N \times B \times F/W \qquad (6)$$

where: E_A, estimated internal exposure, µg/kg-d; R, migration rate, µg/cm^2-h; A, product surface area, cm^2; T, exposure duration, h; N, frequency of exposure, d^{-1}; B, fraction absorbed, unitless; F, exposed fraction of the population; W, body weight, kg.

Average values (means) for all parameters were used to estimate the average population exposure. The 95th percentile concentrations (or for toys, migration rates) were generally used to estimate upper bound exposures. In selected scenarios, we also calculated exposures using the mean concentration (or migration rate) with the 95th percentile value for exposure frequency or duration. Data were not available to estimate upper bound exposures for some scenarios.

For some products, such as aerosols and air fresheners, it was necessary to estimate indoor PE concentrations. For aerosols, the initial PE concentration in a room was estimated by:

$$C_0 = M_P \times C_P \times F_O/V \qquad (7)$$

where: C_0, initial concentration in room air, µg/m^3; M_P, mass of product per use, g; C_P, PE concentration in the product, µg/g; F_O, overspray fraction, unitless; V, room volume, m^3.

The time-dependent PE concentration was given by:

$$C_T = C_0 \times e^{-(ACH+K)\times T} \qquad (8)$$

where: C_T, PE concentration in room air at time=T, µg/m^3; C_0, initial concentration in room air, µg/m^3; ACH, air exchange rate, h^{-1}; K, first order decay rate, h^{-1}; and T, time, h.

For aerosol products (deodorant, hair spray, perfume, air freshener, and paint) the PE concentration in the user's breathing zone was estimated by assuming a 1 m^3 breathing zone (Thompson and Thompson, 1990) that exchanges air with room air at a rate of 10 h^{-1}.

For liquid air fresheners, it was assumed that the PE is released into air at a constant rate. Thus, the PE source strength was estimated by:

$$S = \frac{M_P \times C_P}{L_P \times 24} \qquad (7)$$

where: S, PE source strength, µg/h; M_P, mass of product, g; C_P, PE concentration in the product, µg/g; L_P, product lifetime, days; 24, conversion factor, h/d.

The steady-state PE concentration in room air was given by:

$$C_{SS} = \frac{S/V}{ACH+K} \qquad (8)$$

where: C_{SS}, steady-state PE concentration in room air, µg/m^3; S, source strength, µg/h; V, room volume, m^3; ACH, air exchange rate, h^{-1}; K, first order decay rate, h^{-1}.

2.3 Input Data

Data on PE concentrations in environmental media and products were identified from all available sources, including: the primary scientific literature, government reports (e.g., Danish Ministry of the Environment), literature reviews (Versar/SRC, 2010), CPSC studies (Dreyfus, 2010), previously published exposure assessments (Wormuth *et al.*, 2006; Clark *et al.*, 2011; Versar, 2011), and a database prepared for the Phthalate Ester Panel of the American Chemistry Council (Clark, 2009). Priority was given to studies that were of the highest quality, the most recent, and the most relevant to the U.S. population. We recorded or calculated summary statistics for these concentrations including the mean, 95th percentile, and detection frequency. Non-detects in environmental media and food were assumed to equal one-half the detection limit. Non-detects in consumer and cosmetic products were regarded as zero because we consider PEs to be intentionally added in these products. Non-detects and zero values were included in the calculation of the summary statistics. Data on cosmetics (Table E1-3), household products (Tables E1-4 and E1-5), and environmental media (Table E1-6) are summarized below.

For the purpose of this report, it was assumed that DEHP and DINP are still used in teethers and toys, even though DEHP use in these products is permanently prohibited by the CPSIA and DINP is banned on an interim basis (Table E1-5). This is to assess the potential impact of PE use in these products, as specified in the CPSIA. Currently, toys and child care articles should not contain prohibited PEs; the prohibitions became effective in 2009. Biomonitoring data used to estimate total PE exposure (CHAP Report, Section 2.5) predate the PE prohibition. Exposure from mouthing toys containing other PEs, such as DNOP and DIDP, were not included because

273 **Table E1-3** Phthalate ester (PE) concentrations in cosmetics (µg/g).[a]

Product		DEP	DBP
Shampoo (shampoo/body wash)	n	13	NR
	mean	26	
	0.95	143	
	DF (%)	23	
Shampoo/body wash, infant use	n	13	NR
	mean	26	
	0.95	143	
	DF (%)	23	
Soap/body wash	n	3	NR
	mean	175	
	0.95	313	
	DF (%)	67	
Skin lotion/cream	n	18	NR
	mean	30	
	0.95	108	
	DF (%)	33	
Skin lotion/cream, infant use	n	11	NR
	mean	32	
	0.95	174	
	DF (%)	18	
Perfume/fragrance	n	22	NR
	mean	12545	
	0.95	27453	
	DF (%)	100	
Deodorant	n	35	NR
	mean	441	
	0.95	11462	
	DF (%)	57	
Hair spray, gel, mousse	n	49	NR
	mean	112	
	0.95	328	

Product		DEP	DBP
	DF (%)	67	
Nail polish	n	6	6
	mean	189	19207
	0.95	852	60077
	DF (%)	17	56

[a] Mean and 95th percentile concentrations (µg/g). Non-detects were assumed to equal zero. Abbreviations: n, number of products tested; DF, phthalate ester detection frequency (%), NR, not reported (not present). Sources: Hubinger (2010); Hubinger & Havery (2006); Houlihan et al. (2008).

Table E1-4 Phthalate ester (PE) concentrations in household products (µg/g).[a]

Product		DEP	DBP	DIBP	BBP	DINP	Reference
Air freshener, aerosol	n	8	8	NR [B]	NR	NR	NRDC (2007)
	mean	294	0.19				
	0.95	952	0.24				
	DF (%)	63	25				
	range	1.0 -- 1100	0.12 -- 0.25				
Air freshener, liquid	n	5	5	5	NR	NR	NRDC (2007)
	mean	2436	1.5	1.1			
	0.95	6571	3.9	1.6			
	DF (%)	60	80	60			
	range	0.78 -- 7300	0.19 – 4.5	0.24 -- 1.6			
Adhesive, general purpose	n	NR	NR	NR	4	NR	NLM (2012)
	mean				9,050		
	0.95				30,800		
	DF (%)				25		
	range				36,200		
Paint/coating, aerosol	n	NR	NR	NR	96	96	NLM (2012)
	mean				1,040	400	
	0.95				0	0	
	DF (%)				2.1	1.0	
	range				50,000	39,000	

[a] n, number of products tested; mean, mean concentration; 0.95, 95th percentile concentration; DF, detection frequency (%); range, range of concentrations in products containing phthalates. Summary statistics include zero values.

[b] NR, not reported. The phthalate ester was not present in the product.

Table E1-5 Phthalate esters (PEs) used in PVC products.[a]

Product	DNOP	DEHP	DINP	DIDP	Reference
Teethers & toys	?	X	X	?	Assumed
Changing pad	X	X	X	X	Assumed
Play pen	X	X	X	X	Assumed
Furniture	X	--	X	X	Godwin (2010)
Gloves [b]	X	X	X	X	Godwin (2010)
Adult toys	X	X	X	--	Nilsson et al. (2006)

[a] X, PE present; ?, PE present, but no migration data available; --, PE not present.
[b] Assumes similar PEs as used in medical exam gloves.

Table E1-6 Phthalate ester (PE) concentrations in environmental media.[a]

Medium	DEP	DBP	DIBP	BBP	DNOP	DEHP	DINP	DIDP
Indoor Air ($\mu g/m^3$) [b]								
mean	0.57	0.20	0.11	0.022	3.5x10^{-4}	0.089	NR	NR
95th percentile	1.4	0.44	0.26	0.053	ND	0.17	NR	NR
Outdoor Air ($\mu g/m^3$) [c]								
mean	0.060	0.0035	0.0036	0.0030	3.5x10^{-4}	0.020	NR	NR
95thpercentile	0.16	0.015	0.011	0.0048	ND	0.12	NR	NR
Dust ($\mu g/g$) [d]								
mean	8.5	27	2.9	120	NR	510	130	34
95th percentile	11.0	44	5.0	280	NR	850	1,000	110
Soil ($\mu g/m^3$) [e]								
mean	35	190	NR	100	13	270	78	NR
95th percentile	160	800	NR	1,800	42	1,100	310	NR

[a] ND, not detected; value shown is one-half the detection limit. NR, not reported.
[b] Rudel et al. (2003; 2010).
[c] Rudel et al. (2010).
[d] Abb et al. (2009); Rudel et al. (2003).
[e] Vikelsøe et al. (1999).

migration data for estimating oral exposure were not available. For the same reasons given above, it was assumed that DNOP, DEHP, DINP, and DIDP are used in changing pads and play pens. Only general information on the use of PEs in PVC products is available (Godwin, 2010). Information on PE use in household products (Godwin, 2010) and adult toys (Nilsson *et al.*, 2006) is summarized in Table E1-5.

Data on physiological parameters (Table E1-7) (such as body weight, inhalation rate, and skin surface area) and product use information (Tables E1-8 – E1-11) (amount of product used, frequency and duration of exposure) were generally derived from a standard reference (EPA 2011). Information on infant mouthing duration (Greene, 2002) and PE migration rates from teethers and toys (Chen, 2002) were from CPSC studies (Table E1-12). Migration rates were measured by the Joint Research Centre method (Simoneau *et al.*, 2001). Dermal absorption rates (Table E1-13) were estimated from published data (Stoltz and El-hawari, 1983; Stoltz *et al.*, 1985; Elsisi *et al.*, 1989). In cases where use data were not available, it was necessary to make reasonable assumptions regarding use parameters.

We applied a default value of 1.0, assumed for oral, inhalation, and internal (i.e., intravaginal for adult toys) absorption/bioavailability (Table E1-7) (see Discussion).

For estimating inhalation exposures, we assumed a value of 38 m^3 for the size of an average bedroom in a small home (Persily *et al.*, 2006; small homes). The air exchange rate is the median value for U.S. homes (Murray and Burmaster, 1995). The hypothetical breathing zone had a volume of 1 m^3 (Thompson and Thompson, 1990) and 10 air changes per hour (assumed), which is equivalent to a linear air flow of 0.01 km/h. The first order decay rate of 1 h^{-1} is appropriate for particles in the general range of 1 to 10 µm in diameter (EPA, 2011, Table 19-29).

Information on exposure to diethyl phthalate in prescription drugs (Table E1-14) is from the U.S. Food and Drug Administration (Jacobs, 2011). The maximum daily DEP dose (mg/kg) and number of prescriptions per year were available for four age groups, although these age groups do not correspond exactly to the age groups in this study. The number of prescriptions was divided by the U.S. population for the age range of interest (Census, 2010) as a rough estimate of the fraction of the population taking a given drug.

2.4 Dietary Exposures

The methods for estimating dietary exposure are described in detail in a separate report (Carlson and Patton, 2012; Appendix E3). Food residue data are from a total diet study from the United Kingdom (Bradley, 2011) that contains the most recently reported food residues available. Two hundred and sixty-one retail food items were analyzed for 15 phthalate esters (diesters), nine phthalate monoesters, and phthalic acid. Only the data on the eight diesters listed in Table E1-1

Table E1-7 Physiological parameters.

Parameter	Units	Women	Infants	Toddlers	Children	Reference
Age range		15 to 44	0 to <1	1 to <3	3 to 12	
Body weight [a, b]	kg	75	7.8	12.4	30.7	EPA (2011), Table 8-25 (women); Table 8-1 (juveniles)
Inhalation rate [b, c]	m^3/h	0.60	0.36	0.55	0.53	EPA (2011), Table 6-15
Surface areas: [b]						
Total	cm2	18,500	3,990	5,700	9,200	EPA (2011), Table-7-13 (women);
Hands		900	180	270	420	Tables 7-1 & 7-8 (juveniles)
Palms, both hands [d]		300	60	90	140	
Exposed legs, arms [e]		1600	260	380	680	
Changing pad [f]		N/A	90	130	N/A	
Toys [g]		25	10	10	25	Assumed
Dust consumption	g/d	0.03	0.03	0.06	0.06	EPA (2011), Table 5-1
Soil consumption	g/d	0.02	0.03	0.05	0.05	EPA (2011), Table 5-1
Bioavailability:						
Oral	unitless	1	1	1	1	Assumed (see text)
Inhalation		1	1	1	1	
Internal [h]		1	--	--	--	

[a] Mean body weight for females age 18 to 65, NHANES IV.
[b] Weighted averages were used to average ages ranges with different intervals.
[c] Average daily inhalation rate for females, age 16 to 41. Males and females combined for age 0 to <1; 1 to <3; and 3 to <11 years.
[d] One-third of total hand area.
[e] Estimated skin surface area in contact with a sofa, while sitting, and wearing short pants and short sleeves. Assumes two-thirds of the arms and legs are exposed and one-quarter of exposed area contacts the sofa.
[f] Estimated skin surface area in contact with a changing pad. Assumes one-third of genitals, plus buttocks contact the pad.
[g] Estimated skin surface area in contact with a small (teether or rattle, 10 cm^2) or medium (action figure, 25 cm^2) toy.
[h] Adult toys.

Table E1-8 Product use parameters for women.

Product	Mass per use [a] (g)	Mass on skin (g)	Exposure duration (h)		Over-spray fraction	Uses per day (d^{-1})	Fraction exposed	Reference
			Skin	Air				
Cosmetics								
Shampoo [b]	16	0.16	24		--	0.82	1	EPA (2011), Table 17-3
Soap/body wash [b]	2.6	0.026	24	--	--	1.5	1	
Lotion/cream	0.5	0.5	24	--	--	1	1	
Deodorant [c]	0.5	0.5	24	0.1	0.5	1	1	
Perfume, spray [c]	0.23	0.23	24	0.1	0.5	0.29	1	
Nail polish [d]	0.33	0.033	24	--	--	0.16	1	
Hairspray [c]	1.0	0.5	24	0.1	--	0.25	1	Mass is assumed
Household Products								
Paint, aerosol [c, e]	200	2.0	24	0.25	0.5	0.012	0 or 1	EPA (2011), Tables 17-4,
Adhesive [d]	25	0.25	24	0.25	0.5	0.012	0 or 1	17-5, 17-6
Aerosol air freshener [f]	1	--	--	0.1	1.0	1	0.5	Versar (2011)
Liquid air freshener [f]	1	--	--	--	--	1	0.5	
Dermal Contact								
Handling toys	--	--	0.1	--	--	1	1	Assumed
Vinyl furniture [g]	--	--	4.0	--	--	1	0 or 1	Babich & Thomas (2001)

Product	Mass per use [a] (g)	Mass on skin (g)	Exposure duration (h)		Over-spray fraction	Uses per day (d^{-1})	Fraction exposed	Reference
			Skin	Air				
Vinyl gloves [h]	--	--	0.011	--	--	1	1	EPA (2011), Table 17-12
Adult toys	--	--	0.25		--	0.019	0.5	Nilsson et al. (2006)
Time indoors/outdoors [i]	--	--	21/3		--	--	--	EPA (2011), Table 16-1

[a] Mass per use, amount of product per use, g; mass on skin, residual amount of product remaining on skin after use, g; exposure duration, time that product remains on the skin (dermal) or time user is exposed in the breathing zone (air), h; overspray fraction, fraction of aerosol that does not contact the intended surface, unitless; uses per day (frequency of use), number of times the product is used per day, d^{-1}; fraction exposed, fraction of the population that is exposed to the product, unitless.

[b] For shampoo and soap/body wash, it was assumed that 1 percent of the product remained on the skin for 24 hours. For all other cosmetics, it was assumed that the amount used remains on the skin for 24 hours.

[c] For aerosol products, it was assumed that the user is exposed in a breathing zone during product use. The listed exposure duration for air is the time exposed in the breathing zone. Indirect exposure from room air occurs for the time indoors (21 hours).

[d] For nail polish and adhesive, it was assumed that 1 percent of mass contacts the skin.

[e] For aerosol paint and lacquer, it was assumed that 1 percent of mass contacts the skin. The overspray fraction was assumed. The fraction exposed was assumed to equal either 0 (non-users) or 1 (users of products containing phthalates). The use parameters available were for users only. The fraction of products containing phthalate esters is unknown.

[f] Daily use of aerosol air freshener or continuous use of liquid air freshener was assumed. The fraction exposed was assumed to equal 0.5 for each.

[g] Time spent sitting while reading or watching television. The prevalence of vinyl-covered furniture is unknown. Assume average person is unexposed and that an exposed individual represents the upper bound exposure.

[h] Average dish detergent use is 107 hours per year.

[i] Average time outdoors rounded to the nearest hour. Time indoors assumed to equal 24 minus time outdoors.

Table E1-9 Product use parameters for infants.

Product	Mass per use [a] (g)	Mass on skin (g)	Exposure duration (h) mean	Exposure duration (h) 0.95	Frequency of use (d^{-1})	Fraction exposed (unitless)	Reference
Cosmetics							
Soap/body wash [b]	1	0.01	24	--	1	1	
Lotion/cream [c]	1.4	1.4	24	--	1	1	EPA (2011), Table 17-3 (baby use)
Dermal Contact						1	
Teethers & toys [d]	--	--	4.3	--	1	0.3	EPA (2011), Table 16-62
Changing pad [e]	--	--	0.08	0.17	6	1	O’Reilly (1989)
Play pen [f]	--	--	4.3	12.6	1	0.3	EPA (2011), Table 16-62
Mouthing							
Teethers & toys [g]	--	--	0.073	0.292	1	1	Greene (2002)
Time indoors/outdoors [h]	--	--	23/1	--	1	1	EPA (2011), Table 16-1

[a] Mass per use, amount of product per use, g; mass on skin, residual amount of product remaining on skin after use, g; exposure duration, time that product remains in contact with skin (mean and 95th percentile), h; frequency of use, number of times the product is used per day, d^{-1}; fraction exposed, fraction of the population that is exposed to the product, unitless.

[b] For soap/body wash, it was assumed that 1 percent of the product remained on the skin for 24 hours. Frequency and amount per use for soap/body wash are assumed.

[c] For lotion/cream, it assumed that the amount used remains on the skin for 24 hours. Parameters are for baby use.

[d] Time “playing games” for 3- to 6-month olds.

[e] Exposure duration is assumed to be 5 minutes (mean) or 10 minutes (upper bound). Frequency of use is from O’Reilly (1989).

[f] Average duration is the time playing games; upper bound is the time sleeping/napping. EPA (2011), Table 16-62.

[g] Time spent mouthing “all soft plastic articles, except pacifiers” (Greene, 2002).

[h] Average time outdoors rounded to the nearest hour. Time indoors assumed to equal 24 minus time outdoors. Indirect (room air) exposures to aerosol products occur during the time indoors (23 h).

Table E1-10 Product use parameters for toddlers.

Product	Mass per use [a] (g)	Mass on skin (g)	Exposure duration (h) mean	Exposure duration (h) 0.95	Frequency of use (d^{-1})	Fraction exposed (unitless)	Reference
Cosmetics [b]							
Shampoo [c]	0.5	0.005	24	--	0.27	1	EPA (2011), Table 17-3
Soap/body wash [c]	2.6	0.026	24	--	1.2	1	
Lotion/cream [d]	1.4	1.4	24	--	1.0	1	
Dermal Contact						1	
Teethers & toys [e]	--	--	3.2	--	1	0.64	EPA (2011), Table 16-62
Changing pad [f]	--	--	0.08	0.17	5	1	O'Reilly 1989
Play pen [g]	--	--	3.2	11.8	1	0.64	EPA (2011), Table 16-62
Vinyl-covered furniture [h]	--	--	1.6	--	1	0 or 1	
Mouthing							
Teethers & toys [i]	--	--	0.067	0.263	--	1	Greene (2002)
Time indoors/outdoors [j]	--	--	23/1	--	--	1	EPA (2011), Table 16-1

[a] Mass per use, amount of product per use, g; mass on skin, residual amount of product remaining on skin after use, g; exposure duration, time that product remains in contact with skin (mean and 95th percentile), h; frequency of use, number of times the product is used per day, d^{-1}; fraction exposed, fraction of the population that is exposed to the product, unitless.

[b] Use infant/baby use parameters, where available.

[c] For shampoo and soap, it was assumed that 1 percent of the product remained on the skin for 24 hours. For lotion/cream, it assumed that the amount used remains on the skin for 24 hours. .

[d] For lotion/cream, it assumed that the amount used remains on the skin for 24 hours. Parameters are for baby use.

[e] Time playing games, 1-year olds.

[f] Exposure duration is assumed to be 5 minutes (mean) or 10 minutes (upper bound). Frequency is from O'Reilly (1989).

[g] Average duration is the time playing. Upper bound is the time sleeping/napping. EPA (2011), Table 16-62. One-year olds.

[h] Time watching television. EPA (2011), Table 16-77.

[i] Time spent mouthing "all soft plastic articles, except pacifiers" (Greene, 2002).

[j] Average time outdoors rounded to the nearest hour. Time indoors assumed to equal 24 minus time outdoors. Indirect (room air) exposures to aerosol products occur during the time indoors (23 h).

Table E1-11 Product use parameters for children.

Product	Mass per use [a] (g)	Mass on skin (g)	Exposure duration (h) skin	Exposure duration (h) air	Over-spray fraction	Uses per day (d^{-1})	Fraction exposed (unitless)	Reference
Cosmetics [b]								
Shampoo [c]	16	0.16	24	--	--	0.82	1	EPA (2011), Table 17-3
Soap/body wash [c]	2.6	0.026	24	--	--	1.5	1	
Lotion/cream [c]	0.5	0.5	24	--	--	1	1	
Deodorant [d]	0.5	0.5	24	0.1	0.5	1	1	
Perfume, spray [d]	0.23	0.23	24	0.1	0.5	0.29	0.5	
Nail polish [e]	0.33	0.033	24	--	--	0.16	0.5	
Hairspray [d]	1.0	0.5	24	0.1	--	0.25	0.5	Mass is assumed
Dermal Contact							1	
Toys [f]	--	--	2.1	--	--	1	0.4	EPA (2011), Table 16-62
Vinyl-covered furniture [g]	--	--	2.7	--	--	--	0 or 1	
Time indoors/outdoors [h]	--	--	22/2	--	--	--	1	EPA (2011), Table 16-1

[a] Mass per use, amount of product per use, g; mass on skin, residual amount of product remaining on skin after use, g; exposure duration, time that product remains on the skin (skin) or time user is exposed in the breathing zone (air), h; overspray fraction, fraction of aerosol that does not contact the intended surface, unitless; uses per day (frequency of use), number of times the product is used per day, d^{-1}; fraction exposed, fraction of the population that is exposed to the product, unitless.

[b] Use adult use parameters for children ages 3 to 12.

[c] For shampoo and soap, it was assumed that 1 percent of the product remained on the skin for 24 hours. For lotion/cream, it assumed that the amount used remains on the skin for 24 hours.

[d] For aerosol products, it was assumed that the user is exposed in a breathing zone during product use (duration listed under air), and exposure from room air occurs for the time indoors (22 h).
[e] For nail polish, it was assumed that 1 percent of mass contacts the skin.
[f] Time playing games, average of 3- to 11-year olds.
[g] Average time outdoors rounded to the nearest hour. Time indoors assumed to equal 24 minus time outdoors.

Table E1-12 Phthalate ester (PE) migration into artificial saliva.[a]

Phthalate ester	n [b]	Migration rate (µg/10 cm2-h)	
		Mean	95th Percentile
DINP	25	4.2	10.1
DEHP	3	1.3	1.9

[a] Chen (2002). Migration rate (µg/10 cm^2-h) measured by a modification of the Joint Research Centre method (Simoneau *et al.*, 2001).
[b] n, number of products tested.

Table E1-13 Estimated percutaneous absorption rates (h^{-1}) for phthalate esters.

Phthalate ester	Absorption rate	Reference
Diethyl phthalate (DEP)	1.1×10^{-2}	Elsisi et al. (1989) [a]
Dibutyl phthalate (DBP)	5.3×10^{-3}	Elsisi et al. (1989)
Diisobutyl phthalate (DIBP)	3.2×10^{-3}	Elsisi et al. (1989)
Butylbenzyl phthalate (BBP)	1.7×10^{-3}	Elsisi et al. (1989)
Di-*n*-octyl phthalate (DNOP)	2.4×10^{-4}	Same as DEHP (assumed)
Di(2-ethylhexyl) phthalate (DEHP)	2.4×10^{-4}	Elsisi et al. (1989)
Diisononyl phthalate (DINP)	2.0×10^{-4}	Stoltz & El-hawari (1983); Stoltz et al. (1985)
Diisodecyl phthalate (DIDP)	3.4×10^{-5}	Elsisi et al. (1989)

[a] Rates were estimated from the absorption at 24 hours in Elsisi et al. (1989), Figure 2.

Table E1-14 Maximum diethyl phthalate (DEP) exposure (mg/d) from prescription drugs by age group. [a]

Drug	Adults			0–6 Years			7–11 Years		
	Dose [b]	No.	F	Dose	No.	F	Dose	No.	F
A	134	9.6×10^{5}	4.1×10^{-3}	67	2.5×10^{3}	8.6×10^{-5}	67	1.1×10^{4}	5.6×10^{-4}
B	20	4.4×10^{6}	1.9×10^{-2}	5	4.0×10^{3}	1.4×10^{-4}	10	9.0×10^{3}	4.5×10^{-4}
C	7	2.4×10^{6}	1.0×10^{-2}	7	2.9×10^{2}	9.6×10^{-6}	7	1.4×10^{3}	7.1×10^{-5}
D	3	4.6×10^{5}	2.0×10^{-3}	3	1.7×10^{2}	5.6×10^{-6}	3	2.7×10^{3}	1.3×10^{-4}
E	19	9.6×10^{4}	4.1×10^{-4}	7	1.0×10^{2}	3.4×10^{-6}	7	7.1×10^{1}	3.5×10^{-6}
F	34	4.4×10^{4}	1.9×10^{-4}				11	1.4×10^{1}	6.8×10^{-7}
G	8	1.1×10^{5}	4.6×10^{-4}				8	3.8×10^{1}	1.9×10^{-6}
H	5	1.5×10^{5}	6.4×10^{-4}	5	4.0×10^{1}	1.4×10^{-6}	5	6.0×10^{1}	3.0×10^{-6}
I	15	1.8×10^{4}	7.7×10^{-5}	6	3.3×10^{1}	1.1×10^{-6}	8	2.5×10^{2}	1.2×10^{-5}
J	12	1.4×10^{2}	5.9×10^{-7}	8	6.3	2.1×10^{-7}	10	1.0×10^{1}	5.0×10^{-7}
K	22	4.4×10^{1}	1.9×10^{-7}						
L	20	5.0×10^{1}	2.2×10^{-7}						
M	4	3.8×10^{1}	1.6×10^{-7}						
Total		8.7×10^{6}	3.7×10^{-2}		7.2×10^{3}	2.4×10^{-4}		2.5×10^{4}	1.2×10^{-3}
Population		2.3×10^{8}			3.0×10^{7}			2.0×10^{7}	

[a] Source: Personal communication from Abigail Jacobs, U.S. Food and Drug Administration, Center for Drug Evaluation and Research (Jacobs, 2011). All are oral medications. Data for male and females are combined.

[b] Dose; maximum daily DEP exposure, mg/d; No., number of prescriptions per year; F, fraction of population exposed.

Table E1-15 Mean and 95th percentile concentrations of selected phthalate esters (PEs) in food commodities (µg/g).[a]

Food Commodity		DEP	DBP	DIBP	BBP	DNOP	DEHP	DINP	DIDP
Grain	*Mean*	5.1	12.3	25.2	9.0	12	78	639	393
	0.95	11.4	35.4	91.6	25.7	35	234	2984	1198
Dairy	*Mean*	21.1	6.8	18.2	7.1	12	173	508	326
	0.95	89.2	17.2	69.9	16.4	26	554	1394	943
Fish	*Mean*	13.6	12.8	10.0	14.7	17	98	819	377
	0.95	40.2	51.5	40.7	46.6	45	286	2174	1281
Meat	*Mean*	5.1	6.8	5.5	12.2	11	54	298	236
	0.95	16.1	28.3	14.2	35.0	38	191	927	986
Fat	*Mean*	7.2	20.8	17.3	108.8	47	689	1481	1055
	0.95	29.2	54.2	46.5	93.2	133	2784	2851	2397
Eggs	*Mean*	4.7	5.2	5.7	9.4	20	24	385	259
	0.95	8.2	8.8	10.9	19.8	71	39	742	407

[a] Mean and 95th percentile concentrations were estimated from data in Bradley (2011) as described in Carlson and Patton (2012). Non-detects were treated as one-half the detection limit.

were used. Non-detects were regarded as one-half the detection limit. The mean and 95th percentile concentrations were calculated for each food category (Table E1-15).

Food items in this study were categorized as either: grain products, dairy products, fish products, meat products, fat products, and eggs (EPA, 2007). A few of the food categories were not represented by food item/residue data, since these data were not present in the Bradley (2011) study. These included: vegetable, fruit, soy, and nuts. Categories that were not represented by at least one food item were excluded from further analysis.

PE concentrations in food (Table E1-15) and consumption estimates (Table E1-16) for these categories were used to estimate per capita (population) dietary exposures (EPA, 2007). For each population and PE, mean and 95th percentile dietary exposures (µg/kg-d) were calculated by summing the contribution from each food category, using equation (1). For dietary exposures only, we used the body weights appropriate for the age-specific consumption estimates (EPA, 2007).

Table E1-16 Average daily food consumption (g/d) by age group (EPA, 2007).

Food Type	Women	Infants	Toddlers	Children
Grain	135.05	18.57	86.7	120.58
Dairy	221.92	107.36	420.4	406.84
Fish	15.48	0.29	4.29	5.88
Meat	127.02	10.56	62.04	87.62
Fat	62.71	34.32	45.11	58.21
Eggs	23.4	2.53	15.98	15.65
Age (y):	≥20	0 to <1	1 to 5	6 to 11
Body weight (kg)	73	8.8	15.15	29.7

3 Results

3.1 Total Exposure

Estimates of mean and 95th percentile exposures to eight phthalate esters are shown in Table E1-17 and Figure E1-1. For women, mean PE exposures ranged from 0.15 µg/kg-d (DIBP) to 18.1 µg/kg-d (DEP). Estimated mean DINP exposures were higher than those of any other PE for infants (21 µg/kg-d), toddlers (31 µg/kg-d), and children (14 µg/kg-d). For infants, toddlers, and children, the estimated 95th percentile DINP exposures were as high as 95 µg/kg-d, which is close to the acceptable daily intake for DINP derived by the 2001 CHAP on DINP of 120 µg/kg-d (CPSC, 2001). DEP, DEHP, and DIDP also contributed substantially to the total PE exposure in all subpopulations.

3.2 General Sources of Phthalate Ester (PE) Exposure

Exposure sources and scenarios were grouped into seven categories: diet, prescription drugs, toys, child care articles, cosmetics, indoor environment, and outdoor environment. The categories are defined in Table E1-18. Tables E1-19 – E1-22 and Figure E1-2 give the relative contributions (as percent of total exposure) of the seven sources for each PE and for each subpopulation. Overall, diet was the predominant source of exposure to DIBP, BBP, DNOP, DEHP, DINP, and DIDP. Cosmetics were the major source of exposure to DEP and DBP.

For women (Table E1-18), diet contributes more than 50 percent of the exposure to DIBP, DNOP, DEHP, DINP, and DIDP. Based on the mean (population mean) exposure, prescription drugs are the greatest source of DEP exposure. However, prescription drugs containing DEP are taken by less than 5 percent of the population. Therefore, most women are not exposed to DEP in prescription drugs. Because of the skewed distribution for exposure from drugs, we used the average DEP exposure for women who take prescription drugs containing DEP to estimate an upper bound exposure for the whole population. As with the average, this value overestimates the 95th percentile exposure because it represents less than 5 percent of the population. In the absence of prescription drugs, cosmetics contributed significantly to women’s DEP exposure. Cosmetics, specifically nail polish, were a significant source of DBP exposure (see section 3.3. below).

For infants and toddlers (Tables E1-20, E1-21), more than 50 percent of DIBP, DINP, and DIDP exposure and more than 40 percent of DEHP exposure was from the diet. Dermal contact with child care articles (play pen and changing pad) contributed roughly 80 percent of the estimated DNOP exposure and contributed substantially to the estimated exposures from DEHP and DINP. However, the methodology used to estimate PE exposure for this scenario is uncertain, and data on DNOP exposure from other sources are limited (see Discussion). Toys (including both mouthing and handling) contributed modestly to DINP and DEHP exposures in infants (about 9 to 13%) and toddlers (about 5%). Currently, DINP and DEHP are not allowed in toys and child

Table E1-17 Estimated mean and 95th percentile total phthalate ester (PE) exposure (µg/kg-d) by subpopulation.

PE	Women (15 to <45)		Infants (0 to <1)		Toddler (1 to <3)		Children (3 to 12)	
	mean	*0.95*	*Mean*	*0.95*	*mean*	*0.95*	*mean*	*0.95*
DEP	18.1	398	3.1	14.9	2.8	2187.8	2.8	1149
DBP	0.29	5.7	0.65	1.8	0.83	2.3	0.55	7.4
DIBP	0.15	0.50	0.48	1.5	0.86	3.0	0.45	1.6
BBP	1.1	2.6	1.8	4.1	2.4	5.9	1.1	2.5
DNOP	0.17	21.0	4.5	9.8	5.5	16.1	1.5	2.8
DEHP	1.6	5.6	12.3	33.8	15.8	46.7	4.4	29.2
DINP	5.1	32.5	21.0	58.6	31.1	94.6	14.3	55.1
DIDP	3.2	12.2	10.0	26.4	16.6	47.6	9.1	28.1

Table E1-18 Categories of exposure sources.

Category	Exposure Source
Diet	Food, beverages, water
Prescription Drugs	Prescription drugs only
Toys [a]	Mouthing (infants and toddlers) and dermal (all) exposure to teethers and toys
Child-care Articles [a]	Dermal contact with PVC changing pads, play pens
Cosmetics	Soap, shampoo, lotion, deodorant, perfume, hair spray, and nail polish
Indoor Environment [a]	Indoor air, household dust, furniture, vinyl gloves, air fresheners, adhesive, aerosol paint, and adult toys
Outdoor Environment	Outdoor air and soil

[a] These categories include products under CPSC jurisdiction.

Table E1-19 Sources of phthalate ester (PE) exposure (percent of total exposure) for women.

PE		Diet [a]	Drugs	Toys [b]	Child-care [b]	Cosmetics	Indoors [b]	Outdoors
DEP	*mean*	0.5	76.4	0	0	21.8	1.2	<0.1
	0.95	0.1	92.8	0	0	6.9	0.2	<0.1
DBP	*mean*	26.4	0	0	0	58.6	14.9	<0.1
	0.95	4.0	0	0	0	94.4	1.6	<0.1
DIBP	*mean*	87.0	0	0	0	0	12.9	<0.1
	0.95	90.9	0	0	0	0	9.1	<0.1
BBP	*mean*	14.3	0	0	0	0	85.7	<0.1
	0.95	9.8	0	0	0	0	90.2	<0.1
DNOP	*mean*	75.8	0	4.7	0	0	19.5	<0.1
	0.95	1.7	0	<0.1	0	0	98.3	<0.1
DEHP	*mean*	84.2	0	0.5	0	0	15.2	<0.1
	0.95	87.8	0	0.1	0	0	11.9	0.1
DINP	*mean*	95.3	0	0.1	0	0	4.6	<0.1
	0.95	44.6	0	<0.1	0	0	55.3	<0.1
DIDP	*mean*	99.4	0	<0.1	0	0	0.6	<0.1
	0.95	75.8	0	<0.1	0	0	24.2	<0.1

[a] Categories are defined in Table E1-18. Values are rounded to the nearest 0.1 percent.
[b] These categories include products under CPSC jurisdiction.

Table E1-20 Sources of phthalate ester (PE) exposure (percent of total exposure) for infants.

PE		Diet [a]	Drugs	Toys [b]	Child-care [b]	Cosmetics	Indoors [b]	Outdoors
DEP	*mean*	9.7	0	0	0	64.8	25.3	0.1
	0.95	8.4	0	0	0	78.1	13.5	<0.1
DBP	*mean*	30.9	0	0	0	0	48.2	20.8
	0.95	29.7	0	0	0	0	35.4	34.9
DIBP	*mean*	73.6	0	0	0	0	26.4	<0.1
	0.95	80.8	0	0	0	0	19.1	<0.1
BBP	*mean*	30.4	0	0	0	0	68.3	1.3
	0.95	16.4	0	0	0	0	81.1	2.5
DNOP	*mean*	8.4	0	0	90.5	0	<0.1	1.1
	0.95	10.0	0	0	88.3	0	<0.1	1.7
DEHP	*mean*	41.1	0	9.2	33.0	0	16.6	0.1
	0.95	54.3	0	9.8	25.5	0	10.2	0.1
DINP	*mean*	65.9	0	12.6	16.3	0	3.8	1.4
	0.95	61.2	0	16.3	12.4	0	8.1	2.0
DIDP	*mean*	93.0	0	0	5.7	0	1.3	0
	0.95	93.8	0	0	4.6	0	1.6	0

[a] Categories are defined in Table E1-18. Values are rounded to the nearest 0.1 percent.
[b] These categories include products under CPSC jurisdiction.

Table E1-21 Sources of phthalate ester (PE) exposure (percent of total exposure) for toddlers.

PE		Diet [a]	Drugs	Toys [b]	Child-care [b]	Cosmetics	Indoors [b]	Outdoors
DEP	*mean*	24.2	19.1	0	0	25.3	31.3	0.1
	0.95	0.1	99.6	0	0	0.2	0.1	<0.1
DBP	*mean*	43.1	0	0	0	0	39.9	17.0
	0.95	42.6	0	0	0	0	28.8	28.6
DIBP	*mean*	85.5	0	0	0	0	14.5	<0.1
	0.95	90.2	0	0	0	0	9.7	<0.1
BBP	*mean*	26.5	0	0	0	0	72.5	1.0
	0.95	17.9	0	0	0	0	80.3	1.8
DNOP	*mean*	11.2	0	0	87.9	0	<0.1	1.0
	0.95	9.7	0	0	89.3	0	<0.1	1.1
DEHP	*mean*	48.0	0	5.2	30.6	0	16.1	0.1
	0.95	55.5	0	4.4	30.8	0	9.2	0.1
DINP	*mean*	77.1	0	5.3	13.1	0	3.5	1.0
	0.95	73.4	0	5.9	12.9	0	6.6	1.3
DIDP	*mean*	94.9	0	0	4.1	0	1.0	0
	0.95	94.6	0	0	4.3	0	1.1	0

[a] Categories are defined in Table E1-18. Values are rounded to the nearest 0.1 percent.
[b] These categories include products under CPSC jurisdiction.

Table E1-22 Sources of phthalate ester (PE) exposure (percent of total exposure) for children.

PE		Diet [a]	Drugs	Toys [b]	Child-care [b]	Cosmetics	Indoors [b]	Outdoors
DEP	*mean*	12.4	50.9	0	0	24.9	11.7	0.1
	0.95	0.1	99.3	0	0	0.5	0.1	<0.1
DBP	*mean*	38.2	0	0	0	38.4	23.3	<0.1
	0.95	7.9	0	0	0	88.7	3.4	<0.1
DIBP	*mean*	89.6	0	0	0	0	10.3	<0.1
	0.95	93.1	0	0	0	0	6.9	<0.1
BBP	*mean*	36.8	0	0	0	0	62.8	0.4
	0.95	25.8	0	0	0	0	73.5	0.8
DNOP	*mean*	68.2	0	31.7	0	0	0.0	<0.1
	0.95	5.9	0	1.1	0	0	93.0	<0.1
DEHP	*mean*	78.0	0	3.0	0	0	18.9	0.1
	0.95	88.4	0	1.0	0	0	10.5	0.1
DINP	*mean*	96.1	0	1.0	0	0	3.0	<0.1
	0.95	73.3	0	0.3	0	0	26.5	<0.1
DIDP	*mean*	99.0	0	0.3	0	0	0.7	0
	0.95	91.9	0	0.1	0	0	8.0	0

[a] Categories are defined in Table E1-18. Values are rounded to the nearest 0.1 percent.
[b] These categories include products under CPSC jurisdiction.

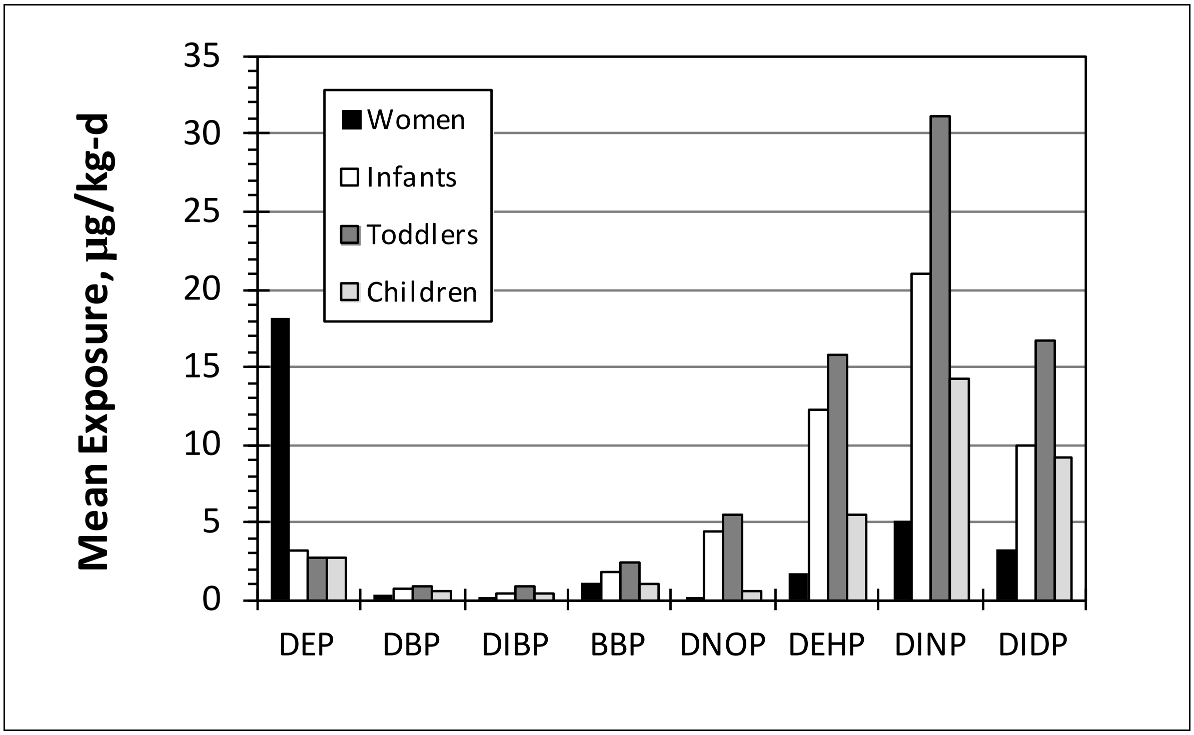

Figure E1-1 Estimated phthalate ester (PE) exposure (µg/kg-d) for eight phthalates and four subpopulations.

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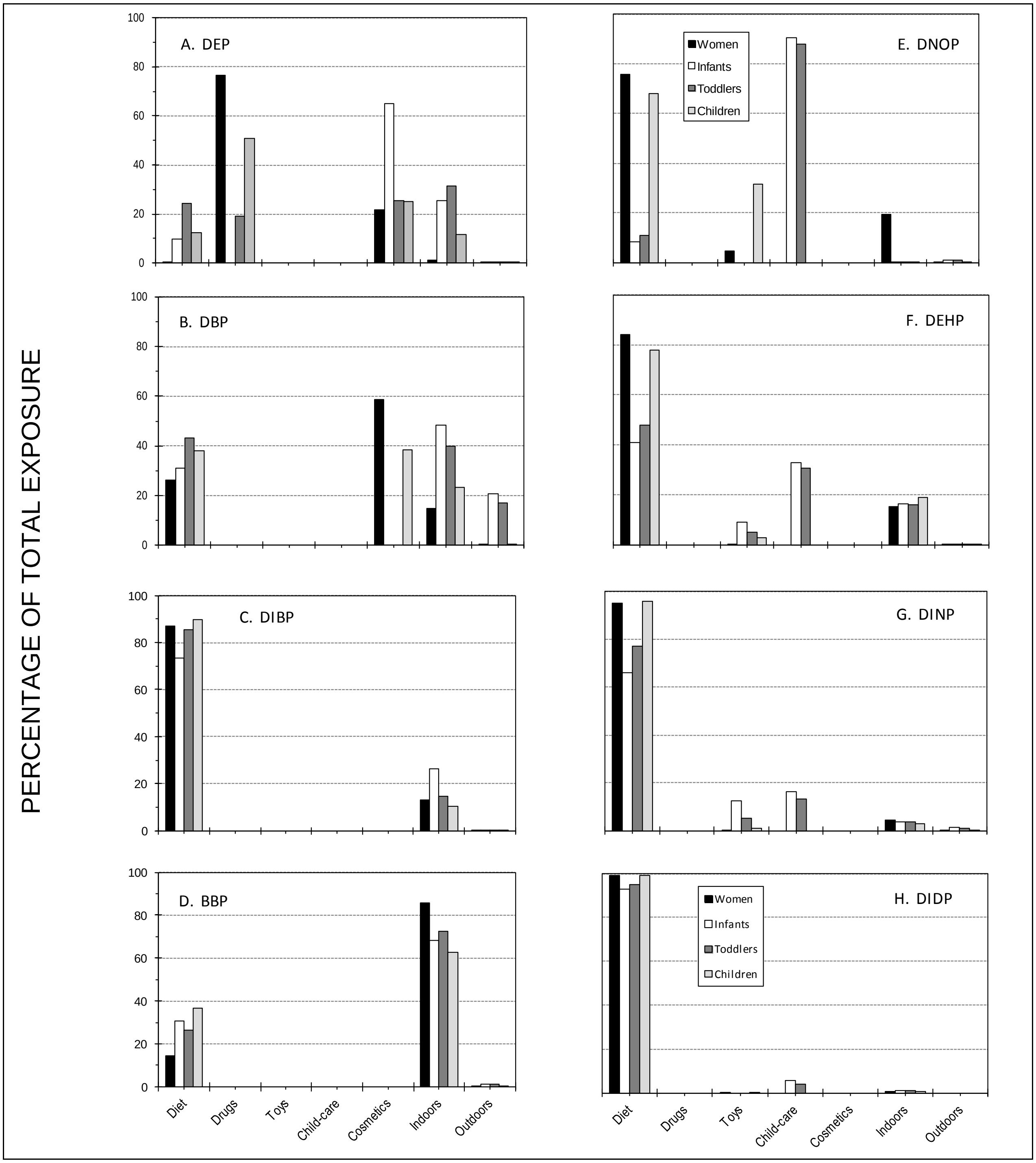

Figure E1-2 Sources of phthalate ester (PE) exposure. Percentage of total exposure for seven sources: (1) diet, (2) prescription drugs, (3) toys, (4) child care articles, (5) cosmetics, (6) indoor sources, and (7) outdoor sources. Sources are defined in Table E1-18. Solid black bars, women; white bars, infants; dark gray bars, toddlers; and light gray bars, children.

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care articles; the estimates described here are based on older residue data for these products. The indoor environment (including indoor air, household dust, air fresheners, and indirect exposure from aerosol paints) contributed substantially (15% to 73%) to infant and toddler exposures to lower molecular weight PEs, including DEP, DBP, DIBP, and BBP. Cosmetics (including indirect exposure from the mother's use) contributed more than 50 percent of DEP exposure to infants.

For children (Table E1-22), diet accounted for more than 50 percent of DIBP, DNOP, DINP, and DIDP exposure and more than 35 percent of DBP and BBP exposure. Handling toys contributed modestly (less than 5%) to DEHP, DINP, and DIDP exposure, and over 30 percent to DNOP exposure. Exposures to DNOP, DEHP, DINP, and DIDP from toys are hypothetical because these PEs currently are not allowed in toys. Cosmetics were a significant source of DBP and DEP exposure. The indoor environment contributed more than 60 percent of exposure to BBP. The indoor environment includes indoor air, household dust, home furnishings, and indirect exposure from aerosol paints.

3.3 Individual Scenarios for Phthalate Ester (PE) Exposure

The estimated exposure from each specific scenario is provided in supplementary data Tables E1-S1 to E1-S4. For women, three scenarios presented potentially high exposures: (i) aerosol paint products (BBP and DINP); (ii) dermal contact with PVC products, such as home furnishings and household gloves (BBP, DNOP, DEHP, DINP, and DIDP); and (iii) adult toy use in combination with an oil-based lubricant (upper bound exposure to DEHP) (Table E1-S1). For various reasons, these scenarios are also more uncertain relative to most other sources, as discussed below (see Discussion).

For infants and toddlers, incidental ingestion of household dust contributed roughly 25 percent to the total BBP exposure and 15 percent to total DEHP exposure (Tables E1-S2, E1-S3). The sources of PEs in household dust are unknown, but may include consumer products (see Discussion). Indoor air contributed roughly one-fourth of the total exposure to the lower molecular weight PEs DEP, DBP, and DIBP.

For children, dust was a significant source of exposure to DEHP (18%). Other significant indoor sources were indirect exposure to aerosol paints (BBP, DINP), nail polish (DBP), and indoor air (DBP) (Table E1-S4).

Individual scenarios that contribute more than 10 percent of the total exposure for a given PE are summarized in Table E1-23. Overall, diet was the primary source of exposure to DIBP, BBP, DNOP, DEHP, DINP, and DIDP. Cosmetics were the primary source of exposure to DEP and DBP. Drugs, air fresheners, and perfume also contributed to DEP exposure. Indoor air

Table E1-23 Scenarios contributing >10% of the total exposure to individual phthalate esters (PEs).

PE	Women	Infants	Toddlers	Children
DEP	drugs > perfume	lotion >indoor air > hair spray, diet	diet > indoor air, drugs, perfume	drugs > diet, perfume
DBP	nail polish >diet > indoor air	indoor air, diet >soil, dust	diet >indoor air >soil, dust	nail polish, diet > indoor air
DIBP	diet >indoor air	diet >indoor air	diet > indoor air	diet
BBP	aerosol paint > gloves > diet	aerosol paint > diet, dust	aerosol paint > diet, dust	aerosol paint, diet > dust
DNOP	diet > gloves	play pen >changing pad	play pen >changing pad >diet	diet >handling toys
DEHP	diet > dust	diet > play pen, dust, changing pad	diet >play pen >dust	diet >dust
DINP	diet	diet > mouthing teethers & toys, play pen	diet >play pen	diet
DIDP	diet	diet	diet	diet

Table E1-24 Comparison of modeled estimates of total phthalate ester (PE) exposure (µg/kg-d).

PE	Study	Adult female		Infants		Toddlers		Children	
		Ave. [a]	U.B.	Ave.	U.B.	Ave.	U.B.	Ave.	U.B.
DEP	Wormuth [b]	1.4	65.7	3.5	19.4	1.5	8.1	0.7	4.6
	Clark [c]	--	--	0.3	1.2	1.2	3.8	0.9	2.8
	This study [d]	18.1	398	3.1	14.9	2.8	2188	2.8	1149
DBP	Wormuth	3.5	38.4	7.6	43.0	2.7	24.9	1.2	17.7
	Clark	--	--	1.5	5.7	3.4	12.0	2.4	8.1
	This study	0.3	5.7	0.6	1.8	0.8	2.3	0.5	7.4
DIBP	Wormuth	0.4	1.5	1.6	5.7	0.7	2.7	0.3	1.2
	Clark	--	--	1.3	5.5	2.6	6.2	2.1	4.8
	This study	0.1	0.5	0.5	1.5	0.9	3.0	0.5	1.6
BBP	Wormuth	0.3	1.7	0.8	7.9	0.3	3.7	0.0	1.1
	Clark	--	--	0.5	6.1	1.5	6.1	1.0	4.0
	This study	1.1	2.6	1.8	4.1	2.4	5.9	1.1	2.5
DEHP	Wormuth	1.4	65.7	3.5	19.4	1.5	8.1	0.7	4.6
	Clark	--	--	5.0	27.0	30.0	124	20.0	81.0
	This study	1.6	5.6	12.3	33.8	15.8	46.7	5.4	16.6
DINP	Wormuth	0.004	0.3	21.7	139.7	7.1	66.3	0.2	5.4
	Clark	--	--	0.8	9.9	2.1	8.7	1.3	5.5
	This study	5.1	32.5	21.0	58.6	31.1	94.6	14.3	55.1

[a] Ave., average; U.B., upper bound.
[b] Wormuth et al. (2006). Mean and maximum exposure estimates. Women (female adults; 18 to 80 years); infants (0 to 12 months); toddlers (1 to 3 years); children (4 to 10 years).
[c] Clark et al. (2011). Median and 95th percentile exposure estimates. Combined male and female adults (20-70 years; not shown here); infants (neonates; 0 to 6 months); toddlers (0.5 to 4 years); children (5 to 11 years).
[d] This study. Mean and 95th percentile exposure estimates. Women (women of reproductive age; 15 to 44 years); infants (0 to <1 year); toddlers (1 to <3 years); children (3 to 12 years).

contributed to total DIBP exposure. Dust contributed to DEHP and BBP exposure. Mouthing and handling toys contributed to total DINP exposure. Use of particular products containing BBP, DNOP, or DINP resulted in substantial exposures in certain scenarios.

3.4 Comparison with Other Studies

Other authors have estimated human exposures to PEs by either modeling or biomonitoring approaches. Clark et al. (2011) and Wormuth et al. (2006) employed a modeling approach to estimate exposure to various subpopulations. Six PEs were common to Clark, Wormuth, and the current study. The metrics used to estimate average and upper bound exposures and the age ranges of the subpopulations differed somewhat among the three studies. Clark et al. (2011) did not include separate estimates for female adults. Differences in total PE exposure are, in part, due to differences in the methods for estimating dietary exposure because diet is a primary source of PE exposure. Despite these differences, total exposure estimates generally agreed within an order of magnitude.

The CHAP estimated human exposure to PEs using a human biomonitoring approach. Biomonitoring is the most direct method for estimating total PE exposure, and in this case, it can be is considered the most reliable (CHAP Report). The CHAP used biomonitoring data from the Study for Future Families (SFF; n=339), which includes biomonitoring data on mothers (prenatal and postnatal data) and their infants (Sathyanarayana *et al.*, 2008a; 2008b). The CHAP also used data from the National Health and Nutritional Survey (NHANES; 2005–2006) to estimate exposures to adult women (n=605). On average, the estimated exposures for individual PEs in the present study were 1.4-fold greater than the biomonitoring results from the SFF data and 2.1-fold greater than the results from the NHANES data (Table E1-25; Figure E1-3). The correlation coefficient between the NHANES results and the current study is 0.98 (Table E1-25). The correlation coefficients between the present study and the SFF results are 0.51 for infants and 0.28 for women.

Table E1-25 Comparison of modeled exposure estimates of total phthalate ester (PE) exposure (µg/kg-d) with estimates from biomonitoring studies.

PE	Study [a]	Women		Infants	
		Ave. [b]	0.95	Ave.	0.95
DEP	This study	18.1	398.0	3.1	14.9
	SFF c	NR	NR	NR	NR
	NHANES	3.4	67.7	NR	NR
DBP	This study	0.3	5.7	0.6	1.8
	SFF	0.7	2.4	2.6	10.4
	NHANES	0.8	3.9	NR	NR
DIBP	This study	0.1	0.5	0.5	1.5
	SFF	0.1	0.6	0.4	2.1
	NHANES	0.2	1.1	NR	NR
BBP	This study	1.1	2.6	1.8	4.1
	SFF	0.5	2.4	1.9	8.5
	NHANES	0.3	1.3	NR	NR
DEHP	This study	1.6	5.6	12.3	33.8
	SFF	2.8	19.1	7.6	28.7
	NHANES	3.6	156.2	NR	NR
DINP	This study	5.1	32.5	21.0	58.6
	SFF	0.8	5.4	3.6	18.0
	NHANES	1.1	15.6	NR	NR
DIDP	This study	3.2	12.2	10.0	26.4
	SFF	2.0	21.3	6.1	28.7
	NHANES	1.7	5.6	NR	NR
r2	SFF	0.28		0.51	
	NHANES	0.93		--	

[a] Biomonitoring results from the CHAP report, based on data from NHANES (adult women; 2005-2006) and the Study for Future Families (SFF).

[b] Ave., average, mean (this study) or median (NHANES and SFF); 0.95, 95th percentile; NR, not reported; r^2, correlation coefficient for this study compared to either NHANES or SFF (average and upper bound exposures combined).

[c] Data for women are the average of prenatal and postnatal values.

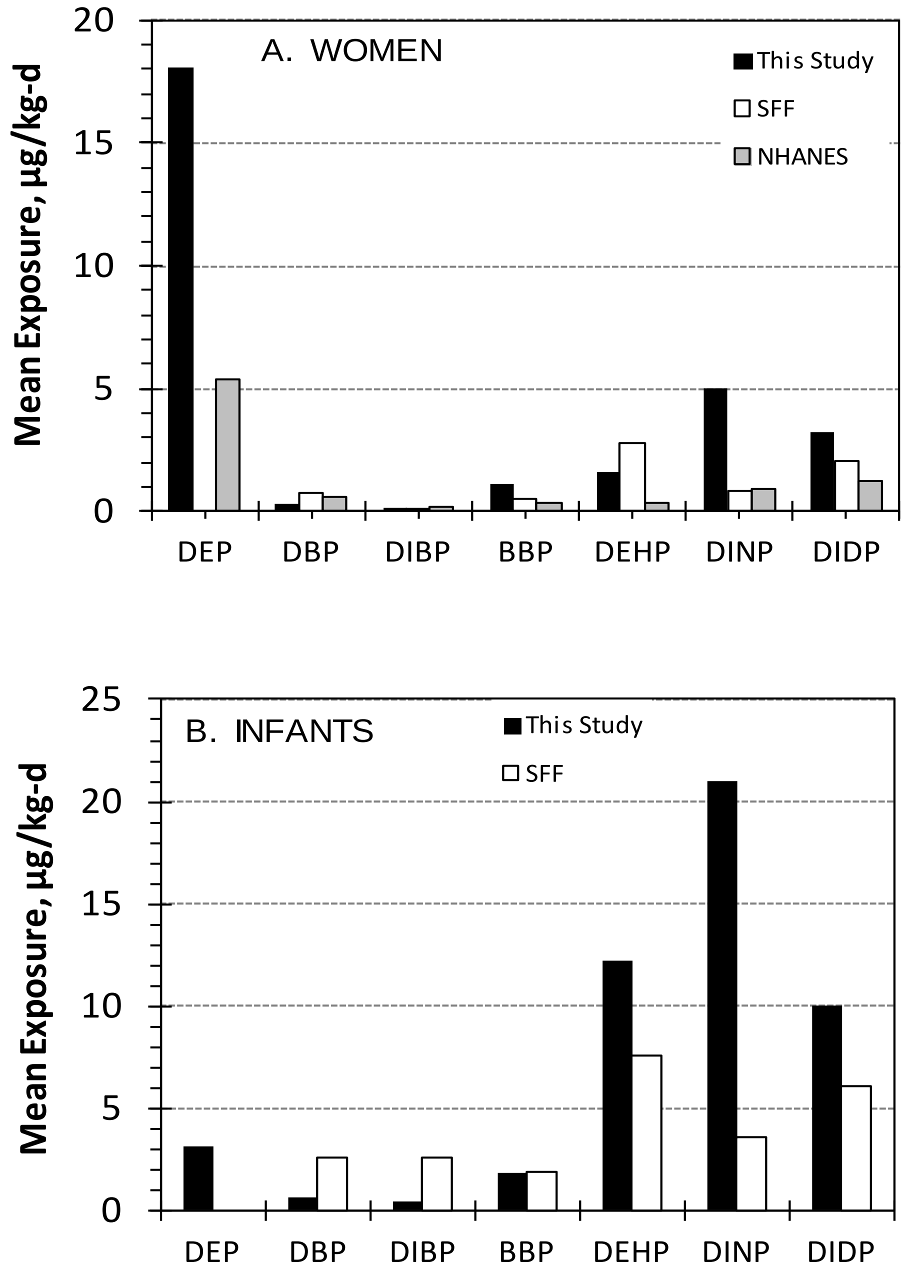

Figure E1-3 Comparison of modeled exposure estimates (this study) with exposures derived from human biomonitoring studies. A. Women; B. Infants. Biomonitoring results from the CHAP report, based on data from NHANES and the Study for Future Families (SFF). SFF data for women are the average of prenatal and postnatal values. Exposure estimates from this study are means; exposures from NHANES and SFF are medians. DEP not reported for SFF.

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4 Discussion

4.1 Uncertainty and Limitations

The modeling approach for estimating human exposure is subject to a number of uncertainties and limitations. This approach is highly dependent on concentration data in environmental media, food, and products, as well as information on consumer behavior. It is also subject to methodological limitations in that it relies on mathematical models and their underlying assumptions.

4.1.1 Scope

4.1.1.1 Phthalate Esters (PEs)

This report includes exposure estimates for eight PEs of primary interest to the CHAP because there are known human exposures from biomonitoring studies, data for assessing exposure are available, and/or there are concerns about possible health effects in humans (CHAP Report). Approximately 50 PEs are produced at an annual rate of at least 25 million pounds per year, of which half are produced at more than 1 million pounds per year (EPA, 2006). Adequate data for estimating human exposure are not available for most PEs.

Limited data on the presence of phthalate monoesters (metabolites or impurities of PEs) in food (Bradley, 2011) and environmental media (Clark, 2009) are available. Monoesters are not included in this report.

4.1.1.2 Sources

Any consideration of the relative importance of different sources must be made with caution because the quality of the underlying data varies for different sources. Overall, confidence in the dietary, environmental, and mouthing exposure estimates is high. Confidence is lower in exposure estimates from other sources, such as dermal contact with PVC products, aerosol paints, and adult toys.

We attempted to include all relevant sources of PE exposure. We excluded sources where there is limited direct contact with consumers, such as wall coverings and shower curtains. Indirect exposures from these sources are likely to occur from indoor air and household dust. There have been reports that PEs may occur naturally in marine flora and medicinal plants (reviewed in Patton, 2011). However, most of these studies fail to rule out possible contamination from anthropogenic sources. Even if some PEs are naturally occurring, there is insufficient information to estimate their impact on human exposure.

Exposure from medical devices containing DEHP is not included. These exposures are limited to individuals undergoing invasive medical procedures, such as thoracic surgery, kidney dialysis, and infants in neonatal intensive care units. The medical conditions in these patients may outweigh concerns about possible health effects of DEHP.

The indoor environment contributed significantly to total PE exposure estimates. The ultimate source of PEs in indoor air and house dust probably includes outdoor sources (air and soil). It is also likely that consumer products and home furnishings contribute to indoor sources. As semi-volatile compounds, PEs may volatilize from PVC products and then adsorb to airborne particles or surfaces (Lioy, 2006; Xu and Little, 2006; Weschler and Nazaroff, 2010). Abraded particles from PVC products also may contribute to PE levels in household dust. Although the dynamics of these processes are not fully understood, it appears likely that much of the indoor exposure presented here ultimately derives from consumer products and cosmetics.

Occupational exposures are outside the scope of this report.

4.1.2 Modeling Assumptions

4.1.2.1 Exposure Models

Exposure assessment relies on mathematical models and numerous assumptions. These necessary limitations may either overestimate or underestimate exposure. Accounting for exposures from multiple sources may lead to overlapping exposure estimates, which is, double counting of some exposures. For example, PE levels in indoor air most likely include contributions from cosmetics and air fresheners. Because separate exposure estimates were also derived for inhalation exposure from cosmetics and air fresheners, there is likely some double-counting of these sources of indoor air exposures. In some scenarios (mouthing and handling of toys, dermal contact with child articles and furniture, aerosol paints), we assumed simultaneous exposure to multiple versions of the same product containing different PEs. A more realistic scenario would be to consider each product as having a single PE, or else a mixture with roughly the same total PE. Furthermore, six PEs are currently prohibited in toys and child care articles. Thus, PE exposure from teethers, toys, and child care articles is largely hypothetical.

4.1.2.2 Bioavailability

Although oral toxicokinetic data are available for several phthalates, we assumed a default value of 1.0 for oral, inhalation, and internal (i.e., intravaginal for adult toys) bioavailability (Table E1-7). This was done for several reasons: (1) most of the bioavailability factors used by Wormuth et al. (2006) were greater than 0.5 and, thus, have a less than two-fold effect on absorbed dose estimates; (2) because the relevant hazard data are based on applied doses, rather than biologically available doses, it is appropriate to estimate exposure using the same metric; (3) human biomonitoring data are used to estimate applied oral doses in humans. Thus, disregarding the bioavailability adjustment aids in the comparison to biomonitoring results; (4) our approach is conservative, in that it tends slightly to overestimate dose.

4.1.2.3 Percutaneous Absorption

Animal data were used to estimate percutaneous absorption rates (Stoltz and El-hawari, 1983; Stoltz *et al.*, 1985; Elsisi *et al.*, 1989). Percutaneous absorption rates may be 5- to10-fold greater in animals than in adult human skin (Wester and Maibach, 1983). Thus, Wormuth et al. (2006) assumed that adult human skin is 7-fold less permeable and infant skin 2-fold less permeable than rodent skin. We did not make any such adjustments, because the permeability of human skin varies by anatomic site, and rodent skin may be an adequate model for neonatal skin because neonatal skin is more permeable than adult human skin (Wester and Maibach, 1983).

We used the fraction of applied dose per hour to estimate percutaneous absorption, which is similar to the method used by Wormuth et al. (2006). Although this method frequently is used for exposure assessment, it can underestimate percutaneous exposure. Percutaneous absorption rates were obtained from animal studies in which PEs were applied at 5 to 8 mg/cm^2 (Elsisi *et al.*, 1989). In contrast, for cosmetics products, such as soap and shampoo, we estimate that DEP contacts the skin at a rate of only 20 to 60 μg/cm^2. Thus, the dose rate in the animal study was 100-fold greater than the equivalent human exposure. The efficiency of absorption (percentage of the applied dose absorbed) may be greater at lower applied doses (Wester and Maibach, 1983). If the dose rate in the animal study was sufficiently high to saturate the absorption kinetics, then the percutaneous absorption in humans could be greatly underestimated (Kissel, 2011). The only way to assess this would be to obtain dose response data for percutaneous absorption of PEs.

4.1.3 Specific Exposure Scenarios

4.1.3.1 Diet

Two studies were considered for food concentration data (Page and Lacroix, 1995; Bradley, 2011). The Bradley study is the most recent available data and it is of high quality. Although it represents exposures in the United Kingdom, it is still relevant to U.S. phthalate exposure. The Page and Lacroix study was conducted in Canada between 1985 and 1989. Although it may be more relevant to the United States, it is now decades old and does not include all the PEs of interest; Page and Lacroix did not measure DINP, DIDP, and DNOP.

Established methods are available for estimating dietary exposures from food contaminants. The simplest scheme was selected to categorize food residues (EPA, 2007) because it reduces the occurrence of categories for which no residue data are available. Thus, the simplest scheme provides exposure estimates that are more stable, that is, less sensitive to the choice of food categories (Carlson and Patton, 2012, at Appendix E3). This approach is limited for estimating infant exposure, however, in that it does not include categories for infant formula, baby food, or breast milk. Nevertheless, comparable exposure estimates were derived from other studies with more detailed food categories (Wormuth *et al.*, 2006; Clark *et al.*, 2011; Carlson and Patton, 2012).

A sensitivity analysis for dietary exposures was also performed (Carlson and Patton, 2012). We calculated dietary PE exposures using two data sets (Page and Lacroix, 1995; Bradley, 2011), three sets of food categories and consumption estimates (Wormuth *et al.*, 2006; EPA, 2007; Clark *et al.*, 2011), and varying assumptions for bioavailability. Generally, the results agreed within a factor of three (Carlson and Patton, 2012).

4.1.3.2 Environmental Media

Quality data were available on PE levels in environmental media, such as indoor and outdoor air, house dust, and soil. However, the best data on soil residues were from a European study (Vikelsøe *et al.*, 1999). The best U.S. data were from a study that measured only DBP and BBP (Morgan *et al.*, 2004). The DBP and BBP levels in the U.S. study were higher than the corresponding levels in the European study. It is possible that the soil exposures estimated here are underestimates for the United States. The data on environmental media are somewhat limited in that several studies did not include all of the PEs of interest, especially DIBP, DNOP, DINP, and DIDP.

4.1.3.3 Mouthing of Teethers and Toys

The method for measuring plasticizer migration into simulated saliva was specifically developed and validated for the purpose of estimating children’s exposure to phthalates from mouthing PVC articles (Simoneau *et al.*, 2001; CPSC, 2002; Babich *et al.*, 2004). The laboratory method was compared to study with adult volunteers who mouthed PVC disks. Saliva was collected and analyzed to measure the PE migration rate *in vivo*. Migration data were available for only two PEs (DINP and DEHP) (Chen, 2002). Exposures resulting from mouthing products containing DIDP, DNOP, and other PEs could not be evaluated.

Mouthing durations are from an observational study of children’s mouthing activity (Greene, 2002). Mouthing duration depends on the child’s age and the type of object mouthed. The category “all soft plastic articles, except pacifiers” was used to estimate children’s exposure from mouthing PVC articles. This category includes articles such as teethers, toys, rattles, cups, and spoons. Pacifiers are not included in this category because they are generally made with natural rubber or silicone (CPSC, 2002).

Products in the “all soft plastic articles, except pacifiers” category are not necessarily made with PVC. About 35 percent of the soft plastic toys, and less than 10 percent of the soft plastic child care articles tested by the CPSC, contained PVC (Table E1-3). Toys and child care articles are also made from other plastics, wood, textiles, and metal. Currently, six PEs are prohibited from use in toys and child care articles. Therefore, the use of mouthing durations for the category “all soft plastic articles, except pacifiers" may be considered a reasonable upper bound estimate for children's exposure to PEs from mouthing PVC children's products.

4.1.3.4 Drugs and Dietary Supplements

Data on prescription drugs containing DEP were provided by the U.S. FDA (Jacobs, 2011). From these data, it was estimated that less than 5 percent of the population uses prescription drugs containing DEP. The highly skewed nature of the exposure distribution suggests that the mean exposure estimate (population mean) overestimates the typical (median) exposure. On the other hand, users can have very high DEP exposures. We estimate the maximum individual exposure from prescription drugs to be about 1,800 µg/kg-d in women and 5,000 µg/kg-d in toddlers. It should be noted that DEP does not induce the same developmental and reproductive effects in animals as some PEs, although the effects in humans are uncertain (reviewed in the CHAP report).

Adequate information on PE exposure from nonprescription drugs and dietary supplements was not available. However, DEP and other PEs are known to be present in some of these products (Hauser *et al.*, 2004; Hernandez-Diaz *et al.*, 2009; Kelley *et al.*, 2012). Maximum PE exposures from these products are as high as 16.8 mg DEP and 48 mg DBP (Kelley *et al.*, 2012), or about 220 µg/kg-d DEP and 640 µg/kg-d DBP in adults. The lack of exposure estimates for nonprescription drugs and dietary supplements may be a significant data gap.

4.1.3.5 Dermal Contact with PVC Products

Consumers regularly come into direct dermal contact with PVC products, such as wall coverings, flooring, vinyl upholstery, protective gloves, child care products (play pens, changing pads), toys, shower curtains, and rain wear. Adequate data on the presence of PEs in consumer products and a validated methodology for estimating these exposures are not available. Not all products in these categories are made with PVC or PEs. We estimated exposure from these scenarios, as described in Wormuth et al. (2006). Wormuth's method was based on a study in which a PVC film containing 40 percent ^{14}C-DEHP was placed on the backs of rats and percutaneous absorption of the DEHP was measured (Deisinger *et al.*, 1998). This method is limited in that DEHP migration/absorption was measured at only one DEHP concentration; thus, it does not account for differences in migration due to different PE concentrations. To adjust for the lack of data for other PEs, Wormuth multiplied the DEHP migration/absorption rate by the ratio of the percutaneous absorption rate of the other PE to that of DEHP (equation 5). This adjustment only accounts for differences in percutaneous absorption between PEs, not for differences in migration from the PVC film.

Wormuth applied this approach to protective gloves. A similar approach was used in this report for other products, including toys (dermal exposure), child care articles, and vinyl upholstery. This was done to satisfy the mandate for the CHAP report to include toys and child care articles and all routes of exposure. This required a number of assumptions, such as the skin surface area in contact with the PVC product, the contact duration, and frequency of contact. It was observed that, depending on the assumptions chosen and the number of products included, estimated exposures from these scenarios could equal or exceed the modeled exposures from food and total exposures estimated from biomonitoring studies. Because biomonitoring studies are considered the most reliable estimates of total PE exposure, it was concluded that the approach for assessing exposures from contact with PVC products likely results in overestimates of dermal exposure.

There are several possible reasons why Wormuth's method might overestimate exposure. Deisinger et al. (1998) measured the average percutaneous absorption of DEHP from a vinyl film over a period of seven days. Consumer contact with PVC products tends to be brief and episodic. The efficiency of PE transfer during brief exposures is unknown. Percutaneous absorption generally has a lag time on the order of an hour before steady-state absorption kinetics is achieved. Vinyl flooring may be covered with a wear layer of inorganic oxides and a polyurethane layer for shine. These layers may limit the migration of PEs from vinyl flooring. Also, percutaneous absorption through the sole of the foot, which has thick skin, may be limited.

We conclude that this scenario (dermal contact with PVC products) provides highly uncertain exposure estimates. It was included to satisfy the CHAP's mandate to include toys and child care articles and all relevant routes and sources of exposure. Data on PE use in consumer products and an improved methodology are needed to improve estimates for this scenario.

4.1.3.6 Aerosol Paints

Data on consumer use of aerosol paints by the general population were not available. The available data on PE concentrations in these products (NLM, 2012) suggest that few of these contain PEs. The average (population average) exposure estimates presented here may overestimate the average exposure. However, the potential exposure to users of these products and others present in the home is high. We estimate a maximum individual exposure of about 100 µg/kg-d for frequent aerosol paint users.

4.1.3.7 Adult Toys

This scenario was included because of its relevance to women of reproductive age and because the fetus is probably the most sensitive life stage for potential adverse effects from phthalate exposure. Thus, the CHAP is concerned about PE exposures to women of reproductive age (CHAP Report). Data for estimating exposure are available from one study (Nilsson *et al.*, 2006), but validated methodologies are not available. We assumed conservatively that 100 percent of PE migrating from the product would be absorbed through the vaginal (or rectal) epithelium. Therefore, the exposure estimates for this scenario are highly uncertain. Although estimated average exposures were minimal, the use of these products with an oil-based lubricant led to higher migration rates and consequently larger exposures (Nilsson *et al.*, 2006). A maximum exposure of 27 µg/kg-d DEHP (highest migration rate and frequency of use) was estimated for this scenario.

4.2 Comparison with Other Studies

Overall, the exposure estimates in this study are in general agreement (within an order of magnitude) of the exposure estimates from two other studies (Wormuth *et al.*, 2006; Clark *et al.*, 2011). This is noteworthy, considering the differences in methodologies among these three studies. Wormuth included a number of consumer scenarios, including mouthing toys and cosmetics use. Wormuth also included a detailed assessment of dietary exposures. The primary limitation of the Wormuth study for the present purpose is that it presents exposure estimates specific to Europe. Clark included a detailed assessment of dietary and environmental exposures, but did not include consumer products. The present study attempted to include a number of household sources, including toys, PVC products, cosmetics, and prescription drugs. A more simplified scheme for assessing dietary exposures was used.

The present study also agreed quite well with total exposure estimates from human biomonitoring studies. This is encouraging because biomonitoring probably provides the most reliable estimates of total exposure. However, the appearance of concordance could also be due to compensating overestimates and underestimates in the present study.

The general agreement among the three modeling studies and two biomonitoring studies tends to increase overall confidence in the conclusions of this study.

4.3 Regulatory Considerations

Considering PE sources by jurisdiction, most exposures are from sources under the purview of the U.S. Food and Drug Administration (FDA): food, prescription drugs, and cosmetics. Food packaging and processing materials are suspected of being the major sources of PEs in food (Rudel *et al.*, 2011). However, food can come into contact with PEs at any point between the farm and dinner table. The relative importance of food contact articles and other sources has not been elucidated.

DEP and DEHP are found in certain prescription drugs and medical devices, respectively. Exposure from these sources affects a small population with overriding medical concerns. The situation regarding nonprescription drugs and dietary supplements is less clear. FDA has issued a draft guidance document on limiting the use of PEs in drugs (FDA, 2012).

The use of DEP and other PEs in cosmetic products has declined over time due to voluntary reformulation by manufacturers (compare Hubinger and Havery, 2006; with Hubinger, 2010).

The U.S. Environmental Protection Agency (EPA) has jurisdiction over production and importation of chemical substances. EPA is in the process of assessing cumulative health risks form PE exposure.

The CPSC has jurisdiction over teethers and toys, child care articles, and other consumer products, such as home furnishings, air fresheners, and aerosol paints. The CPSIA permanently prohibits the use of DBP, BBP, and DEHP in child care articles and toys, and prohibits the use of DNOP, DINP, and DIDP on an interim basis in child care articles and toys that can be placed in a child's mouth. The CHAP on phthalates and phthalate substitutes was convened to advise the CPSC on whether any additional phthalates or phthalate substitutes should be prohibited in toys and child care articles.

4.4 Data Gaps

Modeling exposures to PEs is a data-intensive process. Although recent, high-quality data on PE levels in food are available from the U.K., data on the U.S. food supply are lacking, including data on infant formula, baby food, and breast milk. Similarly, data on environmental sources of PEs are generally more abundant in Europe. Studies of environmental media do not always include DIBP, DNOP, DINP, and DIDP. Except for mouthing of teethers and toys, there is a general lack of data on PE levels in consumer products and child care articles. Standardized methodologies for assessing exposures from many consumer products are also lacking. Some of the methods used here, for example, dermal contact with PVC articles, have not been validated, by comparison, with more direct exposure measures. Additional data on percutaneous absorption are needed to estimate dermal exposure accurately.

4.5 Conclusions

Diet is the primary source of exposure to DIBP, BBP, DNOP, DEHP, DINP and DIDP. Cosmetics are the primary sources of DEP and DBP exposure, while air fresheners and certain prescription drugs contribute to total DEP exposure. Exposures to DIBP, BBP, and DNOP may also arise from a variety of sources, including diet, the environment, and consumer products.

In infants, mouthing and handling toys and contact with child care articles contributes to the total exposure to higher molecular weight PEs. The mouthing of soft plastic products accounts for up to 11 percent of total DINP exposure in this population. Dermal contact with toys and child care articles may contribute up to an additional 18 percent. In infants, about 65 percent of DINP and more than 90 percent of DIDP are estimated to be from the diet.

5 Supplemental Data

Table E1-S1 Estimated phthalate ester (PE) exposure (µg/kg-d) by individual exposure scenario for women.

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Total	1.8 E+01	4.0 E+02	2.9 E-01	5.7 E+00	1.5 E-01	5.0 E-01	1.1 E+00	2.6 E+00	1.7 E-01	2.1 E+01	1.6 E+00	5.6 E+00	5.1 E+00	3.3 E+01	3.2 E+00	1.2 E+01
Diet	9.3 E-02	3.6 E-01	7.8 E-02	2.3 E-01	1.3 E-01	4.6 E-01	1.6 E-01	2.5 E-01	1.3 E-01	3.6 E-01	1.4 E+00	4.9 E+00	4.8 E+00	1.5 E+01	3.2 E+00	9.3 E+00
Drugs [a]	1.4 E+01	3.7 E+02														
Cosmetics, dermal																
Shampoo	1.2 E-02	6.5 E-02														
Soap / body wash	2.3 E-02	4.1 E-02														
Lotion	5.0 E-02	1.8 E-01														
Deodorant	7.4 E-01	1.9 E+01														
Perfume	2.8 E+00	6.2 E+00														
Nail polish	3.4 E-03	1.5 E-02	1.7 E-01	5.4 E+00												
Hair spray	4.7 E-02	1.4 E-01														
Cosmetics, inhalation [b]																
Deodorant	5.1 E-02	1.3 E+00														
Perfume	2.0 E-01	4.2 E-01														

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Hair spray	6.2 E-03	1.8 E-02														
Dermal, PVC [c]																
Toys [d]									8.0 E-03	8.0 E-03	8.0 E-03	8.0 E-03	6.7 E-03	6.7 E-03	1.1 E-03	1.1 E-03
Furniture [e]									0.0 E+00	2.0 E+01			0.0 E+00	1.7 E+01	0.0 E+00	2.9 E+00
Gloves							2.3 E-01	2.3 E-01	3.3 E-02	3.3 E-02	3.3 E-02	3.3 E-02	2.8 E-02	2.8 E-02	4.7 E-03	4.7 E-03
Household-dermal [e]																
Paint/ lacquer							5.4 E-04	1.5 E-03					2.5 E-05	0.0 E+00		
Adhesive							1.0 E-03	3.6 E-03								
Household, inhalation [f]																
Air freshener, spray [b]	1.1 E-01	3.6 E-01	1.6 E-05	2.0 E-05												
Air freshener, liquid	1.5 E-02	4.0 E-02	9.2 E-06	2.4 E-05	6.8 E-06	9.8 E-06										
Paint, spray [b]							6.6 E-01	2.0 E+00					1.5 E-01	3.1 E-01		
Indirect ingestion																
Dust	3.4 E-03	4.3 E-03	1.1 E-02	1.8 E-02	1.2 E-03	2.0 E-03	5.0 E-02	1.1 E-01			2.0 E-01	3.4 E-01	5.2 E-02	4.0 E-01	1.4 E-02	4.4 E-02
Soil			9.3 E-05	4.3 E-04			1.6 E-05	6.9 E-05	3.5 E-05	1.1 E-04	7.2 E-04	3.1 E-03	2.1 E-04	8.1 E-04		

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Inhalation, air																
Indoor air	9.5 E-02	2.4 E-01	3.3 E-02	7.4 E-02	1.8 E-02	4.4 E-02	3.8 E-03	8.9 E-03	5.9 E-05	5.9 E-05	1.5 E-02	2.9 E-02				
Outdoor air	1.4 E-03	3.8 E-03	8.4 E-05	3.6 E-04	8.6 E-05	2.6 E-04	7.2 E-05	1.2 E-04	8.4 E-06	8.4 E-06	4.8 E-04	2.9 E-03				
Adult toys [g]									3.8 E-04	8.0 E-02	1.9 E-04	2.6 E-01				

[a] Average exposure is the population average. 95th percentile is the average user.
[b] Includes exposure from the breathing zone during application and subsequent exposure to room air.
[c] 95th percentile estimate not available.
[d] Exposure is conditional on the presence of phthalates in toys. Six phthalates are currently prohibited.
[e] Prevalence of vinyl-covered or imitation leather furniture is unknown. Assume average user is not exposed; upper bound is exposed.
[f] Use information is available for “users” only. 95th percentile PE concentration is 0; 95th percent for frequency of use was used to estimate 95th percentile exposure.
[g] Upper bound DEHP exposure is with an oil-based lubricant.

Table E1-S2 Estimated phthalate ester (PE) exposure (µg/kg-d) by individual exposure scenario for infants.

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Total	3.1 E+00	1.5 E+01	6.5 E-01	1.8 E+00	4.8 E-01	1.5 E+00	1.8 E+00	4.1 E+00	4.5 E+00	9.8 E+00	1.2 E+01	3.4 E+01	2.1 E+01	5.9 E+01	1.0 E+01	2.6 E+01
Diet	3.0 E-01	1.2 E+00	2.0 E-01	5.3 E-01	3.5 E-01	1.2 E+00	5.5 E-01	6.7 E-01	3.8 E-01	9.8 E-01	5.0 E+00	1.8 E+01	1.4 E+01	3.6 E+01	9.3 E+00	2.5 E+01
Drugs [a]	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00	0.0 E+00
Teethers & toys [b]																
Mouthing [c]											7.3 E-01	2.9 E+00	2.3 E+00	9.2 E+00		
Dermal											4.0 E-01	4.0 E-01	3.3 E-01	3.3 E-01		
Cosmetics, dermal																
Body wash/ shampoo	8.8 E-03	4.8 E-02														
Lotion	1.5 E+00	8.2 E+00														
Cosmetics, inhalation [d]																
Perfume	4.8 E-02	1.0 E-01														
Deodorant	1.1 E-01	2.9 E+00														
Hair spray	3.6 E-01	3.6 E-01														
Dermal, PVC [b]																
Changing pad									1.7 E+00	1.7 E+00	1.7 E+00	1.7 E+00	1.4 E+00	1.4 E+00	2.4 E-01	2.4 E-01
Play pen									2.4	7.0	2.4	7.0	2.0	5.9	3.4	9.9

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
									E+00	E+00	E+00	E+00	E+00	E+00	E-01	E-01
Indirect ingestion																
Dust	3.3 E-02	4.2 E-02	1.1 E-01	1.7 E-01	1.1 E-02	1.9 E-02	4.8 E-01	1.1 E+00			1.9 E+00	3.3 E+00	5.0 E-01	3.8 E+00	1.3 E-01	4.2 E-01
Soil			1.3 E-01	6.3 E-01			2.3 E-02	1.0 E-01	5.0 E-02	1.6 E-01	1.0 E-02	4.4 E-02	3.0 E-01	1.2 E+00		
Inhalation																
Indoor air	6.0 E-01	1.5 E+00	2.1 E-01	4.7 E-01	1.1 E-01	2.8 E-01	2.4 E-02	5.6 E-02	3.7 E-04	3.7 E-04	9.4 E-02	1.8 E-01				
Outdoor air	2.8 E-03	7.4 E-03	1.6 E-04	6.9 E-04	1.7 E-04	5.1 E-04	1.4 E-04	2.2 E-04	1.6 E-05	1.6 E-05	9.2 E-04	5.5 E-03				
Air freshener, spray [d]	1.0 E-01	3.2 E-01	6.4 E-05	8.0 E-05												
Air freshener, liquid [d]	5.9 E-02	1.6 E-01	3.6 E-05	9.5 E-05	2.7 E-05	3.9 E-05										
Paint, spray [d,e]							7.3 E-01	2.2 E+00					3.0 E-01	8.9 E-01		

[a] Drugs were not included for infants, because data specific for children 0 to 1 year old were not available.
[b] Assumes that phthalate esters are present in these products. Currently six phthalates are prohibited.
[c] 95th percentile exposure is based on the 95th percentile mouthing duration.
[d] Incidental exposure from product use by others in the home.
[e] Prevalence of phthalate esters in these products in unknown, but believed to be low. Consumer use information is available for users only. Assumes that the average exposure is zero; upper bound exposure is for the average user.

Table E1-S3 Estimated phthalate ester (PE) exposure (µg/kg-d) by individual exposure scenario for toddlers.

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Total	2.8 E+00	2.2 E+03	8.3 E-01	2.3 E+00	8.6 E-01	3.0 E+00	2.4 E+00	5.9 E+00	5.5 E+00	1.6 E+01	1.6 E+01	4.7 E+01	3.1 E+01	9.5 E+01	1.7 E+01	4.8 E+01
Diet	6.7 E-01	2.7 E+00	3.6 E-01	9.8 E-01	7. 3E-01	2.7 E+00	6.4 E-01	1.1 E+00	6.1 E-01	1.6 E+00	7.6 E+00	2.6 E+01	2.4 E+01	6.9 E+01	1.6 E+01	4.5 E+01
Drugs [a]	5.3 E-01	2.2 E+03														
Teethers & toys [b]																
Mouthing [c]											4.2 E-01	1.7 E+00	1.3 E+00	5.2 E+00		
Dermal											4.0 E-01	4.0 E-01	3.3 E-01	3.3 E-01		
Cosmetics, dermal																
Shampoo	7.2 E-05	3.9 E-04														
Soap	1.1 E-02	2.1 E-02														
Lotion	9.1 E-02	5.0 E-01														
Cosmetics, inhalation [d]																
Perfume	4.4 E-01	9.5 E-01														
Deodorant	1.1 E-01	3.0 E+00														
Hair spray	3.8 E-02	1.1 E-01														
Dermal, PVC [b]																
Changing									1.3 E+00	1.3 E+00	1.3 E+00	1.3 E+00	1.1 E+00	1.1 E+00	1.8 E-01	1.8 E-01

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
pad																
Play pen									3.6 E+00	1.3 E+01	3.6 E+00	1.3 E+01	3.0 E+00	1.1 E+01	5.1 E-01	1.9 E+00
Indirect ingestion																
Dust	4.1 E-02	5.2 E-02	1.3 E-01	2.1 E-01	1.4 E-02	2.4 E-02	6.0 E-01	1.3 E+00			2.4 E+00	4.1 E+00	6.2 E-01	4.8 E+00	1.6 E-01	5.3 E-01
Soil			1.4 E-01	6.6 E-01			2.4 E-02	1.0 E-01	5.2 E-02	1.7 E-01	1.1 E-02	4.6 E-02	3.1 E-01	1.2 E+00		
Inhalation																
Indoor air	5.8 E-01	1.4 E+00	2.0 E-01	4.5 E-01	1.1 E-01	2.7 E-01	2.3 E-02	5.4 E-02	3.6 E-04	3.6 E-04	9.0 E-02	1.7 E-01				
Outdoor air	2.7 E-03	7.1 E-03	1.6 E-04	6.7 E-04	1.6 E-04	4.9 E-04	1.3 E-04	2.1 E-04	1.6 E-05	1.6 E-05	8.9 E-04	5.3 E-03				
Air freshener, spray [d]	1.5 E-01	4.9 E-01	9.9 E-05	1.2 E-04												
Air freshener, liquid [d]	9.1 E-02	2.5 E-01	5.6 E-05	1.5 E-04	4.1 E-05	6.0 E-05										
Paint, spray [d,e]							1.1 E+00	3.4 E+00					4.6 E-01	1.4 E+00		

[a] Drugs were not included for infants, because data specific for children 0 to 1 year old were not available.
[b] Assumes that phthalate esters are present in these products. Currently six phthalates are prohibited.
[c] 95th percentile exposure is based on the 95th percentile mouthing duration.
[d] Incidental exposure from product use by others in the home.
[e] Prevalence of phthalate esters in these products in unknown, but believed to be low. Consumer use information is available for users only. Assumes that the average exposure is zero; upper bound exposure is for the average user.

Table E1-S4 Estimated phthalate ester (PE) exposure (µg/kg-d) by individual exposure scenario for children.

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Total	2.8E+00	1.1E+03	5.5E-01	7.4E+00	4.5E-01	1.6E+00	1.1E+00	2.5E+00	5.2E-01	1.5E+01	5.4E+00	1.7E+01	1.4E+01	5.5E+01	9.1E+00	2.8E+01
Diet	3.4E-01	1.4E+00	2.1E-01	5.8E-01	4.1E-01	1.5E+00	3.9E-01	6.4E-01	3.5E-01	9.2E-01	4.2E+00	1.5E+01	1.4E+01	4.0E+01	9.0E+00	2.6E+01
Drugs [a]	1.4E+00	1.1E+03														
Cosmetics, dermal																
Shampoo	2.8E-03	1.5E-02														
Soap	5.6E-03	1.0E-02														
Lotion/cream	1.2E-02	4.4E-02														
Deodorant	1.8E-01	4.7E+00														
Perfume	2.7E-01	6.0E-01														
Nail polish	4.1E-04	1.8E-03	2.1E-01	6.6E+00												
Hair spray	5.7E-03	1.7E-02														
Cosmetics, inhalation [b]																
Deodorant	7.0E-02	7.0E-02														
Perfume	1.3E-01	2.9E-01														
Hair spray	5.8E-03	1.7E-02														
Dermal, PVC [c]																

Source	DEP		DBP		DIBP		BBP		DNOP		DEHP		DINP		DIDP	
	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95	ave.	0.95
Toys [d]									1.6 E-01	1.6 E-01	1.6 E-01	1.6 E-01	1.4 E-01	1.4 E-01	2.3 E-02	2.3 E-02
Furniture [e]									0.0 E+00	1.4 E+01			0.0 E+00	1.2 E+01	0.0 E+00	2.0 E+00
Indirect ingestion																
Dust	1.7 E-02	2.1 E-02	5.3 E-02	8.6 E-02	5.7 E-03	9.8 E-03	2.4 E-01	5.4 E-01			9.9 E-01	1.7 E+00	2.5 E-01	2.0 E+00	6.6 E-02	2.2 E-01
Soil			9.8 E-05	4.2 E-04			4.4 E-03	1.9 E-02	2.1 E-04	6.9 E-04	4.4 E-03	1.9 E-02	1.3 E-03	5.0 E-03		
Inhalation																
Indoor air	2.1 E-01	5.3 E-01	7.4 E-02	1.7 E-01	4.1 E-02	9.9 E-02	8.5 E-03	2.0 E-02	1.3 E-04	1.3 E-04	3.4 E-02	6.5 E-02				
Outdoor air	2.1 E-03	5.5 E-03	1.2 E-04	5.2 E-04	1.2 E-04	3.8 E-04	1.0 E-04	1.7 E-04	1.2 E-05	1.2 E-05	6.9 E-04	4.1 E-03				
Air freshener, spray [b]	5.7 E-02	1.8 E-01	3.7 E-05	4.6 E-05												
Air freshener, liquid [b]	3.4 E-02	9.1 E-02	2.1 E-05	5.4 E-05	1.5 E-05	2.2 E-05										
Paint, spray [b,f]							4.2 E-01	1.2 E+00					1.7 E-01	5.1 E-01		

[a] Average exposure is the population average. 95th percentile is the average user.
[c] 95th percentile estimate not available.
[d] Exposure is conditional on the presence of phthalates in toys. Six phthalates are currently prohibited.
[e] Prevalence of vinyl-covered or imitation leather furniture is unknown. Assume average user is not exposed; upper bound is exposed.
[b] Includes exposure from the breathing zone during application and subsequent exposure to room air.
[f] Use information is available for "users" only. 95th percentile PE concentration is 0; 95th percent for frequency of use was used to estimate 95th percentile exposure.

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PEER REVIEW DRAFT

Draft Report to the
U.S. Consumer Product Safety Commission
by the
CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES

August 15, 2012

APPENDIX E2

CHILDREN'S ORAL EXPOSURE TO PHTHALATE ALTERNATIVES FROM MOUTHING SOFT PLASTIC CHILDREN'S ARTICLES*

* These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

Memorandum

Date: April 24, 2012

TO : Mary Ann Danello, Ph.D., Associate Executive Director for Health Sciences

THROUGH : Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Michael A. Babich, Ph.D., Chemist, Division of Health Sciences

SUBJECT : Children's oral exposure to phthalate alternatives from mouthing soft plastic children's articles[*]

The attached report provides the U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences' staff assessment of children's oral exposures to phthalate alternatives from mouthing soft plastic articles made from polyvinyl chloride (PVC). This work was performed at the request of the Chronic Hazard Advisory Panel (CHAP) on phthalates and phthalate alternatives.

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1 Introduction

The Consumer Product Safety Improvement Act (CPSIA)[*] of 2008 (CPSC, 2008) was enacted on August 14, 2008. Section 108 of the CPSIA permanently prohibits the sale of any "children's toy or child care article" individually containing concentrations of more than 0.1 percent of dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), or di(2-ethylhexyl) phthalate (DEHP). Section 108 prohibits on an interim basis the sale of "any children's toy that can be placed in a child's mouth" or "child care article" containing concentrations of more than 0.1 percent of di-*n*-octyl phthalate (DNOP), diisononyl phthalate (DINP), or diisodecyl phthalate (DIDP). These restrictions became effective in February 2009. In addition, section 108 of the CPSIA directs CPSC to convene a Chronic Hazard Advisory Panel (CHAP) "to study the effects on children's health of all phthalates and phthalate alternatives as used in children's toys and child care articles." The CHAP will recommend to the U.S. Consumer Product Safety Commission (CPSC) whether any phthalates or phthalate alternatives other than those permanently banned should be declared banned hazardous substances.

The number of possible phthalate alternatives is potentially very large. CPSC staff identified five compounds as the most likely to be used in children's products (Versar/SRC, 2010) (Table E2-1; Figure E2-1). A sixth alternative (2,2,4-trimethyl-1,3 pentanediol diisobutyrate, TXIB®, TPIB) [†] was added when it was found in toys (see below). TPIB is an additive that is typically used in combination with other plasticizers. CPSC staff prepared toxicity reviews for the six phthalate alternatives to support the CHAP's analysis (Versar/SRC, 2010; Patton, 2011).

CPSC staff also performed laboratory studies of children's toys and child care articles to assist the CHAP. In December 2008, two months prior to the effective date of the new phthalate restrictions, CPSC staff purchased 63 children's toys and child care articles to:

1. Identify the plastic used in all component parts;
2. Identify the plasticizer(s), if present;
3. Determine the concentration (mass percent) of plasticizer where present; and
4. Measure the migration of plasticizers into simulated saliva to estimate oral exposure.

The results of the laboratory study have been reported (Dreyfus, 2010; Dreyfus and Babich, 2011). This memorandum uses the information obtained in the laboratory study to estimate children's oral exposure to phthalate alternatives from mouthing soft plastic articles.

[*] Public Law 110-314.

[†] TXIB® is a registered trademark of Eastman Chemical Company. Although "TXIB" is the commonly used abbreviation for 2,2,4-trimethyl-1,3 pentanediol diisobutyrate, the alternate abbreviation TPIB is used here to represent the generic chemical.

Table E2-1 Possible phthalate alternatives for use in children's toys and child care articles (Versar/SRC, 2010).

Common Name [a]	Systematic Name	Abbr. [b]	CAS	MF	MW (range) [c]
TXIB®	2,2,4-trimethyl-1,3 pentanediol diisobutyrate	TPIB	6846-50-0	$C_{16}H_{30}O_4$	286.4
di(2-ethylhexyl) adipate	hexanedioc acid, 1,6-bis(2-ethylhexyl) ester	DEHA	103-23-1	$C_{22}H_{42}O_4$	370.6
acetyl tributyl citrate	1,2,3-propanetricarboxylic acid, 2-(acetyloxy)-, tributyl ester	ATBC	77-90-7	$C_{20}H_{34}O_8$	402.5
diisononyl hexahydrophthalate	1,2-cyclohexanedicarboxylic acid, diisononyl ester	DINX	166412-78-8 474919-59-0	$C_{26}H_{48}O_4$	424.7 (396.6—452.7)
di(2-ethylhexyl) terephthalate	1,4-benzenedicarboxylic acid, 1,4-bis(2-ethylhexyl) ester	DEHT [d]	6422-86-2	$C_{24}H_{38}O_4$	542.6
tris(2-ethylhexyl) trimellitate	1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester	TOTM	3319-31-1	$C_{33}H_{54}O_6$	546.8

[a] National Library of Medicine (NLM, 2011). ChemID data base.
[b] Abbr., abbreviation; CAS, Chemical Abstracts Service number, MF, molecular formula; MW, molecular weight.
[c] DINX includes isomers with C8–C10 ester groups.
[d] Di(2-ethylhexyl) terephthalate is also commonly abbreviated as "DOTP."

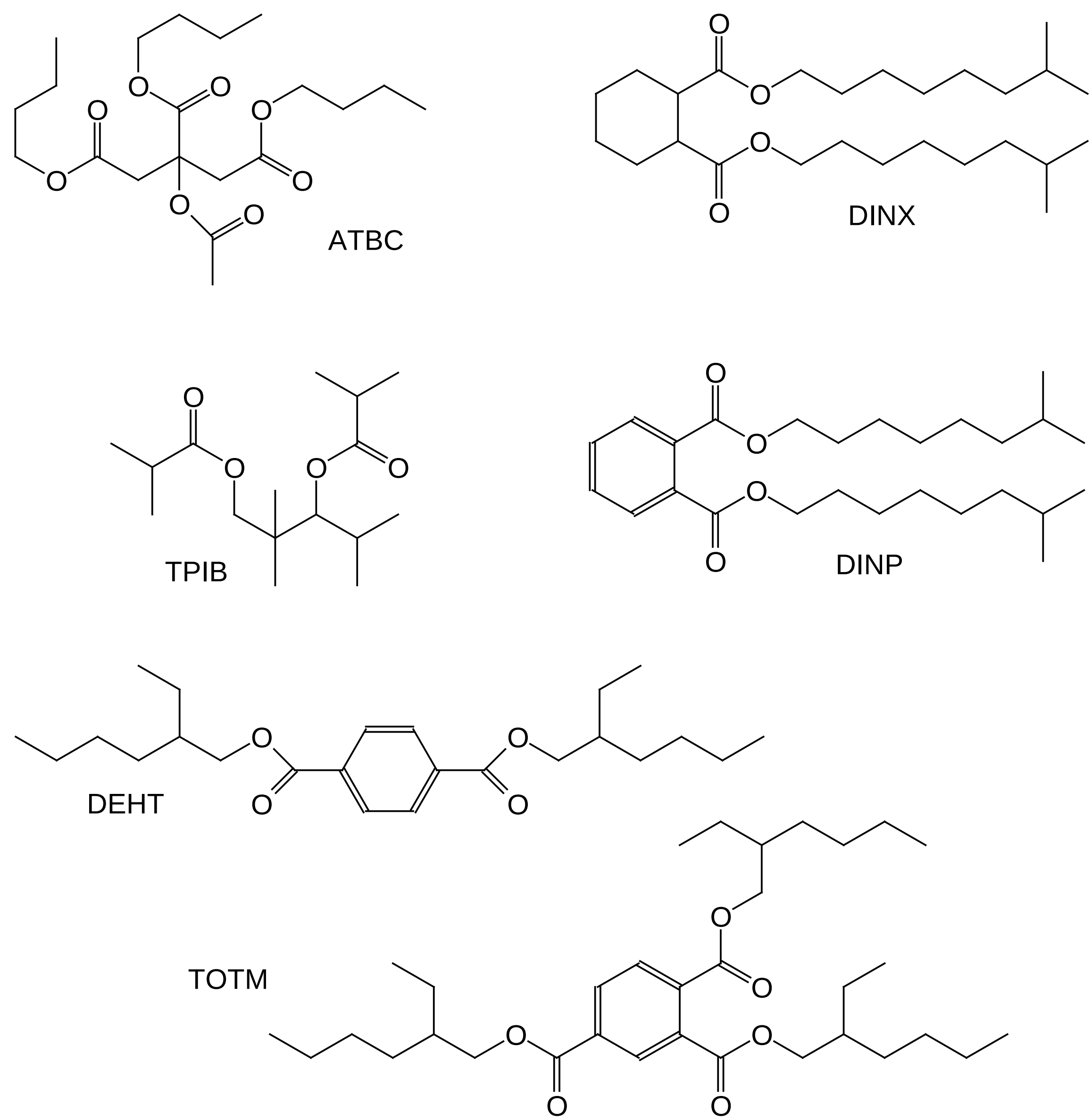

Figure E2-1 Chemical structures of phthalate alternatives.

2 Methodology

2.1 Migration

The methods for measuring plasticizer migration have been described in detail previously (Dreyfus, 2010; Dreyfus and Babich, 2011). Briefly, plasticizer migration into simulated saliva was measured by a variation (Chen, 2002) of the Joint Research Centre (JRC) method (Simoneau *et al.*, 2001). A punch press was used to cut three 10 cm^2 test disks from each sample. The three disks from each sample were extracted two times each in 50 ml of simulated saliva (JRC formulation) in a 250 ml Schott Duran bottle for 30 minutes. The two volumes of simulated saliva were combined, and then extracted with 50 mL of cyclohexane. The cyclohexane extract was analyzed by gas chromatography/mass spectrometry (GC-MS).

2.2 Calculations

Exposure from mouthing soft plastic teethers and toys was estimated by:

$$E = R \times A \times T / W \qquad (1)$$

where: E, estimated daily exposure, µg/kg-d; R, migration rate, µg/10 cm^2-h; A, area of the article in the child's mouth, cm^2; T, exposure duration, minutes/d; W, body weight, kg.

Mouthing durations for various objects and age groups are from a CPSC study of children between 3 months and less than 36 months old (CPSC, 2002) (Table E2-2). The mouthing duration depends on the child's age and the type of object mouthed (Greene, 2002). Generally, children up to 3 years old mouth fingers most, followed by pacifiers, and teethers and toys. The category "all soft plastic articles, except pacifiers" was used as the mouthing duration. Pacifiers are made from either natural rubber or silicone, not PVC. The mean migration rate and mouthing duration were used to estimate the mean oral exposure. The 95th percentile exposure was estimated in two ways, using either the 95th percentile migration rate or 95th percentile mouthing duration.

Body weights were as follows: 3 to <12 months, 8.6 kg; 12 to <24 months, 11.4 kg; 24 to <36 months; 13.8 kg (EPA, 2011, Table 8-1). The body weight for 3 to <12 months is a weighted average of the 3 to <6 month and 6 to <12 month values. A standard surface area of 10 cm^2 was assumed for the surface area of the article in the child's mouth (Simoneau *et al.*, 2001; CPSC, 2002).

Table E2-2 Mouthing duration (minutes per day) for various objects by age group (Greene, 2002).

Age	N [a]	Object mouthed	Duration (minutes/day)		
			Mean	*Median*	*0.95*
3-12 months	54	soft plastic toys	1.3	0	7.1
		soft plastic teethers & rattles	1.8	0	12.2
		all soft plastic, except pacifiers	4.4	1.2	17.5
		non-soft plastic teethers, toys, & rattles	17.4	12.6	58
		pacifiers	33	0	187.4
		non-pacifiers	70.1	65.6	134.4
12-24 months	66	soft plastic toys	1.9	0.1	8.8
		soft plastic teethers, rattles	0.2	0	0.9
		all soft plastic, except pacifiers	3.8	2.2	13
		non-soft plastic teethers, toys, & rattles	5.7	3.2	18.6
		pacifiers	26.6	0	188.5
		non-pacifiers	47.4	37	121.5
24-36 months	49	soft plastic toys	0.8	0	3.3
		soft plastic teethers, rattles	0.2	0	0.8
		all soft plastic, except pacifiers	4.2	1.5	18.5
		non-soft plastic teethers, toys, & rattles	2.2	0.8	10.7
		pacifiers	18.7	0	136.5
		non-pacifiers	37	23.8	124.3

[a] N, number of children observed; 0.95, 95th percentile.

3 Results

3.1 Composition of Toys and Child Care Articles

CPSC staff purchased 63 children's products, including 43 toys, 12 child care articles, and 8 art or school supplies (Table E2-3). These products comprised 128 component parts, of which 37 (28.9 %) were made from polyvinyl chloride (PVC). One child care article (a teether) and one art material (modeling clay) were made with PVC; both were plasticized with phthalate alternatives. The remaining PVC components were toys. Some of the products tested might not be subject to the CPSIA phthalates restrictions.

Of the 37 PVC components, one toy contained DINP and another contained DEHP in excess of the 0.1 percent regulatory limit.[*] The remainder of the PVC components contained phthalate alternatives, including acetyl tributyl citrate (ATBC), di(2-ethylhexyl terephthalate (DEHT), 1,2-cyclohexanedicarboxylic acid, diisononyl ester (DINCH®, DINX)[†], and 2,2,4-trimethyl-1,3 pentanediol diisobutyrate (TPIB) at concentrations from 2 to 60 percent by mass (Table E2-4). About half of these components contained more than one plasticizer.

3.2 Migration

Migration rates for phthalate alternatives ranged from 0.14 to 14.0 µg/10 cm^2-h (Table E2-5). These are roughly comparable to the migration rates previously measured with DINP (Chen, 2002), which ranged from 1.0 to 11.1 µg/10 cm^2-h. Data for DINP and DEHP are included for comparison.

Plots of migration rate against plasticizer concentration show that migration rates with ATBC, DEHT, and TPIB generally increased with increasing concentration (Figure E2-2). The slope of the migration rate over concentration was highest with TPIB and lowest with DEHT. Migration rates with DINP and DINX did not exhibit a monotonic relationship with concentration.

3.3 Oral Exposure

The mouthing duration depends on the child's age and the type of object mouthed (Greene, 2002). Generally, children up to 3 years old mouth fingers most, followed by pacifiers, and teethers and toys (Table E2-2). Mouthing duration generally decreases with age. Mouthing

[*] The DINP-containing toy could not be placed in a child's mouth and, therefore, would comply with the CPSIA phthalates restrictions. The DEHP-containing toy would not comply, because DEHP is permanently banned from toys and child care articles at levels greater than 0.1 percent, regardless of whether they can be placed in a child's mouth.

[†] DINCH® is a registered trademark of BASF. Although "DINCH" is the commonly used abbreviation for 1,2-cyclohexanedicarboxylic acid, diisononyl ester, the alternate abbreviation DINX is used here to represent the generic chemical.

durations were multiplied by migration rates to estimate oral exposures for various plasticizers and types of objects.

For infants less than 12 months old, estimated mean exposures ranged from 0.60 µg/kg-d for DEHT to 3.3 µg/kg-d for ATBC (Table E2-6). Based on 95th percentile *migration rates*, upper bound exposures in this age group ranged from 1.8 µg/kg-d for DEHT to 7.2 µg/kg-d for ATBC. Based on the 95th percentile *mouthing duration*, upper bound exposures ranged from 2.8 µg/kg-d for DEHT to 5.1 µg/kg-d for ATBC.

Estimated exposures were generally lower in the older age groups. In children 12 to 23 months old, mean exposures ranged from 0.45 µg/kg-d for DEHT to 1.5 µg/kg-d for ATBC. The maximum upper bound exposure was 4.7 µg/kg-d for ATBC, based on the 95th percentile migration rate. In children 24 to 35 months old, mean exposures ranged from 0.41 µg/kg-d for DEHT to 1.4 µg/kg-d for ATBC. The maximum upper bound exposure was 4.3 µg/kg-d for ATBC, based on the 95th percentile migration rate.

Table E2-3 Children's products tested by CPSC staff. [a]

Product Type [b]	Examples	N [c]	Parts [d]	PVC (%) [e]	
Child-care articles	Teethers, sipper cups, spoons	12	18	1	(5.6)
Toys <3 years [f]	Links, stacking rings, tub toys dolls	24	43	16	(37.2)
Toys ≥3 years [f]	Action figures, trucks, balls	19	58	19	(32.8)
Art materials	Modeling clays	6	7	1	(14.3)
School supplies	Pencil grip, eraser	2	2	0	(0.0)
Total		63	128	37	(28.9)

[a] Purchased December 2008. Phthalates regulations became effective February 2009.
[b] These categories are not necessarily the same as CPSIA definitions of "children's toys" or "child care article." Some of the products tested might not be subject to the CPSIA phthalates restrictions.
[c] N – number of products tested
[d] Parts – number of component parts tested
[e] PVC – number of component parts containing polyvinyl chloride (percent)
[f] Age recommendation on product label

Table E2-4 Phthalate alternatives identified in children's products made with polyvinyl chloride (PVC) (Dreyfus, 2010).

Plasticizer	N [a]	% [b]	Mass Percent
Acetyltributyl citrate (ATBC)	19	51.4	5 to 43
Di(2-ethylhexyl) terephthalate (DEHT)	14	37.8	3 to 60
1,2-cyclohexanedicarboxylic acid, diisononyl ester (DINX)	13	35.1	3 to 25
2,2,4-trimethyl-1,3 pentanediol diisobutyrate (TPIB)	9	24.3	2 to 19
Total	37		

[a] N – number of articles tested
[b] % – percentage of articles containing the plasticizer of interest

Table E2-5 Plasticizer migration rate (µg/10 cm^2-min) into simulated saliva measured by the Joint Research Centre method.[a]

Plasticizer	ATBC	DEHT	DINX	TPIB	DINP	DEHP
N [b]	18	13	11	8	25	3
mean	4.4	1.4	3.0	6.2	4.2	1.3
median	2.5	1.4	2.7	1.8	3.5	1.1
standard deviation	4.38	0.91	2.49	3.82	2.76	0.60
minimum	0.75	0.14	0.52	0.90	1.05	0.90
maximum	14.0	3.6	7.3	11.3	11.1	2.0
95^{th} percentile	14.0	2.7	7.0	9.8	10.1	1.9

[a] Joint Research Centre method described in Simoneau *et al.* (2001). Data on ATBC, DEHT, DINX, and DEHT are from Dreyfus (2010). DEHP; DINP and DEHP included for comparison (Chen, 2002).
[b] N – number of articles tested

Table E2-6 Estimated oral exposure (µg/kg-d) from mouthing soft plastic objects.[a]

Plasticizer	Age Range								
	3 to <12 months			12 to <24 months			24 to <36 months		
	Mean [b]	*R(0.95)* [c]	*T(0.95)* [d]	*Mean* [b]	*R(0.95)* [c]	*T(0.95)* [d]	*Mean* [b]	*R(0.95)* [c]	*T(0.95)* [d]
ATBC	2.3	7.2	5.1	1.5	4.7	2.8	1.4	4.3	3.4
DINX	1.4	3.6	5.4	0.89	2.3	3.1	0.82	2.1	3.6
DEHT	0.69	1.8	2.8	0.45	1.2	1.5	0.41	1.1	1.8
TPIB	0.92	5.8	3.8	0.60	3.8	2.0	0.55	3.4	2.4

[a] Calculated with equation (1). Results rounded to two significant figures.
[b] Mean – calculated with the mean migration rate and mouthing duration
[c] R(0.95) – calculated with the 95th percentile migration rate and mean mouthing duration
[d] T(0.95) – calculated with the mean migration rate and 95th percentile mouthing duration

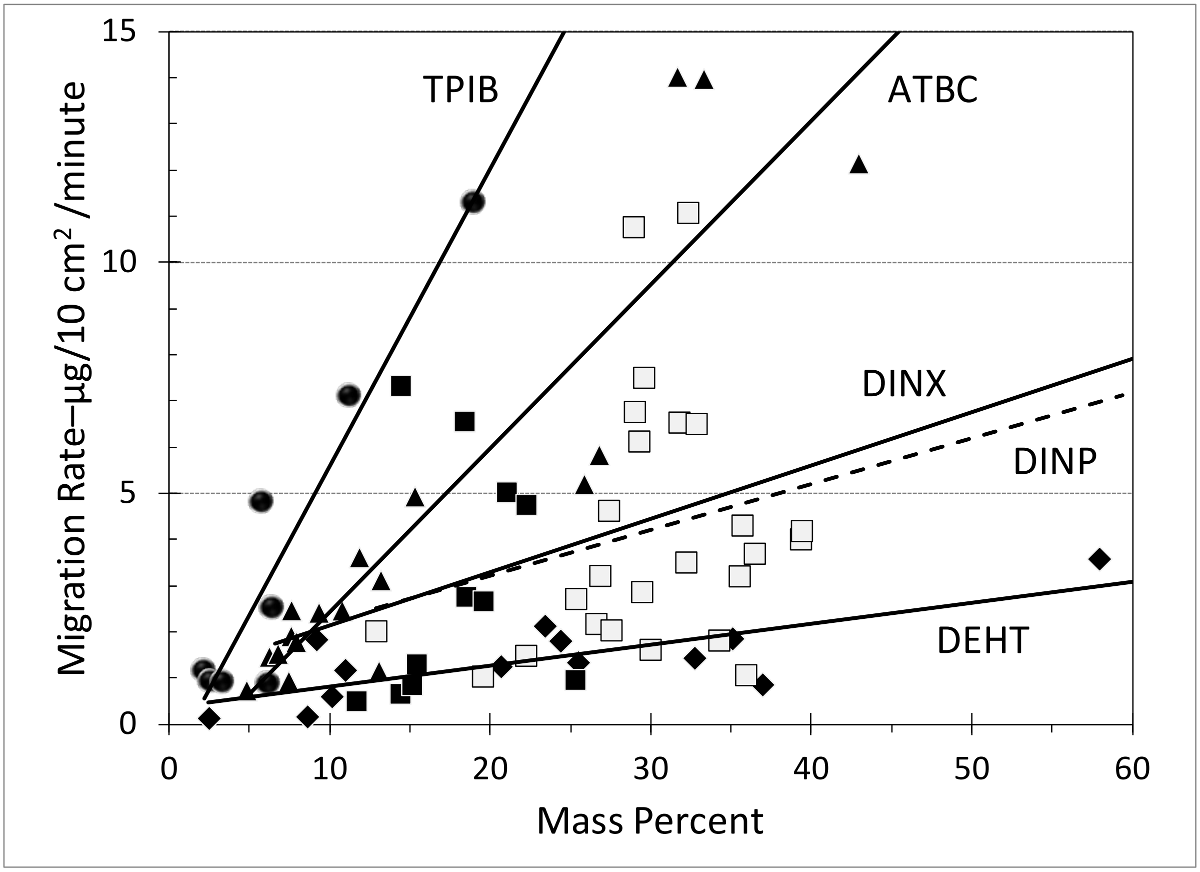

Figure E2-2 Migration of plasticizers into saliva stimulant. Migration was measured by the Joint Research Centre method (Simoneau and Rijk 2001). Lines are linear trends. DINP is from a previous study (Chen, 2002); all other data from Dreyfus (2010). TPIB (● — ●); ATBC (▲ — ▲); DINX (■ – – ■); DINP (□ - - - □); DEHT (◆ — ◆). Adapted from Dreyfus and Babich (2011). [*TPIB, solid circles; ATBC, solid triangles; DINX, solid squares; DINP, open squares; DEHT, solid diamonds.*]

4 Discussion

4.1 Methodology and Assumptions

The method for measuring plasticizer migration into simulated saliva was specifically developed and validated for the purpose of estimating children's exposure to phthalates from mouthing PVC articles (Simoneau *et al.*, 2001). The method is used here to estimate children's exposure to phthalate alternatives.

Mouthing durations are from an observational study of children's mouthing activity (Greene, 2002). Mouthing duration depends on the child's age and the type of object mouthed. The category "all soft plastic articles, except pacifiers" was used to estimate children's exposure from mouthing PVC articles. This category includes articles such as teethers, toys, rattles, cups, and spoons. Pacifiers are not included in this category because they are generally made with natural rubber or silicone (CPSC, 2002). Products in the "all soft plastic articles, except pacifiers" category are not necessarily made with PVC. About 35 percent of the soft plastic toys and less than 10 percent of the soft plastic child care articles tested by CPSC staff contained PVC (Table E2-3). Toys and child care articles are also made from other plastics, wood, textiles, and metal. Therefore, the use of mouthing durations for the category "all soft plastic articles, except pacifiers" provides a reasonable upper bound estimate for children's exposure from mouthing PVC children's products.

The products tested by CPSC staff were purchased in 2008. The products selected for study may not necessarily be representative of children's products on the market at that time or currently. ATBC, DEHT, DINX, and TPIB are still commonly used in children's products.[*] Other non-phthalate plasticizers, such as DEHA and benzoates, are also used. There are many possible phthalate alternatives and their uses may change in response to market demands cost.

4.2 Other Sources of Exposure

The phthalate alternatives considered here are general purpose plasticizers and additives that have multiple uses. Three of the six alternatives (ATBC, DEHA, and DEHT) are high-production volume (HPV) chemicals. That is, more than 1 million pounds per year of the alternatives are manufactured in or imported into the United States. Children and other consumers may be exposed to phthalate alternatives from a variety of sources, not only toys and child care articles.

ATBC is an HPV chemical (reviewed in Versar/SRC, 2010). ATBC is approved for use in food packaging, including fatty foods, and as a flavor additive. It is also used in medical devices, cosmetics, adhesives, and pesticide inert ingredients. ATBC was present in about half of the

[*] CPSC compliance test data.

PVC toys and child care articles tested by the CPSC (Table E2-4) (Dreyfus, 2010; Dreyfus and Babich, 2011).

DEHA is also an HPV chemical (Versar/SRC, 2010). DEHA is approved for use as an indirect food additive as a component of adhesives and in food storage wraps. Total intake of DEHA was estimated to be 0.7 µg/kg-d in a European population, based on biomonitoring data (Fromme *et al.*, 2007b). Dietary intake of DEHA was estimated to be 12.5 µg/kg-d in a Japanese study of duplicate dietary samples (Tsumura *et al.*, 2003). CPSC staff estimated the dietary intake of DEHA to be between 137 and 259 µg/kg-d (Carlson and Patton, 2012), from food residue data obtained in Canada in the 1980s (Page and Lacroix, 1995).

DEHA is also found in adhesives, vinyl flooring, carpet backing, and coated fabrics (Versar 2010). CPSC staff previously found DEHA in toys (Chen, 2002). DEHA was found at 2.0 ng/m^3 in the indoor air of an office building (reviewed in Versar/SRC, 2010).

DEHT is an HPV chemical used as a plasticizer in several polymers, including PVC (Versar/SRC, 2010). DEHT was present in more than one-third of the PVC toys and child care articles tested by CPSC staff (Table E2-4) (Dreyfus, 2010; Dreyfus and Babich, 2011).

DINX was developed as a phthalate alternative for use in “sensitive” applications, such as food packaging, toys, and medical devices (Versar/SRC, 2010). DINX was found in 35 percent of PVC toys and child care articles tested by CPSC staff (Table E2-4) (Dreyfus, 2010; Dreyfus and Babich, 2011). DINX has been approved for use in food contact materials in Europe and Japan. It is used in food packaging and food processing equipment (Versar/SRC, 2010).

TOTM is an HPV plasticizer that is preferred for use in high temperature applications (Versar/SRC, 2010). It is reported to have lower volatility and migration, as compared to other plasticizers. TOTM is used in electrical cable, lubricants, medical tubing, and in controlled-release pesticide formulations.

TPIB is a secondary plasticizer used in combination with other plasticizers (reviewed in Patton, 2011). It is not an HPV chemical. TPIB is used in PVC and polyurethane. TPIB may be found in weather stripping, furniture, wallpaper, nail care products, vinyl flooring, sporting goods, traffic cones, vinyl gloves, inks, water-based paints, and toys. TPIB has been detected in indoor air in office buildings, schools, and residences (Patton, 2011). It was measured at levels from 10 to 100 µg/m^3 in the indoor air of office buildings. TPIB was found in about one-quarter of the PVC toys and child care articles tested by CPSC staff (Table E-24) (Dreyfus, 2010; Dreyfus and Babich, 2011).

4.3 Data Gaps

Migration data were available for only four of the six phthalate alternatives discussed in this report. Migration data on DEHA and TOTM are needed to estimate children’s oral exposure to these plasticizers. Additional data on the occurrence of phthalate alternatives in current children's articles would be helpful.

The phthalate alternatives are general purpose compounds with multiple uses. ATBC, DEHA, and DEHT are HPV chemicals. Exposure may occur from sources other than consumer products, such as the indoor environment and diet. Other exposures to phthalate alternatives may also occur through dermal contact and inhalation of alternative-laden dust or air. Information on other exposure routes and sources is needed to estimate aggregate exposure to phthalate alternatives.

4.4 Conclusions

About 30 percent of the soft plastic toys and child care articles tested by CPSC staff were made of PVC. Most of the products tested were made with alternative plastics that do not require plasticizers. The most common plasticizers in PVC articles were ATBC, DEHT, DINX, and TPIB. Half of the PVC articles had two or more plasticizers. The migration rate into saliva simulant generally increased with the plasticizer concentration. The migration rate into saliva simulant at a given plasticizer concentration was, in general: TPIB >ATBC >DINX ~DINP > DEHT.

Migration rate data were used to estimate children's oral exposure from mouthing soft plastic articles, except pacifiers. Estimated oral exposures for the phthalate plasticizer alternatives tested by CPSC alternatives ranged from 0.41 to 7.2 µg/kg-d. Exposure to similar phthalate alternatives from diet and the indoor environment occurs. However, quantitative estimates of total exposure to most phthalate alternatives are not available.

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PEER REVIEW DRAFT

Draft Report to the

U.S. Consumer Product Safety Commission

by the

CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES AND PHTHALATE ALTERNATIVES

March 7, 2013

APPENDIX E3

PHTHALATE DIETARY EXPOSURE

UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
Bethesda, MD 20814

Memorandum Date: February 03, 2012

TO : Michael A. Babich, Ph.D., Project Manager, Phthalates, Section 108 of CPSIA

THROUGH: Mary Ann Danello, Ph.D., Associate Executive Director, Directorate for Health Sciences

Lori E. Saltzman, M.S., Director, Division of Health Sciences

FROM : Kent R. Carlson, Ph.D., Toxicologist, Directorate for Health Sciences

Leslie E. Patton, Ph.D., Toxicologist, Directorate for Health Sciences

SUBJECT : U.S. CPSC Staff Assessment of Phthalate Dietary Exposure using Two Food Residue Data Sets and Three Food Categorization Schemes [*]

The following memo provides the U.S. Consumer Product Safety Commission's (CPSC's) Health Sciences staff assessment of the dietary exposure to various phthalates. The information in this report will be provided to the Chronic Hazard Advisory Panel (CHAP) on Phthalates.

A detailed dietary exposure assessment was requested by the CHAP in order to evaluate the relationship of dietary phthalate exposure to total phthalate exposure.

[*] These comments are those of the CPSC staff, have not been reviewed or approved by, and may not necessarily reflect the views of, the Commission.

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1 Introduction

The Consumer Product Safety Improvement Act (CPSIA)† of (2008) was enacted on August 14, 2008. Section 108 of the CPSIA permanently prohibits the sale of any "children's toy or child care article" containing concentrations of more than 0.1 percent of dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), or di(2-ethylhexyl) phthalate (DEHP). Section 108 prohibits on an interim basis the sale of "any children's toy that can be placed in a child's mouth" or "child care article" containing concentrations of more than 0.1 percent of di-*n*-octyl phthalate (DNOP), diisononyl phthalate (DINP), or diisodecyl phthalate (DIDP). In addition, section 108 of the CPSIA directs CPSC to convene a CHAP "to study the effects on children's health of all phthalates and phthalate alternatives as used in children's toys and child care articles." The CHAP will recommend to the Commission whether any phthalates (including DINP) or phthalate alternatives other than those permanently banned should be declared banned hazardous substances.

In order to fulfill part of this charge, the CHAP is considering exposure to phthalates from all routes, including the diet (food). The CHAP has requested that CPSC staff utilize phthalate residues in food items (as reported in the published literature) to calculate dietary exposure to phthalate residues.

In this memo, the CPSC staff have provided analyses for seven target populations of interest (infants, toddlers, children, teen females, teen males, adult females, adult males). For each one, the following information has been provided in either numeric or graphical constructs:

1) Total average and 95th percentile dietary exposure (organized by phthalate for the UK food item/residue data set),
2) Total average and 95th percentile dietary exposure (organized by phthalate for the P&L food item/residue data set),
3) The relative change in exposure (percent of #1 and #2) when some food items are removed from the analysis,
4) The relative contribution of each phthalate to the total exposure from diet (using different food categorization schemes and food item/residue data sets),
5) The relative contribution of each phthalate to exposure for each food category (i.e., breads, meats, etc; using different food categorization schemes and food item/residue data sets).

† Public Law 110-314.

2 Methods

2.1 Food Item Phthalate Residues: Bradley, Page and LaCroix

CPSC staff utilized two datasets of phthalate residues in food items (Page and Lacroix, 1995; Bradley, 2011) to calculate potential phthalate exposures that result from food consumption. Exposures calculated from both datasets are presented for the CHAP's consideration.

2.1.1 Bradley, 2011 (UK)

The Bradley (2011) dataset (hereafter referred to as the UK study) is a total diet study carried out in the United Kingdom, and contains the most recently reported food residue data that CPSC staff could identify. In the study, two hundred and sixty-one retail food items were analyzed for 15 phthalate diesters (dimethyl phthalate (DMP), diethyl phthalate (DEP), diisopropyl phthalate (DiPP), diallyl phthalate (DAP), diisobutyl phthalate (DiBP), di-n-butyl phthalate (DBP), di-n-pentyl phthalate (DPP), di-n-hexyl phthalate (DHP), benzyl butyl phthalate (BBP), dicyclohexyl phthalate (DCHP), di-(2-ethylhexyl) phthalate (DEHP), di-n-octyl phthalate (DOP), diisononyl phthalate (DiNP), diisodecyl phthalate (DiDP), and di-n-decyl phthalate (DDP)). Nine phthalate monoesters and phthalic acid were also determined in food items. Distinct food items in this study were categorized into: bread products, dairy products, fish and fish products, infant food, infant formula, meat and meat products, miscellaneous cereal products, oils and fat products, liver products, and eggs. Consumption estimates for these food categories were not provided, however.

2.1.2 Page and LaCroix, 1995 (P&L)

The dataset in Page and LaCroix (1995) analyzed phthalate residues in a wide variety of foods, making the data useful despite their age. The P&L study analyzed ninety-eight food items for DEP, BBP, DBP, DEHP, as well as the non-phthalate plasticizer, diethyl hexyl adipate (DEHA). The food they analyzed was primarily packaged and fell into the following general categories: cheese, meat, fish, frozen foods (meat, fish, poultry), beverages (soda, juice, bottled water, wine), fruits and vegetables, oil and fat, bread, dairy, and infant food. As with the UK dataset, consumption estimates were not published for these particular food categories.

2.2 Food Categorization and Consumption Estimates: NCEA, Clark, Wormuth

CPSC staff recombined food items from both food item/residue datasets into alternate food categories that had published consumption estimates (see Table ES-5 and Section 4.1). Unknown food items were researched online in order to bin them into the "correct" food categories.

2.2.1 NCEA, 2007

The first and simplest food categorization scheme was based on the food groups used by U.S. EPA NCEA (2007) in the publication, *Analysis of Total Food Intake and Composition of Individual's Diet Based on USDA's 1994–1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII).* In this reference, food was divided into the following (total) categories: grain, dairy, fish, meat, fat, vegetable, fruit, soy, nut, and eggs.

2.2.2 Clark *et al.,* 2011

The second, intermediate in complexity, categorization scheme was retrieved from Clark *et al.,* (2011). This paper divided food into: tap water, beverages, cereals, dairy products (excluding milk), eggs, fats/oils, fish, fruits, grains, meats, milk, nuts and beans, other foods, poultry, processed meats, vegetables, infant formula (powder), and breast milk.

2.2.3 Wormuth *et al.,* 2006

The third, and most complex, food categorization scheme was taken from a 2006 publication by Wormuth *et al.,* (2006). The authors in this study categorized food into the following groups: pasta/ rice, cereals, breakfast cereals, bread, biscuits/crispy bread, cakes/ buns/puddings, bakeries/snacks, milk/milk beverages, cream, ice cream, yogurt, cheese, eggs, spreads, animal fats, vegetable oils, meat/meat products, sausage, poultry, fish, vegetables, potatoes, fruits, nuts/nut spreads, preserves/sugar, confectionary, spices, soups/sauces, juices, tea/coffee, soft drinks, beer, wine, spirits, tap water, bottled water, commercial infant food, infant formulas, and breast milk.

2.3 Food Categories with No Food Items/Residues

Both the UK (2011) and P&L (1995) food item/residue datasets had gaps in the representation of available food commodities. These gaps in food or beverage coverage sometimes affected the number of food items per category in all categorization schemes.

A few of NCEA (2007) categories were not represented by food item/residue data. These included: vegetable, fruit, soy, nut (UK data set); and soy, nut (P&L dataset). As with NCEA groupings, a few of the Clark categories did not have food item/residue data. These included: tap water, beverages, fruit, nuts and beans, vegetables, breast milk (UK dataset); tap water, nuts and beans, breast milk (P&L dataset). A few of Wormuth *et al.,* (2006) categories were also not filled by food item/residue data. These were: ice cream, vegetables, potatoes, fruits, nuts and nut spreads, preserves and sugar, confectionary, spices, soups and sauces, juices, tea and coffee, soft drinks, beer, wine, spirits, tap water, bottled water, breast milk (UK dataset); vegetable oils, spices, spirits, tap water, breast milk (P&L dataset). Even though the P&L dataset was comprised of less actual samples, representative category coverage was better that that provided by the UK dataset. Categories that were not represented by at least one food item were excluded from further analysis.

2.4 Summary Statistics from Food Item/Residue Data

Prior to data summarization, all food items in both datasets with “non-detects” were assigned a value of ½ the Level of Detection (LOD) or ½ the Level of Quantification (LOQ), depending on which was reported. Replacing non-detects into ½ the LOD/LOQ is one method commonly initially employed in conservative dietary exposure assessments to ensure that the exposures are not underestimated (by using zeros for non-detects) or overestimated (biased high by a few reported residue values) (EPA, 2000). Replacement is justified when there is the expectation that residues are present, but below the LOD (i.e., a crop has been treated with a pesticide, but pesticide residues are not detected on the crop). This expectation holds for phthalates since they are ubiquitous in the environment and therefore, ubiquitous in food commodities. Because of replacement, most categories were represented predominantly by ½ the LOD or LOQ values. It is expected that the effects of replacement substantially affected the summary residue values for many food categories that were comprised of fewer food items (without doing a sensitivity analysis). Broader categorization schemes (i.e., EPA, 2007), however, were expected to be less affected by the replacement of non-detects with ½ the LOD/LOQ.

Residues that were “not confirmed” in the UK dataset were left as is and combined with non-detects (½ the LOD/LOQ), and detects. Many of these “not confirmed” residues had concentrations that were similar to other reported residue concentrations within the same category.

Ultimately, individual phthalate diester residues, including ½ LOD/LOQ values, and values listed as “not confirmed” were combined within each food category and reported as both the average and 95th percentile. Monoester and phthalic acid residues in foods (conceivably created by catalytic activity in the food) were not considered in this exposure assessment summarization.

2.5 Calculation of Phthalate Exposure Estimates from Food

2.5.1 Phthalate Concentration in Food

For each population and residue dataset, daily average dietary exposures (µg/kg-day) and daily 95th percentile phthalate exposures (µg/kg-day) from the ingestion of food item *f* were calculated for each individual phthalate ester *i* as the sum of:

$$\frac{\text{Phthalate}_i \text{ Concentration in Food}_f\ (\mu g/g)\ x\ \text{Food Consumption}_f\ (g/day)\ x\ \text{Absorption Factor}_f}{\text{Body Weight (kg)}}$$

2.5.2 Consumption Factors for Conversion to Per-Capita (eaters + non-eaters)

Dietary exposures using the Wormuth scheme of product categorization were also expressed using a consumption factor (CF) to account for the fraction of the population eating the specific food type. Consumption factors were obtained from the Wormuth *et al.,* (2006) paper and applied using the following equation:

$$\frac{\text{Phthalate}_i \text{ Concentration in Food}_f \text{ (µg/g) } x \text{ Food Consumption}_f \text{ (g/day) } x \text{ Absorption Factor}_f \; x \text{ CF}_f}{\text{Body Weight (kg)}}$$

No CFs were available for the Clark food categorizations, and therefore, a CF of 1 was used. This conservative assumption meant that 100% of the given population would consume a specific food item. NCEA consumption estimates were already expressed as per-capita, so did not need the application of a CF.

2.5.3 Food Consumption

Population-based food consumption estimates specific to each of the seven populations of interest were extracted from the three sources of food categories (U.S. EPA/NCEA, (2007); Clark *et al.*, (2003); Wormuth *et al.*, (2006), see Table E3-1).

2.5.4 Phthalate Absorption

Phthalate absorption was considered separately in two manners, at 100% (1), and as a factor calculated from the mean oral uptake rate (i.e., the fraction of dose applied) derived from Wormuth *et al.,* (2006). Both of these factors were unitless. When no information on absorption was identified for a specific phthalate, a value of 1 was used, indicating a conservative 100% absorption of the phthalate.

2.5.5 Body Weight

Body weight information used in exposure calculations was derived from each respective study (U.S. EPA/NCEA, (2007); Clark *et al.*, (2011); and Wormuth *et al.*, (2006)). This information is summarized in Table E3-1 along with the associated age ranges for the populations.

Table E3-1 Population age and body weight used to calculate phthalate exposure.

Population	Age in Years (M&F combined)			Body Weights (kg; Gender)		
	NCEA (2007)	Clark *et al.*, (2011)	Wormuth *et al.*, (2006)	NCEA (2007)	Clark *et al.*, (2011)	Wormuth *et al.*, (2006)
Infant	<1	0-0.5	0-1	8.8	7.5	5.5
Toddler	1-5	0.5-4	1-3	15.15	15	13
Children	6-11	5-11	4-10	29.7	27	27
Teen	12-19	12-19	11-18	59.7	60	57.5
Adult	20+	20-70	18-80	73	71	70 (M), 60 (F)

2.5.6 Other Factors Not Considered in the Dietary Exposure Estimates

The effect of preparing, cooking and/or baking (i.e., cooking and baking factors), and the percent of food items expected to have phthalates (i.e., akin to percent of crop treated in pesticide parlance) were not considered in this dietary exposure assessment because the data was either not available or the food item was already analyzed "as prepared or eaten." Application of these factors would be expected to decrease overall phthalate exposure (i.e., fewer food items with phthalates, less phthalates in prepared food). Their exclusion, therefore, biases current results towards being more conservative.

2.6 Sensitivity Analysis to Determine the Effect of Categories with <3 Food Items

Total exposures from food categories with at least one food item were compared to those with more than three food items. This sensitivity analysis was performed in order to determine how a low N affected overall total phthalate exposure from foods.

3 Results

3.1 Total Phthalate Exposure from Food Items When Utilizing Two Food Items/Residue Data Sets and Three Methods for Categorizing Food Items

Total exposure from phthalates in food was evaluated for each residue data set (Bradley, 2011); (Page and Lacroix, 1995) food categorization scheme (Wormuth *et al.*, 2006; EPA, 2007; Clark *et al.*, 2011) and population (infant, toddler, children, teen, adult). Average and 95th percentile total exposure values calculated assuming 100% phthalate absorption, fractional absorption (Wormuth *et al.,* (2006) absorption factors), and the percent of total exposure when considering food categories with only N=3+ food items can be seen in Section 4.2.

3.2 Relative Contribution of Each Phthalate to Total Dietary Exposure

Pie charts illustrating the relative contribution of all phthalates to total average dietary exposure were generated next. These can be seen in Section 4.3.

The relative contribution of phthalates was not substantially different when comparing total average exposures calculated assuming 100% phthalate absorption (Section 4.3) and total average exposure calculated using absorption data from Wormuth *et al.*, (2006); pie charts not shown).

3.2.1 UK Dataset

When considering the UK (Bradley, 2011) residue dataset, all three food categorization schemes resulted in average total exposures (µg/kg-day) with the same comparative relationship (DINP > DIDP > DEHP > DDP) for all populations (Section 4.3). Total average exposures from other phthalates via food were substantially less than these four phthalates.

DINP residues were present for most of the food categories, but the majority of "residues" were replacement values (½ the LOD/LOQ). Replacement values for DINP moderated the overall total dietary exposure from DINP, since these were substantially lower than actual residues. DIDP and DDP total exposures were calculated entirely from replacement values (½ LOD/LOQ). Comparison to DINP residue values suggested that values for DIDP (at least) were reasonable. DEHP total exposure estimates were calculated using a substantial number of residue values (when compared to replacement values).

3.2.2 P&L Dataset

When considering P&L residue data (Page and Lacroix, 1995), the non-phthalate DEHA contributed to the largest portion of the average total exposure when assessing all categorization schemes and populations. Four other relationships were possible and dependent on the population and way food residues were categorized. Relationship 1 (DEHP>BBP>DEP>DBP) was primarily observed when food residues were grouped by NCEA categories (for infants, toddlers, children, female teens, and male teens). Relationship 2 (BBP>DEHP>DBP>DEP) was only observed following grouping by Wormuth *et al.*, (2006; infants). Relationship 3 (DEHP>BBP>DBP>DEP) was observed following grouping with NCEA (EPA, 2007; female adult and male adult), Clark *et al.*, (2011; infants), and Wormuth *et al.*, (2006; toddler, female teen, male teen, female adult, and male adult). Relationship 4 (DEHP>DBP>BBP>DEP) was observed following grouping residues with Clark *et al.*, (2011; toddler, children, female teen, male teen, female adult, and male adult), and Wormuth *et al.*, (2006; children).

In this analysis, BBP exposures were calculated from only a few actual food residue data points. It is expected that this probably did not affect the phthalate order because of the moderating influence of the additional replacement values for BBP. Other phthalates (and DEHA) calculations were performed with a substantial number of residues in addition to the replacement values.

3.3 Relative Contribution of Each Phthalate to Each Food Category

Bar charts illustrating the relative contribution of all phthalates to total average dietary exposure in specific food categories were generated. These can be seen in Section 4.4. Summaries of this information can be seen in Tables E3-2, E3-3, and E3-4 below.

Table E3-2 Comparison of the contributors to exposure: NCEA (2007) categorization scheme.

Table 2. Comparison of the Contributors to Exposure: NCEA Categorization Scheme				
Population	**Residue data set**	**Categorization**	**Relative Commodity Contribution to Exposure**	**Relative Phthalate Relationship**
Infant	UK	NCEA	Dairy=fat>grain>meat>others	DINP>DIDP>DEHP>DMP
Infant	P&L	NCEA	Dairy>fat>grain>others	DEHP>others
Toddler	UK	NCEA	Dairy>fat>grain>meat>others	DINP>DIDP>DEHP>DMP
Toddler	P&L	NCEA	Dairy>fat>grain>meat>others	DEHP>others
Children	UK	NCEA	Dairy>fat>grain>meat>others	DINP>DIDP>DEHP>DDP
Children	P&L	NCEA	Dairy>fat>grain>meat>others	BBP>meat; DEHP>all others
Female teen	UK	NCEA	Dairy>fat>grain>meat>others	DINP>DIDP>DEHP>DDP
Female teen	P&L	NCEA	Dairy>fat>grain>meat>others	DEHP>others
Male teen	UK	NCEA	Dairy>fat>grain>meat>others	DINP>DIDP>DEHP>DDP
Male teen	P&L	NCEA	Dairy>fat>grain>meat>others	BBP>meats; DEHP>all others
Female adult	UK	NCEA	Dairy>fat>grain>meat>others	DINP>DIDP>DEHP>DDP
Female adult	P&L	NCEA	Dairy>fat>grain>meat>others	BBP>meats; DEHP>all others
Male adult	UK	NCEA	Dairy>fat>grain>meat>others	DINP>DIDP>DEHP>DDP
Male adult	P&L	NCEA	Dairy>fat>grain>meat>others	BBP>meat; DEHP>all others

Table E3-3 Comparison of the contributors to exposure: Clark *et al.*, (2011) categorization scheme.

Table 3. Comparison of the Contributors to Exposure: Clark Categorization Scheme

Population	Residue data set	Categorization	Relative Commodity Contribution to Exposure	Relative Phthalate Relationship
Infant	UK	Clark	Infant formulas	DINP>DIDP>DEHP>DDP
Infant	P&L	Clark	Infant formulas	DEHP>others
Toddler	UK	Clark	Milk>other foods>grains>dairy>cereal>fats and oils>meat>others	DINP>DIDP>DEHP>DDP
Toddler	P&L	Clark	Other foods>dairy>milk>cereal>vegetables>meat>others	BBP>meat; DBP>other foods; DEHP>all others
Children	UK	Clark	Milk>other foods>grains>dairy>cereal>fats and oils>cereal>meat>others	DINP>DIDP>DEHP>DDP
Children	P&L	Clark	Other foods>dairy>vegetables>milk>meat>fats and oils>others	BBP>cereal, meat; DBP>other foods; DEHP>all others
Female teen	UK	Clark	Other foods>milk>grains>fats and oils>dairy meats>others	DINP>DIDP>DEHP>DDP
Female teen	P&L	Clark	Other foods>dairy>meats>vegetables>fats>milk>beverages>others	BBP>meats; DBP>other foods; DEHP> all others
Male teen	UK	Clark	Other foods>milk>grains>fats and oils>dairy meats>others	DINP>DIDP>DEHP>DDP
Male teen	P&L	Clark	Other foods>dairy>meat>vegetables>fats and oils>others	BBP>meat; DBP>other foods; DEHP>all others
Female adult	UK	Clark	Other foods>grains>milk>dairy>fats and oils>meat>others	DINP>DIDP>DEHP>DDP
Female adult	P&L	Clark	Other foods>dairy>beverages>meats>vegetables>other	BBP>meats; DBP>other foods; DEHP> all others
Male adult	UK	Clark	Other foods>grains>milk>dairy>fats and oils>meat>others	DINP>DIDP>DEHP>DDP
Male adult	P&L	Clark	Other foods>dairy>beverages>meats>vegetables>fats and oils>others	BBP>meats; DBP>other foods; DEHP> all others

Table E3-4 Comparison of the contributors to exposure: Wormuth *et al.*, (2006) categorization scheme.

Table 4. Comparison of the Contributors to Exposure: Wormuth Categorization Scheme

Population	Residue data set	Categorization	Relative Commodity Contribution to Exposure	Relative Phthalate Relationship
Infant	UK	Wormuth	Infant formula>milk>cereal>bread>commerical infant food>others	DINP>DIDP>DEHP>DDP
Infant	P&L	Wormuth	Cereal>commercial infant food>milk>cakes, buns, puddins>bread>cereal>others	BBP>cereal, sausage, potatoes; DBP>biscuits, crispy bread, cakes, buns, pudding, fruits, confectionary; DEP>yogurt; DEHP>all others
Toddler	UK	Wormuth	Milk>bread>infant formula>yogurt>cereal>vegetable oils>others	DINP>DIDP>DEHP>DDP
Toddler	P&L	Wormuth	Biscuits, crispy bread>cereal>confectionary>milk>soft drinks>yogurt>bread>others	BBP>cereal, sausage, potatoes; DBP>biscuits, crispy bread, cakes, buns, pudding, fruits, confectionary; DEP>yogurt; DEHP>all others
Children	UK	Wormuth	Milk>bread>cakes, buns, puddings>meat>vegetable oil>cereal>others	DINP>DIDP>DEHP>DDP
Children	P&L	Wormuth	Confectionary>meat>cakes, buns, puddings>cereals>soft drinks>milk>others	BBP>cereal, sausage, potatoes; DBP>cakes, buns, pudding, fruits, confectionary; DEP>yogurt; DEHP>all others
Female teen	UK	Wormuth	Bakeries, snacks>cheese>bread>milk>cakes,buns, puddings>meat>others	DINP>DIDP>DEHP>DDP
Female teen	P&L	Wormuth	Bakeries, snacks>cheese>meat>confectionary>bread>vegetables>others	BBP>cereal>sausage>potatoes; DBP>cakes, buns, puddings, confectionary; DEP>yogurt; DEHP>all others
Male teen	UK	Wormuth	Bakeries, snacks>cheese>bread>milk>cakes,buns,puddings>meat>others	DINP>DIDP>DEHP>DDP
Male teen	P&L	Wormuth	Bakeries, snacks>cheese>meat>confectionary>bread>others	BBP>cereal, sausage, potatoes; DBP>cakes, buns, puddings, confectionary; DEP>yogurt; DEHP>all others
Female adult	UK	Wormuth	Breakfast cereals>bread>milk>cakes, buns, puddings>cheese>spreads>cereals>others	DINP>DIDP>DEHP>DDP
Female adult	P&L	Wormuth	Meat>cheese>sausage>confectionary>vegetables>bread>spreads>cereals>others	BBP>cereal, sausage,potatoes; DBP>cakes, buns, puddings, fruits, confectionary; DEP>yogurt; DEHP>all others
Male adult	UK	Wormuth	Bread>milk>meat>cheese>fish>cakes, buns, puddings, animal fats>others	DINP>DIDP>DEHP>DDP
Male adult	P&L	Wormuth	Meat>cheese>sausage>confectionary>bread>vegetables>spreads>others	BBP>cereals,sausage, potatoes; DBP>biscuits, crispy bread, cakes, buns, puddings, confectionary; DEP>yogurt; DEHP>all others

3.4 Effect of Removing Food Categories with N<3 Food Items on Total Exposure Estimates

Total exposure estimates from food were initially calculated using all residue data (and ½ LOD for nondetects) for either the UK (Bradley, 2011) or the Page and LaCroix (1995) datasets. This calculation included food categories that had only one food item (or composite sample).

Additional calculations for total food exposure were performed only using food categories that had N=3+ food items in order to determine how the number of items per category affected the total exposure.

Removing food categories with N<3 food items did not substantially affect the total exposures for any population (infants, toddlers, children, teens, or adults) when calculated using NCEA (EPA, 2007) or Clark *et al.*, (2011) categorization schemes and the UK (Bradley, 2011) or Page and LaCroix (1995) food items/residue datasets.

Removing food categories with N<3 food items marginally reduced the total average exposure (but not the 95^{th} percentile) when considering Wormuth *et al.*, (2006) food categorization scheme and the UK (Bradley, 2011) food item/residue data set. Reductions of >10% of total exposure were seen for DPP (infants, toddlers, children, teens, female adults), DCHP (toddlers, female teens), DEHP (toddlers), DOP (toddlers, female teens), DINP (toddlers, children), DIDP (toddlers, children), and DDP (toddlers, female teens).

Substantial decreases in total average and 95th percentile exposure were seen following removal of food categories with N<3 food items when considering Wormuth *et al.*, (2006) food categorization scheme and the Page and LaCroix (1995) food residue data set. Specifically, DEP, BBP, and DBP total average and 95th percentile exposures were reduced to 27-77 percent of the total exposure, and DEHP total average and 95th percentile exposures were reduced to 57-94 percent of the total exposure for all populations when removing the food categories with N<3 food items (calculations not shown).

4 Supplemental Data

4.1 Food Categorization Schemes Organized by Publication

Table E3-5 Food product groupings organized by study.

General Food Category	NCEA (Total)	Clark *et al.*, 2011	Wormuth *et al.*, 2006
Dairy	Dairy	Milk	Milk, milk beverage
		Dairy (excl. milk)	Cream
			Ice cream
			Yogurt
			Cheese
Meat and egg	Meat	Meat	Meat, meat product
		Processed meat	Sausage
			Soup, sauce
		Poultry	Poultry
	Fish	Fish	Fish
	Egg	Egg	Egg
Grain, fruit, nut, and vegetable	Grain	Grain	Pasta, rice
		Cereals	Cereal
			Breakfast cereal
			Bread
			Biscuit, crispy bread
			Cake bun, pudding
			Bakeries, snack
	Vegetable	Vegetable	Vegetable
			Potato
	Soy		Soup, sauce
	Fruit	Fruit	Fruit
			Preserves, sugar
	Nut	Nut and bean	Nuts, nut spread
Fat and oil	Fat	Fat and oil	Animal fats
			Vegetable oil
			Spread
Other and composite food		Other food	Confectionary
			Spice
Baby nutrition		Infant formula (powder)	Infant formula
		Breast milk	Breast milk
			Commercial infant food

Liquid (excl. milk)		Beverage	Juices
			Tea, coffee
			Soft drink
			Beer
			Wine
			Spirits
			Bottled water
		Tap water	Tap water

4.2 Total Exposure (µg/kg-day) Estimates for Various Populations (Wormuth Estimates Adjusted for the Fraction of the Population Consuming)

4.2.1 Infants

Table E3-6 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.061	0.304	0.056	0.201	0.351	0.200	0.156	0.157	0.548	0.194	5.033	0.375	13.814	9.291	0.656
Wormuth		Average	0.351	0.543	0.285	1.283	0.807	0.728	0.474	0.452	0.875	0.584	4.670	1.014	36.858	30.451	2.046
Clark		Average	0.096	0.116	0.064	0.302	0.132	0.182	0.074	0.124	0.212	0.111	0.818	0.190	8.157	7.325	0.334
NCEA		95th %ile	0.203	1.250	0.179	0.653	1.249	0.534	0.448	0.425	0.667	0.484	18.366	0.977	35.819	24.721	1.435
Wormuth		95th %ile	1.236	1.443	0.853	3.855	2.033	1.808	1.209	1.061	2.239	1.203	11.698	2.430	94.123	73.991	3.806
Clark		95th %ile	0.401	0.342	0.254	1.104	0.308	0.483	0.206	0.304	0.600	0.248	2.294	0.560	28.352	20.173	0.750

Table E3-7 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.042	0.208	0.056	0.201	0.240	0.137	0.156	0.157	0.397	0.194	2.778	0.375	11.396	7.665	0.656
Wormuth		Average	0.240	0.372	0.285	1.283	0.553	0.499	0.474	0.452	0.634	0.584	2.578	1.014	30.408	25.122	2.046
Clark		Average	0.066	0.079	0.064	0.302	0.090	0.125	0.074	0.124	0.153	0.111	0.452	0.190	6.730	6.043	0.334
NCEA		95th %ile	0.139	0.856	0.179	0.653	0.856	0.366	0.448	0.425	0.484	0.484	10.138	0.977	29.550	20.395	1.435
Wormuth		95th %ile	0.847	0.989	0.853	3.855	1.392	1.238	1.209	1.061	1.623	1.203	6.457	2.430	77.652	61.043	3.806
Clark		95th %ile	0.275	0.234	0.254	1.104	0.211	0.331	0.206	0.304	0.435	0.248	1.266	0.560	23.390	16.643	0.750

Table E3-8 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		Average	97.4	98.4	97.7	97.9	95.5	97.4	85.4	95.3	95.4	92.4	91.7	92.9	90.3	90.5	93.5
Clark		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		95th %ile	99.1	99.4	99.3	99.3	97.8	98.8	94.2	97.7	98.0	95.2	96.5	97.0	96.0	96.0	96.5
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table E3-9 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	3.887	5.258	3.163	27.371	841.753
Wormuth		Average	2.162	12.867	3.868	12.820	175.134
Clark		Average	0.867	0.867	0.867	10.111	0.867
NCEA		95th %ile	7.852	10.791	7.034	87.769	2882.414
Wormuth		95th %ile	2.209	15.451	9.072	41.113	602.361
Clark		95th %ile	0.867	0.867	0.867	45.760	0.867

Table E3-10 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors)

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	2.663	3.812	2.166	15.109	464.648
Wormuth		Average	1.481	9.328	2.650	7.076	96.674
Clark		Average	1.513	11.202	6.214	22.695	332.503
NCEA		95th %ile	5.378	7.824	4.818	48.448	1591.093
Wormuth		95th %ile	1.513	11.202	6.214	22.695	332.503
Clark		95th %ile	0.594	0.628	0.594	25.260	0.478

Table E3-11 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	99.6	99.7	99.5	99.9	99.6
Wormuth		Average	37.9	39.3	61.7	83.8	95.4
Clark		Average	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	99.8	99.9	99.8	100.0	99.8
Wormuth		95th %ile	36.6	62.8	69.1	93.8	97.3
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0

4.2.2 Toddlers

Table E3-12 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.116	0.666	0.104	0.399	0.731	0.358	0.272	0.269	0.636	0.350	7.563	0.612	24.009	15.782	1.173
Wormuth		Average	0.095	0.164	0.086	0.369	0.286	0.199	0.173	0.131	0.285	0.201	1.758	0.354	10.611	8.371	0.735
Clark		Average	0.214	0.466	0.204	0.868	0.985	0.579	0.341	0.409	0.652	0.501	5.141	0.915	31.389	19.806	1.795
NCEA		95th %ile	0.391	2.714	0.311	1.234	2.684	0.981	0.742	0.755	1.058	0.814	25.918	1.561	69.432	44.981	2.497
Wormuth		95th %ile	0.274	0.396	0.204	0.934	0.739	0.456	0.409	0.281	0.733	0.395	4.273	0.754	21.592	19.433	1.248
Clark		95th %ile	0.618	1.315	0.496	2.253	2.912	1.590	0.925	1.306	1.347	1.087	13.885	2.312	98.535	53.600	3.561

Table E3-13 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.080	0.456	0.104	0.399	0.501	0.245	0.272	0.269	0.461	0.350	4.175	0.612	19.808	13.021	1.173
Wormuth		Average	0.065	0.112	0.086	0.369	0.196	0.136	0.173	0.131	0.207	0.201	0.970	0.354	8.754	6.906	0.735
Clark		Average	0.146	0.320	0.204	0.868	0.674	0.396	0.341	0.409	0.472	0.501	2.838	0.915	25.896	16.340	1.795
NCEA		95th %ile	0.268	1.859	0.311	1.234	1.839	0.672	0.742	0.755	0.767	0.814	14.307	1.561	57.281	37.109	2.497
Wormuth		95th %ile	0.187	0.271	0.204	0.934	0.506	0.312	0.409	0.281	0.531	0.395	2.358	0.754	17.813	16.032	1.248
Clark		95th %ile	0.424	0.901	0.496	2.253	1.994	1.089	0.925	1.306	0.976	1.087	7.665	2.312	81.291	44.220	3.561

Table E3-14 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		Average	94.0	97.3	96.0	96.4	94.1	95.3	79.2	91.2	93.6	87.6	87.0	87.8	86.6	86.8	89.3
Clark		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		95th %ile	97.4	98.9	98.4	98.6	96.8	97.7	91.3	95.3	97.3	91.3	94.5	94.1	92.6	94.0	93.8
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table E3-15 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	7.779	9.118	6.683	54.021	1881.092
Wormuth		Average	2.504	5.044	4.279	8.506	127.384
Clark		Average	2.104	5.276	10.044	21.789	516.823
NCEA		95th %ile	14.543	16.760	15.685	175.753	6621.423
Wormuth		95th %ile	2.517	8.163	8.124	21.645	399.093
Clark		95th %ile	4.218	15.511	43.499	70.827	1914.344

Table E3-16 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	5.328	6.611	4.578	29.819	1038.363
Wormuth		Average	1.715	3.657	2.931	4.695	70.316
Clark		Average	1.441	3.825	6.880	12.028	285.286
NCEA		95th %ile	9.962	12.151	10.744	97.015	3655.026
Wormuth		95th %ile	1.724	5.918	5.565	11.948	220.299
Clark		95th %ile	2.889	11.245	29.797	39.097	1056.718

Table E3-17 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	99.3	99.4	99.2	99.9	99.4
Wormuth		Average	27.3	46.2	33.4	75.8	93.4
Clark		Average	94.8	97.9	98.9	98.0	96.6
NCEA		95th %ile	99.6	99.7	99.7	100.0	99.7
Wormuth		95th %ile	26.7	66.1	45.5	88.9	96.1
Clark		95th %ile	97.4	99.3	99.7	99.4	98.3

4.2.3 Children

Table E3-18 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.068	0.344	0.061	0.229	0.406	0.209	0.160	0.157	0.391	0.199	4.224	0.353	13.697	9.039	0.649
Wormuth		Average	0.045	0.086	0.042	0.177	0.154	0.101	0.079	0.065	0.151	0.096	0.940	0.174	5.588	4.122	0.354
Clark		Average	0.120	0.265	0.115	0.475	0.585	0.331	0.215	0.237	0.418	0.288	3.200	0.509	17.376	12.350	0.969
NCEA		95th %ile	0.242	1.386	0.181	0.708	1.477	0.584	0.439	0.447	0.635	0.473	14.644	0.918	40.358	25.856	1.435
Wormuth		95th %ile	0.138	0.222	0.097	0.443	0.414	0.245	0.209	0.154	0.432	0.200	2.524	0.387	11.900	10.193	0.648
Clark		95th %ile	0.358	0.777	0.279	1.209	1.811	0.892	0.561	0.720	0.797	0.616	8.736	1.289	51.247	35.163	1.939

Table E3-19 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, 2006 absorbtion factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.047	0.236	0.061	0.229	0.278	0.143	0.160	0.157	0.283	0.199	2.332	0.353	11.300	7.457	0.649
Wormuth		Average	0.031	0.059	0.042	0.177	0.105	0.069	0.079	0.065	0.109	0.096	0.519	0.174	4.610	3.400	0.354
Clark		Average	0.082	0.182	0.115	0.475	0.401	0.227	0.215	0.237	0.303	0.288	1.766	0.509	14.335	10.188	0.969
NCEA		95th %ile	0.166	0.949	0.181	0.708	1.011	0.400	0.439	0.447	0.461	0.473	8.083	0.918	33.295	21.332	1.435
Wormuth		95th %ile	0.095	0.152	0.097	0.443	0.283	0.168	0.209	0.154	0.313	0.200	1.393	0.387	9.817	8.409	0.648
Clark		95th %ile	0.245	0.532	0.279	1.209	1.240	0.611	0.561	0.720	0.578	0.616	4.823	1.289	42.278	29.010	1.939

Table E3-20 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		Average	95.3	98.1	96.8	97.1	95.7	96.4	83.6	93.2	95.5	90.5	91.8	91.3	89.6	88.9	92.3
Clark		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		95th %ile	98.0	99.3	98.6	98.8	97.8	98.2	93.4	96.6	98.3	93.7	96.8	95.8	94.4	95.1	95.7
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table E3-21 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	4.052	5.371	3.642	28.485	967.766
Wormuth		Average	0.726	2.309	3.498	5.640	83.413
Clark		Average	1.443	3.576	4.776	13.282	307.143
NCEA		95th %ile	7.553	9.974	9.501	93.994	3357.234
Wormuth		95th %ile	0.724	3.985	7.555	15.430	268.840
Clark		95th %ile	2.877	10.192	19.452	42.932	1001.810

Table E3-22 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	2.775	3.894	2.495	15.724	534.207
Wormuth		Average	0.497	1.674	2.396	3.113	46.044
Clark		Average	0.988	2.593	3.272	7.332	169.543
NCEA		95th %ile	5.174	7.231	6.508	51.885	1853.193
Wormuth		95th %ile	0.496	2.889	5.175	8.517	148.400
Clark		95th %ile	1.971	7.389	13.324	23.699	552.999

Table E3-23 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	99.3	99.5	99.3	99.9	99.4
Wormuth		Average	44.7	54.9	33.3	72.9	92.6
Clark		Average	94.9	97.9	98.4	96.5	97.2
NCEA		95th %ile	99.7	99.7	99.7	100.0	99.7
Wormuth		95th %ile	44.6	72.8	40.9	87.0	95.6
Clark		95th %ile	97.4	99.3	99.6	98.9	98.4

4.2.4 Female Teens

Table E3-24 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.038	0.158	0.033	0.123	0.203	0.113	0.089	0.086	0.228	0.105	2.172	0.190	7.197	4.783	0.331
Wormuth		Average	0.030	0.109	0.028	0.105	0.152	0.091	0.065	0.064	0.121	0.081	1.083	0.139	5.768	3.815	0.248
Clark		Average	0.058	0.128	0.055	0.223	0.285	0.163	0.106	0.120	0.215	0.141	1.640	0.250	8.675	6.061	0.458
NCEA		95th %ile	0.145	0.622	0.100	0.379	0.724	0.323	0.248	0.247	0.360	0.257	7.657	0.510	21.381	13.737	0.769
Wormuth		95th %ile	0.101	0.324	0.069	0.253	0.447	0.233	0.144	0.155	0.353	0.173	2.641	0.293	13.686	9.248	0.475
Clark		95th %ile	0.186	0.383	0.137	0.576	0.892	0.453	0.280	0.373	0.398	0.306	4.613	0.646	26.190	17.346	0.950

Table E3-25 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.026	0.108	0.033	0.123	0.139	0.077	0.089	0.086	0.165	0.105	1.199	0.190	5.937	3.946	0.331
Wormuth		Average	0.021	0.075	0.028	0.105	0.104	0.063	0.065	0.064	0.088	0.081	0.598	0.139	4.758	3.147	0.248
Clark		Average	0.040	0.088	0.055	0.223	0.195	0.112	0.106	0.120	0.156	0.141	0.905	0.250	7.157	5.000	0.458
NCEA		95th %ile	0.099	0.426	0.100	0.379	0.496	0.221	0.248	0.247	0.261	0.257	4.227	0.510	17.639	11.333	0.769
Wormuth		95th %ile	0.069	0.222	0.069	0.253	0.306	0.160	0.144	0.155	0.256	0.173	1.458	0.293	11.291	7.630	0.475
Clark		95th %ile	0.127	0.262	0.137	0.576	0.611	0.310	0.280	0.373	0.289	0.306	2.546	0.646	21.606	14.310	0.950

Table E3-26 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		Average	93.5	98.5	96.0	95.9	96.3	96.5	81.0	93.5	95.4	89.6	92.8	89.6	91.5	90.1	89.7
Clark		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		95th %ile	97.3	99.5	98.3	98.3	98.2	98.4	91.6	96.8	98.4	93.2	97.1	94.8	95.7	95.6	94.4
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table E3-27 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	1.902	3.002	1.812	13.685	440.915
Wormuth		Average	1.092	2.399	1.759	8.067	157.098
Clark		Average	0.806	2.090	2.521	6.858	163.198
NCEA		95th %ile	3.514	5.545	5.132	46.683	1476.424
Wormuth		95th %ile	1.062	3.974	3.563	20.166	481.277
Clark		95th %ile	1.621	5.902	10.285	22.274	526.376

Table E3-28 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	1.303	2.177	1.242	7.554	243.385
Wormuth		Average	0.748	1.739	1.205	4.453	86.718
Clark		Average	0.552	1.516	1.727	3.786	90.085
NCEA		95th %ile	2.407	4.020	3.515	25.769	814.986
Wormuth		95th %ile	0.728	2.881	2.441	11.132	265.665
Clark		95th %ile	1.110	4.279	7.045	12.295	290.560

Table E3-29 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	99.1	99.5	99.1	99.9	99.2
Wormuth		Average	49.5	54.3	54.8	54.8	89.3
Clark		Average	95.6	98.3	98.6	96.7	97.5
NCEA		95th %ile	99.5	99.7	99.7	100.0	99.5
Wormuth		95th %ile	48.1	65.4	58.7	75.4	93.3
Clark		95th %ile	97.8	99.4	99.7	99.0	98.5

4.2.5 Male Teens

Table E3-30 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.038	0.158	0.033	0.123	0.203	0.113	0.089	0.086	0.228	0.105	2.172	0.190	7.197	4.783	0.331
Wormuth		Average	0.039	0.156	0.038	0.141	0.189	0.119	0.081	0.084	0.154	0.103	1.332	0.177	7.693	5.024	0.323
Clark		Average	0.058	0.128	0.055	0.223	0.285	0.163	0.106	0.120	0.215	0.141	1.640	0.250	8.675	6.061	0.458
NCEA		95th %ile	0.145	0.622	0.100	0.379	0.724	0.323	0.248	0.247	0.360	0.257	7.657	0.510	21.381	13.737	0.769
Wormuth		95th %ile	0.129	0.472	0.092	0.347	0.567	0.309	0.186	0.211	0.444	0.223	3.335	0.385	18.987	12.676	0.630
Clark		95th %ile	0.186	0.383	0.137	0.576	0.892	0.453	0.280	0.373	0.398	0.306	4.613	0.646	26.190	17.346	0.950

Table E3-31 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.026	0.108	0.033	0.123	0.139	0.077	0.089	0.086	0.165	0.105	1.199	0.190	5.937	3.946	0.331
Wormuth		Average	0.026	0.107	0.038	0.141	0.130	0.082	0.081	0.084	0.111	0.103	0.735	0.177	6.347	4.145	0.323
Clark		Average	0.040	0.088	0.055	0.223	0.195	0.112	0.106	0.120	0.156	0.141	0.905	0.250	7.157	5.000	0.458
NCEA		95th %ile	0.099	0.426	0.100	0.379	0.496	0.221	0.248	0.247	0.261	0.257	4.227	0.510	17.639	11.333	0.769
Wormuth		95th %ile	0.088	0.323	0.092	0.347	0.388	0.212	0.186	0.211	0.322	0.223	1.841	0.385	15.665	10.458	0.630
Clark		95th %ile	0.127	0.262	0.137	0.576	0.611	0.310	0.280	0.373	0.289	0.306	2.546	0.646	21.606	14.310	0.950

Table E3-32 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		Average	96.0	99.2	97.6	97.5	97.6	97.8	87.9	96.0	97.1	93.4	95.5	93.5	94.6	93.6	93.8
Clark		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		95th %ile	98.4	99.7	99.0	99.0	98.9	99.0	94.8	98.1	99.0	95.8	98.2	96.9	97.4	97.3	96.7
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table E3-33 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	1.902	3.002	1.812	13.685	440.915
Wormuth		Average	1.151	3.078	2.484	10.750	211.258
Clark		Average	0.806	2.090	2.521	6.858	163.198
NCEA		95th %ile	3.514	5.545	5.132	46.683	1476.424
Wormuth		95th %ile	1.109	5.824	5.104	26.006	658.394
Clark		95th %ile	1.621	5.902	10.285	22.274	526.376

Table E3-34 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	1.303	2.177	1.242	7.554	243.385
Wormuth		Average	0.788	2.231	1.702	5.934	116.614
Clark		Average	0.552	1.516	1.727	3.786	90.085
NCEA		95th %ile	2.407	4.020	3.515	25.769	814.986
Wormuth		95th %ile	0.759	4.222	3.497	14.355	363.434
Clark		95th %ile	1.110	4.279	7.045	12.295	290.560

Table E3-35 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	99.1	99.5	99.1	99.9	99.2
Wormuth		Average	62.9	61.8	58.9	57.2	89.7
Clark		Average	95.6	98.3	98.6	96.7	97.5
NCEA		95th %ile	99.5	99.7	99.7	100.0	99.5
Wormuth		95th %ile	61.6	72.6	62.9	76.3	93.7
Clark		95th %ile	97.8	99.4	99.7	99.0	98.5

4.2.6 Female Adult

Table E3-36 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.027	0.093	0.024	0.086	0.130	0.078	0.063	0.060	0.159	0.071	1.384	0.129	4.812	3.198	0.215
Wormuth		Average	0.017	0.042	0.016	0.066	0.099	0.051	0.037	0.032	0.067	0.041	0.556	0.066	2.619	2.102	0.118
Clark		Average	0.036	0.087	0.034	0.131	0.193	0.108	0.068	0.084	0.142	0.090	1.142	0.159	5.908	3.983	0.273
NCEA		95th %ile	0.108	0.357	0.071	0.261	0.459	0.227	0.175	0.175	0.255	0.176	4.916	0.356	14.518	9.259	0.524
Wormuth		95th %ile	0.052	0.114	0.036	0.151	0.254	0.117	0.084	0.078	0.186	0.086	1.423	0.144	6.018	5.860	0.243
Clark		95th %ile	0.122	0.280	0.086	0.342	0.616	0.310	0.178	0.267	0.261	0.201	3.242	0.429	18.706	11.581	0.611

Table E3-37 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.018	0.064	0.024	0.086	0.089	0.053	0.063	0.060	0.115	0.071	0.764	0.129	3.970	2.638	0.215
Wormuth		Average	0.012	0.029	0.016	0.066	0.068	0.035	0.037	0.032	0.049	0.041	0.307	0.066	2.161	1.734	0.118
Clark		Average	0.025	0.060	0.034	0.131	0.132	0.074	0.068	0.084	0.103	0.090	0.630	0.159	4.874	3.286	0.273
NCEA		95th %ile	0.074	0.244	0.071	0.261	0.314	0.156	0.175	0.175	0.185	0.176	2.713	0.356	11.977	7.638	0.524
Wormuth		95th %ile	0.036	0.078	0.036	0.151	0.174	0.080	0.084	0.078	0.135	0.086	0.786	0.144	4.965	4.835	0.243
Clark		95th %ile	0.084	0.192	0.086	0.342	0.422	0.212	0.178	0.267	0.190	0.201	1.790	0.429	15.433	9.554	0.611

Table E3-38 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		Average	95.7	98.6	97.4	97.2	97.0	97.3	87.9	95.5	96.2	92.3	94.8	92.1	92.1	91.8	92.0
Clark		Average	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
NCEA		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Wormuth		95th %ile	98.3	99.5	99.0	98.8	98.4	98.7	94.9	97.8	98.5	95.1	97.9	96.3	95.9	96.6	96.1
Clark		95th %ile	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table E3-39 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	1.139	2.091	1.179	8.472	258.454
Wormuth		Average	0.967	3.012	2.244	5.341	127.802
Clark		Average	0.741	1.847	2.018	5.826	136.634
NCEA		95th %ile	2.057	3.843	3.569	30.076	829.443
Wormuth		95th %ile	1.000	5.947	4.545	17.907	398.377
Clark		95th %ile	1.535	5.087	7.965	18.926	432.221

Table E3-40 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	0.781	1.516	0.807	4.677	142.667
Wormuth		Average	0.662	2.184	1.537	2.948	70.547
Clark		Average	0.508	1.339	1.382	3.216	75.422
NCEA		95th %ile	1.409	2.786	2.445	16.602	457.853
Wormuth		95th %ile	0.685	4.311	3.113	9.885	219.904
Clark		95th %ile	1.051	3.688	5.456	10.447	238.586

Table E3-41 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	98.6	99.2	98.7	99.8	98.6
Wormuth		Average	44.9	60.8	47.5	73.0	95.4
Clark		Average	95.4	98.2	98.3	97.3	96.4
NCEA		95th %ile	99.2	99.6	99.6	99.9	99.2
Wormuth		95th %ile	40.4	76.3	56.0	87.8	97.2
Clark		95th %ile	97.8	99.3	99.6	99.2	97.8

4.2.7 Male Adult

Table E3-42 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are 100% absorbed.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.027	0.093	0.024	0.086	0.130	0.078	0.063	0.060	0.159	0.071	1.384	0.129	4.812	3.198	0.215
Wormuth		Average	0.035	0.087	0.033	0.119	0.140	0.094	0.080	0.070	0.145	0.081	1.041	0.140	5.218	3.988	0.236
Clark		Average	0.036	0.087	0.034	0.131	0.193	0.108	0.068	0.084	0.142	0.090	1.142	0.159	5.908	3.983	0.273
NCEA		95th %ile	0.108	0.357	0.071	0.261	0.459	0.227	0.175	0.175	0.255	0.176	4.916	0.356	14.518	9.259	0.524
Wormuth		95th %ile	0.129	0.251	0.089	0.304	0.381	0.247	0.196	0.178	0.448	0.177	2.871	0.329	11.834	10.485	0.521
Clark		95th %ile	0.122	0.280	0.086	0.342	0.616	0.310	0.178	0.267	0.261	0.201	3.242	0.429	18.706	11.581	0.611

Table E3-43 Total Exposure (µg/kg-day) calculated using UK (Bradley, 2011) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	0.018	0.064	0.024	0.086	0.089	0.053	0.063	0.060	0.115	0.071	0.764	0.129	3.970	2.638	0.215
Wormuth		Average	0.024	0.060	0.033	0.119	0.096	0.064	0.080	0.070	0.105	0.081	0.575	0.140	4.305	3.290	0.236
Clark		Average	0.025	0.060	0.034	0.131	0.132	0.074	0.068	0.084	0.103	0.090	0.630	0.159	4.874	3.286	0.273
NCEA		95th %ile	0.074	0.244	0.071	0.261	0.314	0.156	0.175	0.175	0.185	0.176	2.713	0.356	11.977	7.638	0.524
Wormuth		95th %ile	0.088	0.172	0.089	0.304	0.261	0.169	0.196	0.178	0.324	0.177	1.585	0.329	9.763	8.651	0.521
Clark		95th %ile	0.084	0.192	0.086	0.342	0.422	0.212	0.178	0.267	0.190	0.201	1.790	0.429	15.433	9.554	0.611

Table E3-44 Percent of Total Exposure calculated using UK (Bradley, 2011) food residue data which has been edited to discard food item categories with less than three residues.

			DMP	DEP	DiPP	DAP	DiBP	DBP	DPP	DHP	BBP	DCHP	DEHP	DOP	DINP	DIDP	DDP
NCEA		Average	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000
Wormuth		Average	96.948	98.909	98.043	97.836	97.683	97.975	91.052	96.665	97.126	94.353	96.182	94.460	93.684	93.466	94.255
Clark		Average	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000
NCEA		95th %ile	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000
Wormuth		95th %ile	98.860	99.609	99.252	99.123	98.812	99.077	96.266	98.437	98.901	96.520	98.459	97.427	96.791	97.350	97.215
Clark		95th %ile	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000

Table E3-45 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are 100% absorbed.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	1.139	2.091	1.179	8.472	258.454
Wormuth		Average	0.917	3.180	2.290	5.635	129.684
Clark		Average	0.741	1.847	2.018	5.826	136.634
NCEA		95th %ile	2.057	3.843	3.569	30.076	829.443
Wormuth		95th %ile	0.950	6.256	4.540	18.775	415.293
Clark		95th %ile	1.535	5.087	7.965	18.926	432.221

Table E3-46 Total Exposure (µg/kg-day) calculated using Page and LaCroix (1995) food residue data and the assumption that phthalates are fractionally absorbed (using Wormuth *et al.*, (2006) absorption factors).

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	0.781	1.516	0.807	4.677	142.667
Wormuth		Average	0.628	2.305	1.569	3.111	71.585
Clark		Average	0.508	1.339	1.382	3.216	75.422
NCEA		95th %ile	1.409	2.786	2.445	16.602	457.853
Wormuth		95th %ile	0.651	4.536	3.110	10.364	229.242
Clark		95th %ile	1.051	3.688	5.456	10.447	238.586

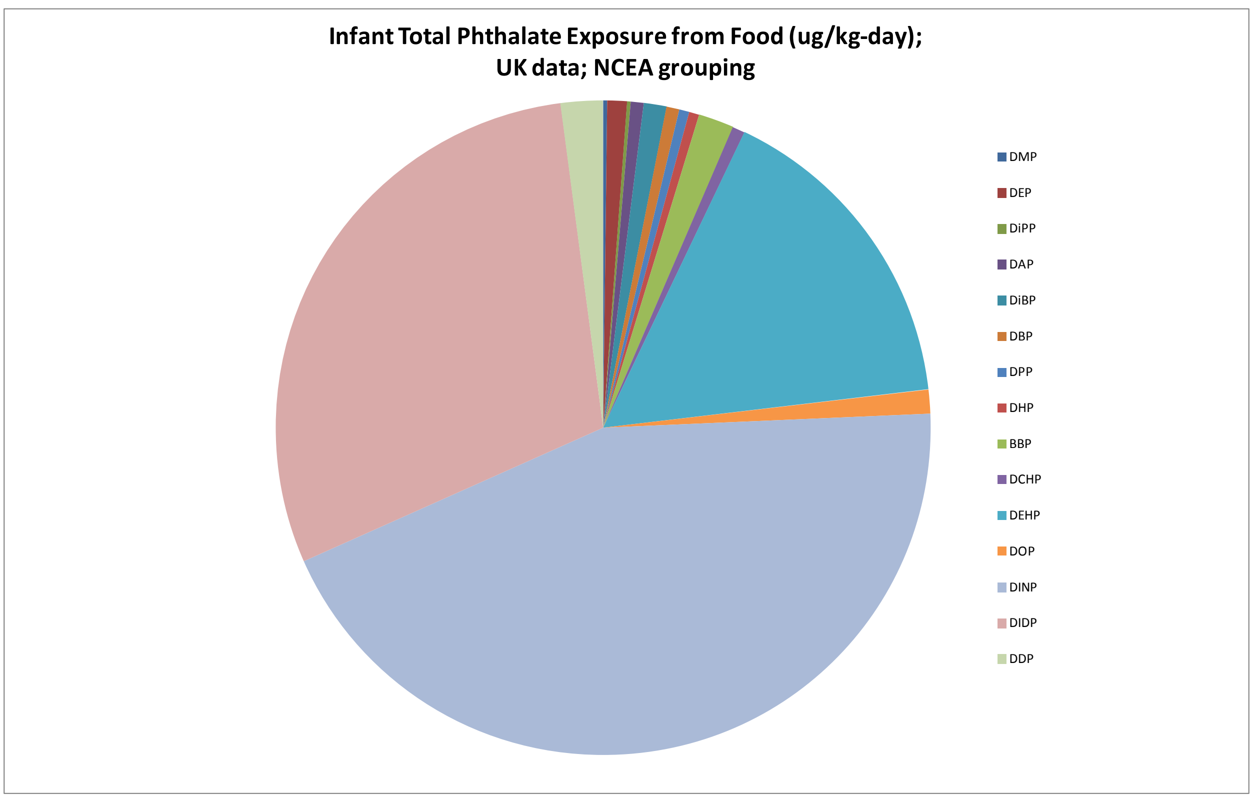
Table E3-47 Percent of Total Exposure calculated using Page and LaCroix (1995) food residue data which has been edited to discard food item categories with less than three residues.

			DEP	BBP	DBP	DEHP	DEHA
NCEA		Average	98.6	99.2	98.7	99.8	98.6
Wormuth		Average	48.5	61.8	46.0	73.9	95.3
Clark		Average	95.4	98.2	98.3	97.3	96.4
NCEA		95th %ile	99.2	99.6	99.6	99.9	99.2
Wormuth		95th %ile	43.1	76.8	54.3	88.2	97.2
Clark		95th %ile	97.8	99.3	99.6	99.2	97.8

4.3 Population-based Dietary Exposures and the Relative Contribution of Various Phthalates

4.3.1 Infant Total Phthalate Exposure from Food, Phthalate Relative Contribution (assuming 100% phthalate absorption)

Figure E3-1 Infant total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.



860 **Figure E3-2** Infant total phthalate exposure from food (ug/kg-day); UK data; Clark grouping.

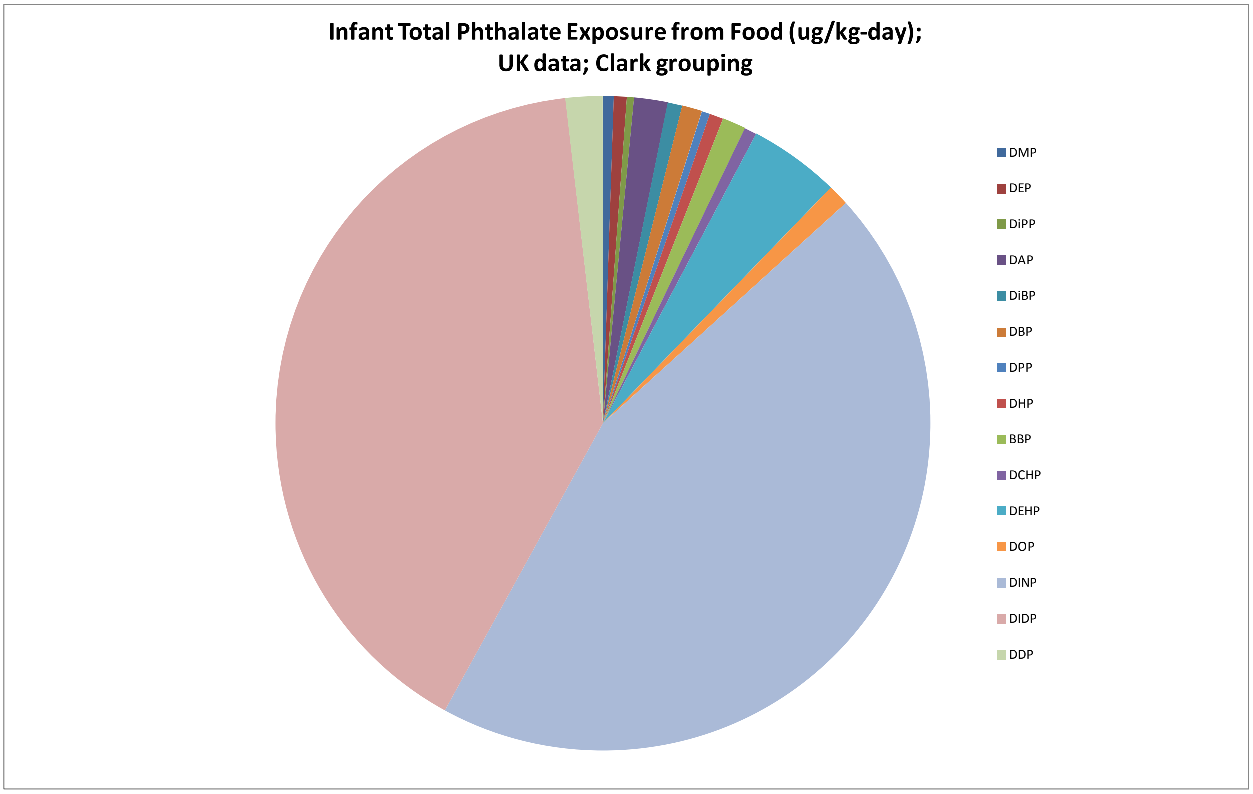


Figure E3-3 Infant total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

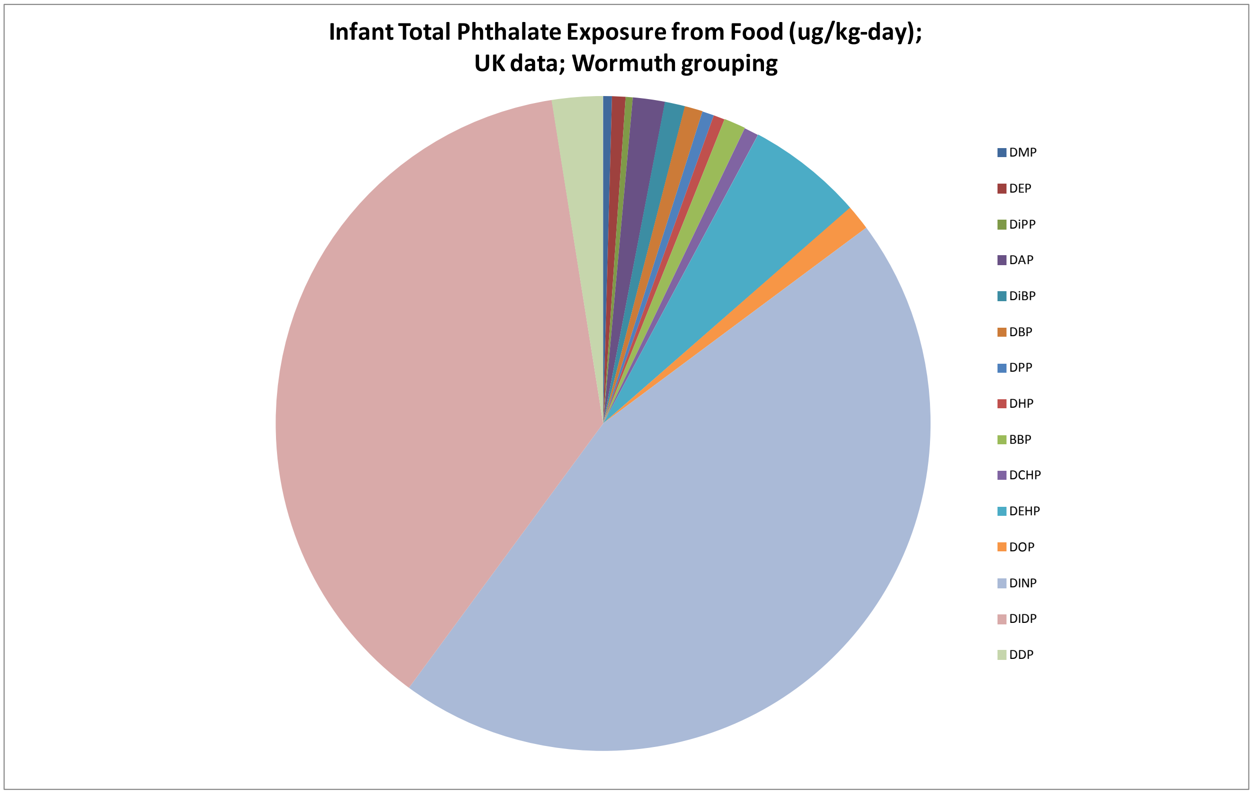


Figure E3-4 Infant total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

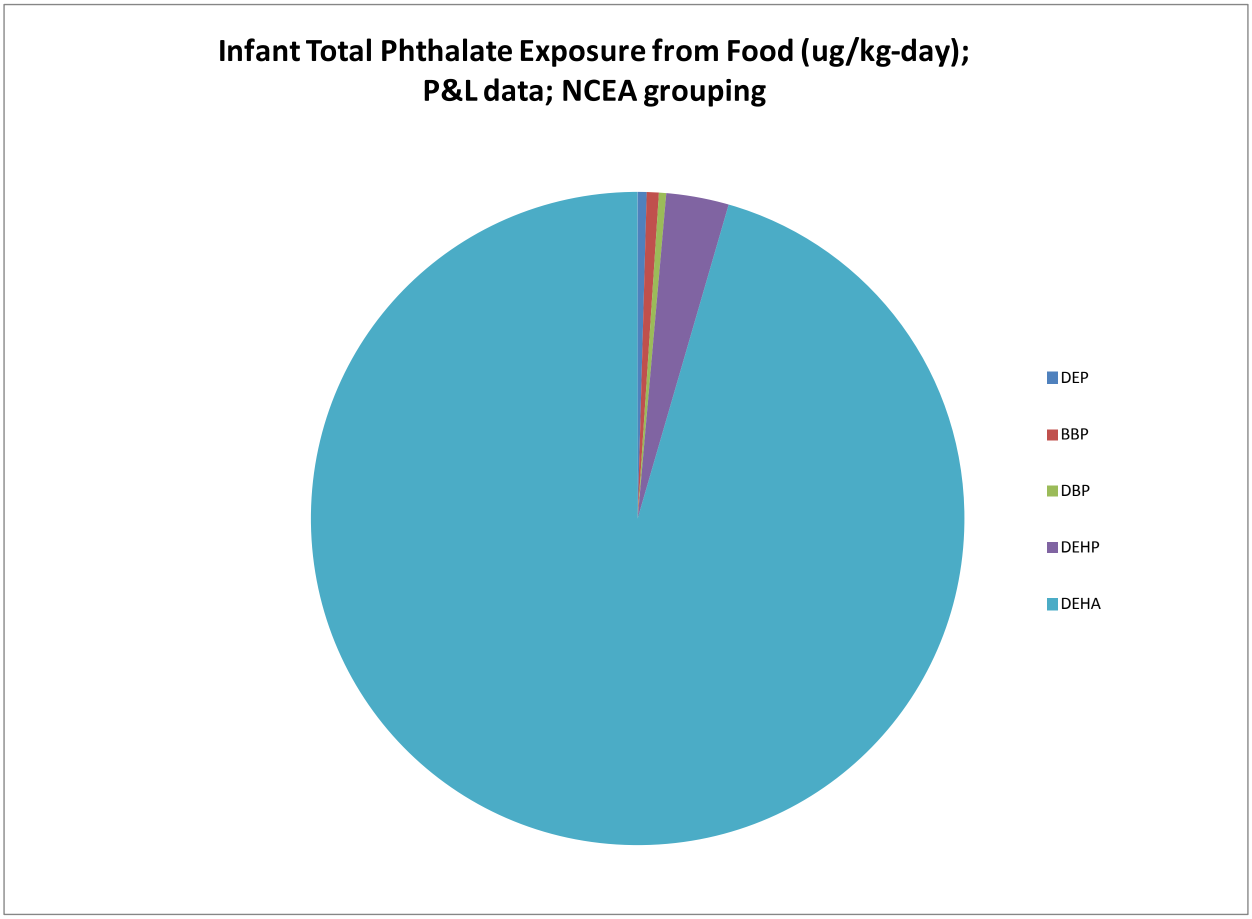


Figure E3-5 Infant total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

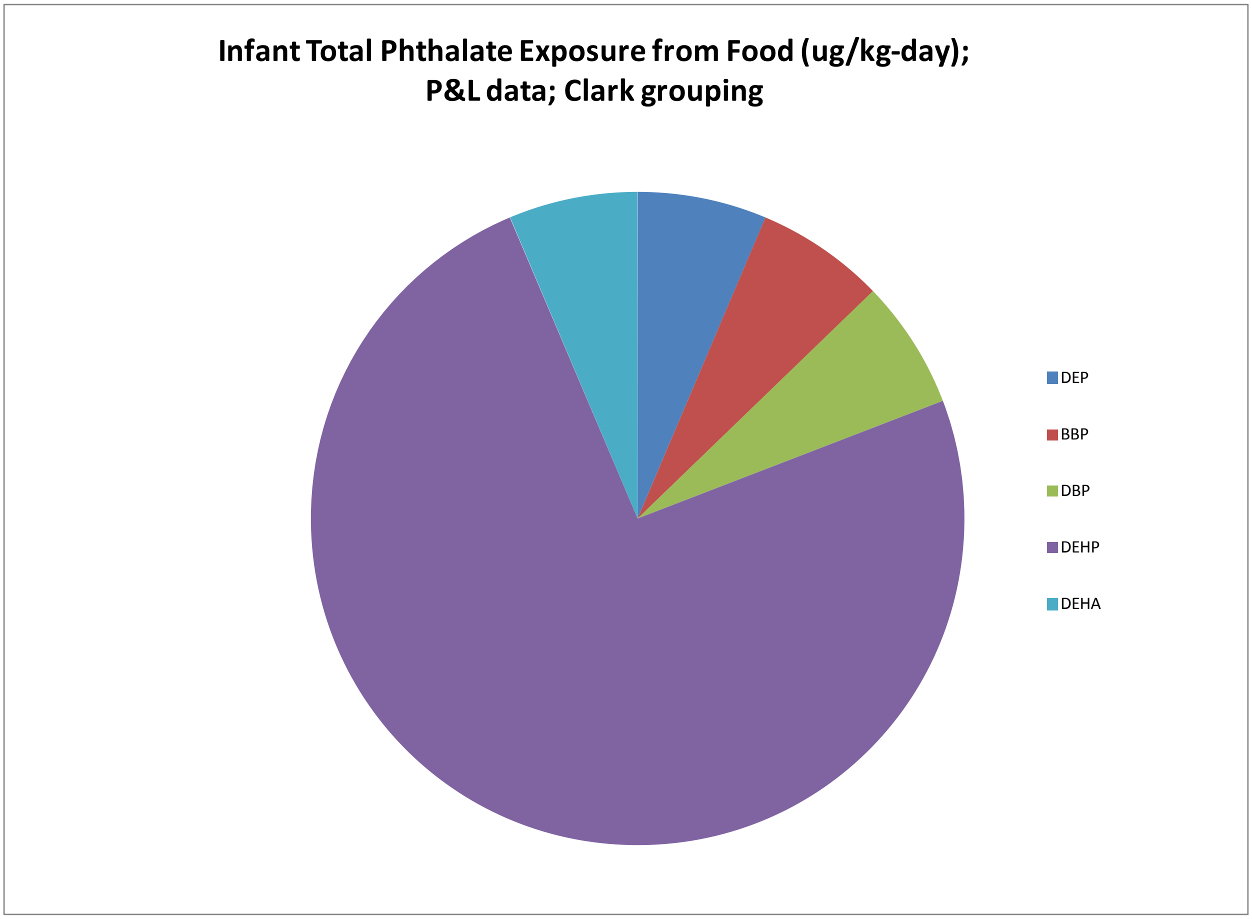
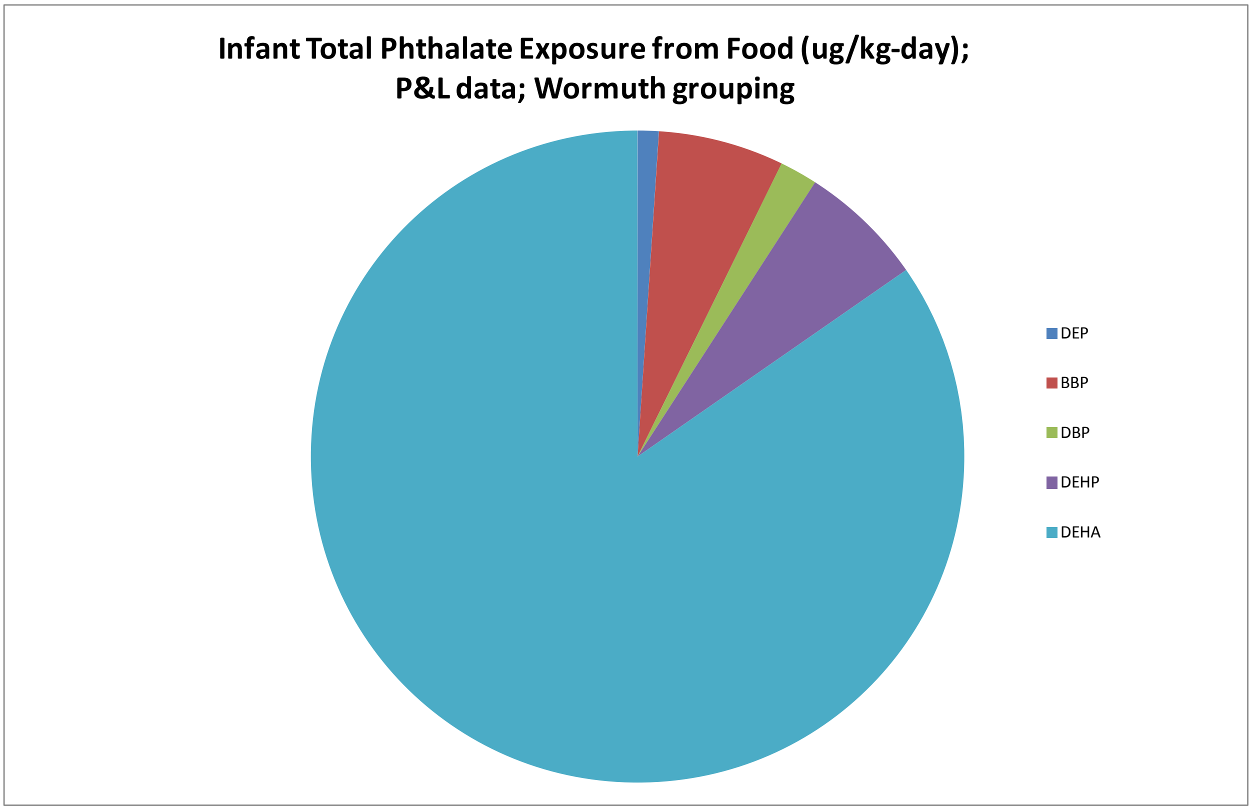


Figure E3-6 Infant total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.3.2 Toddler Total Phthalate Exposure from Food, Phthalate Relative Contribution (assuming 100% phthalate absorption)

Figure E3-7 Toddler total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.

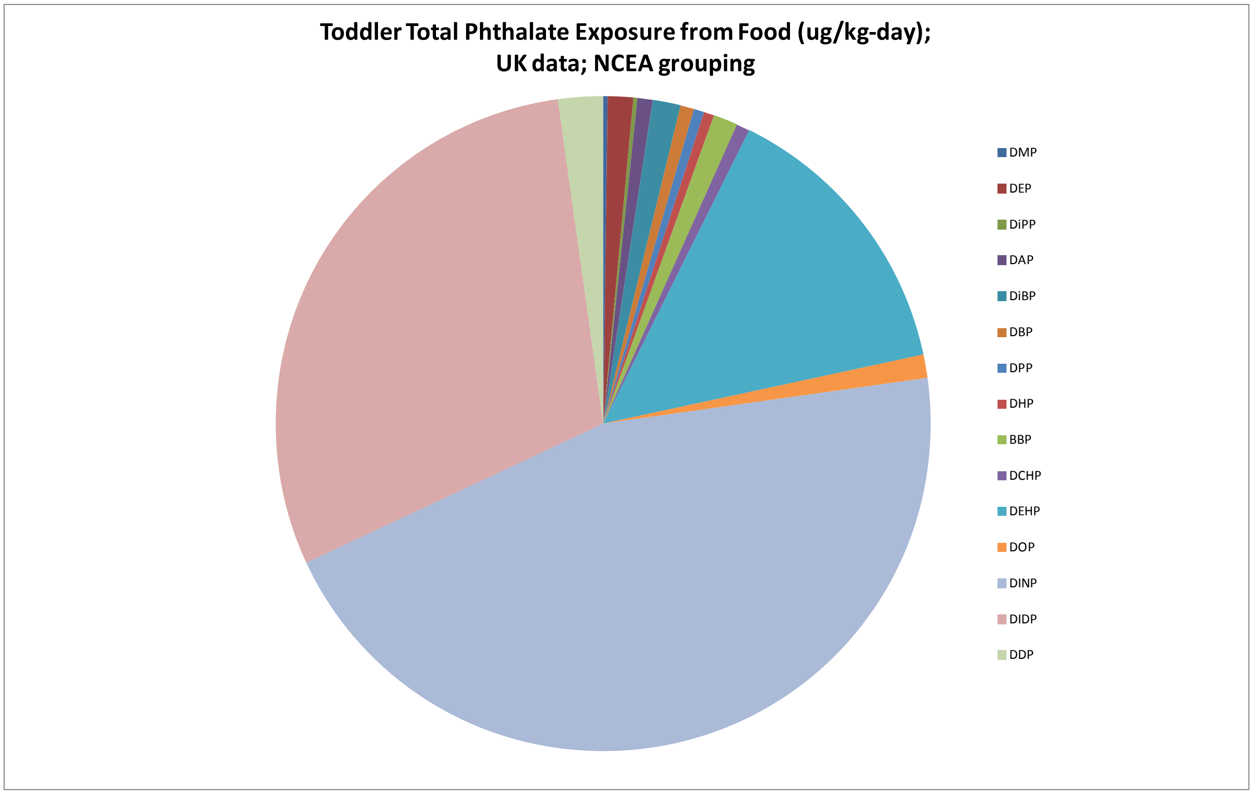


Figure E3-8 Toddler phthalate exposure from food (ug/kg-day); UK data; Clark grouping.

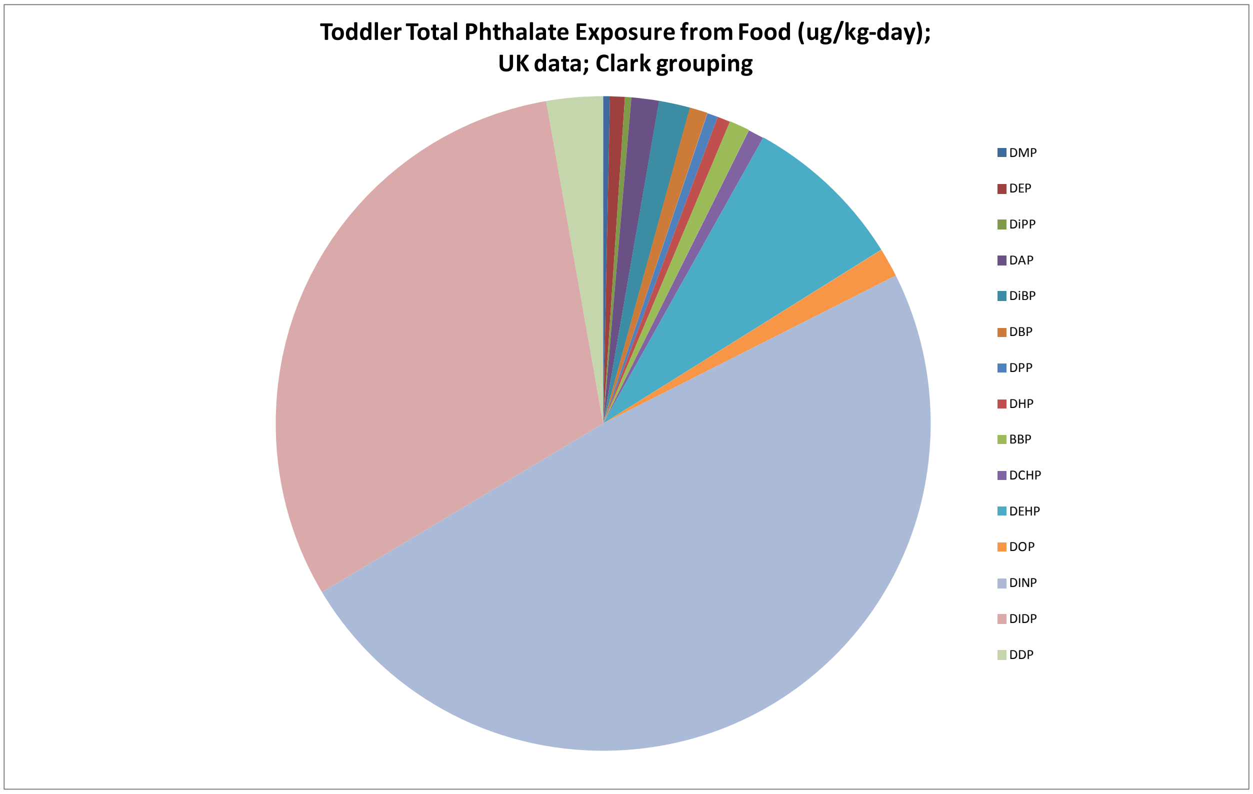


Figure E3-9 Toddler total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

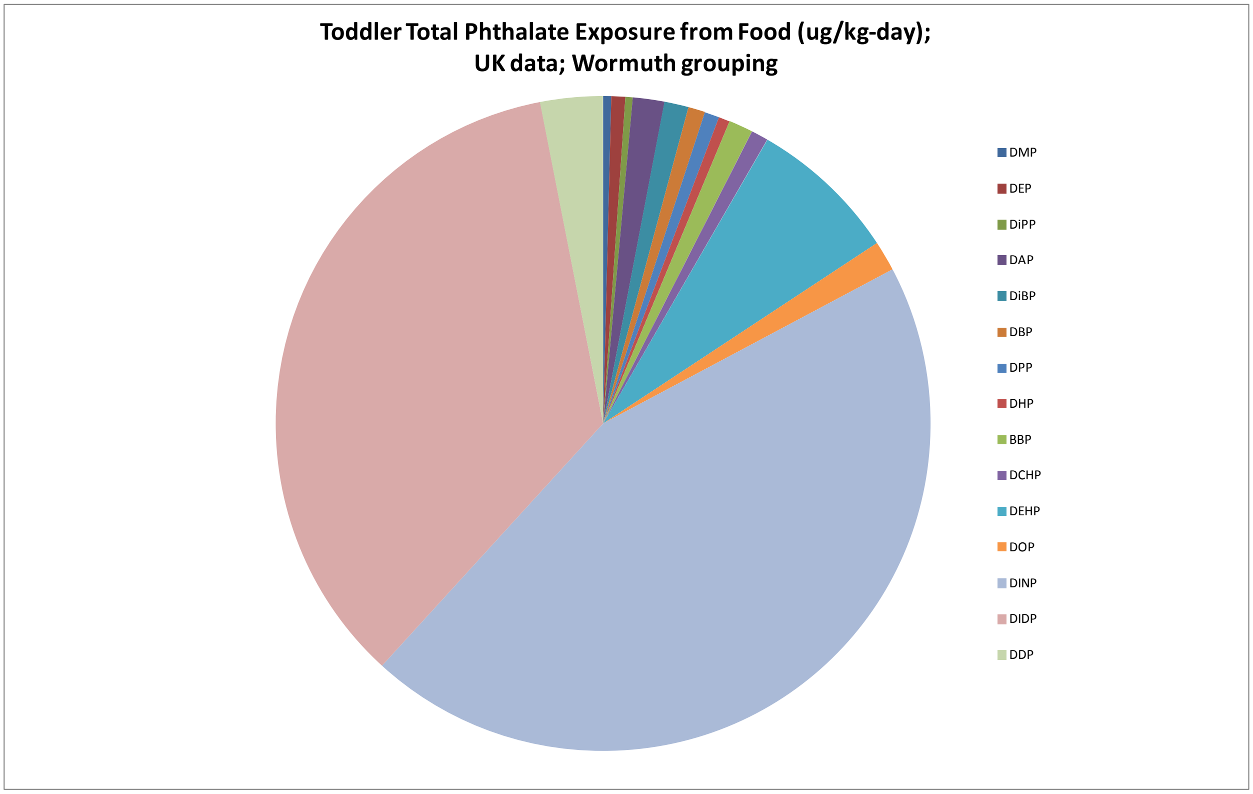


Figure E3-10 Toddler total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

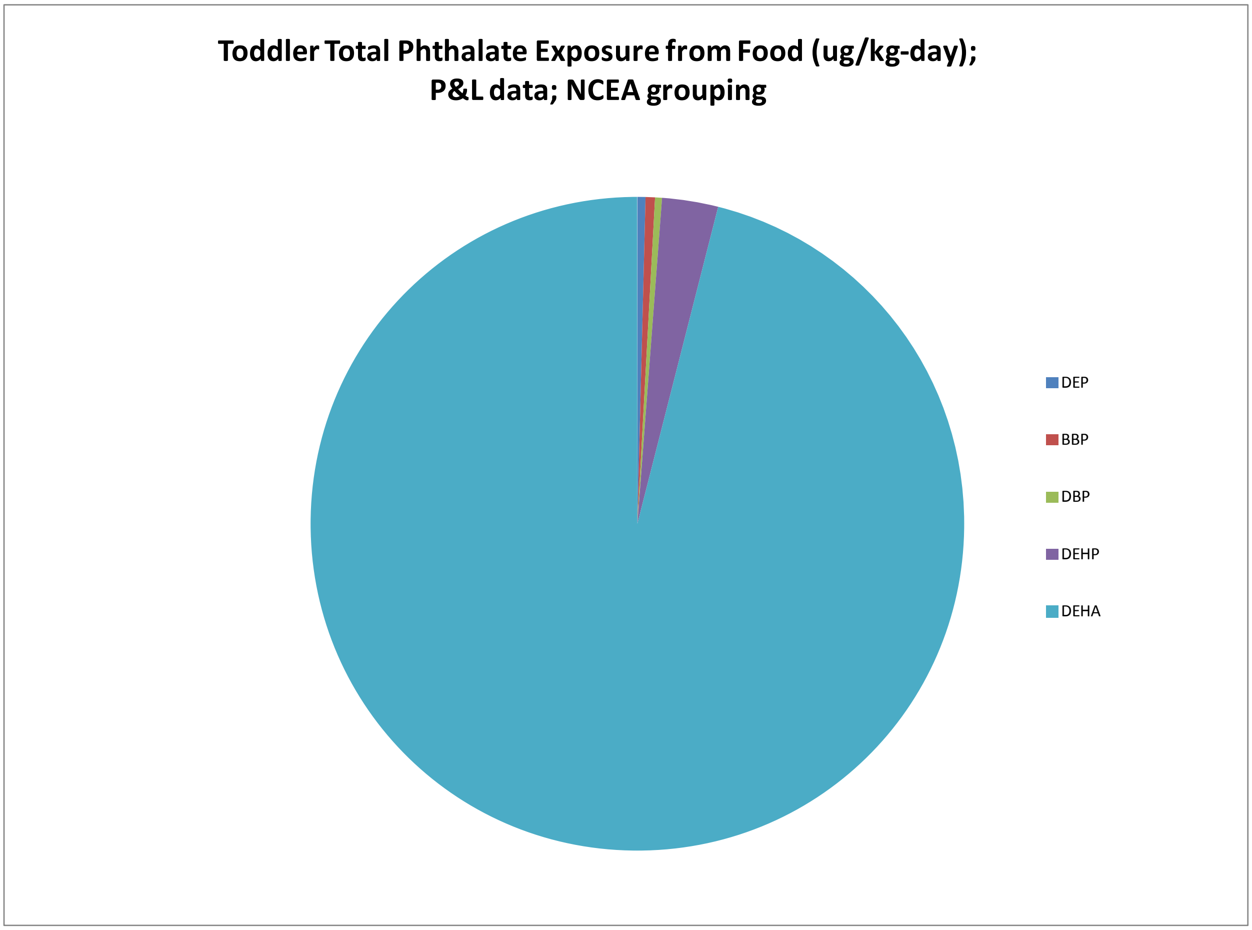


Figure E3-11 Toddler total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

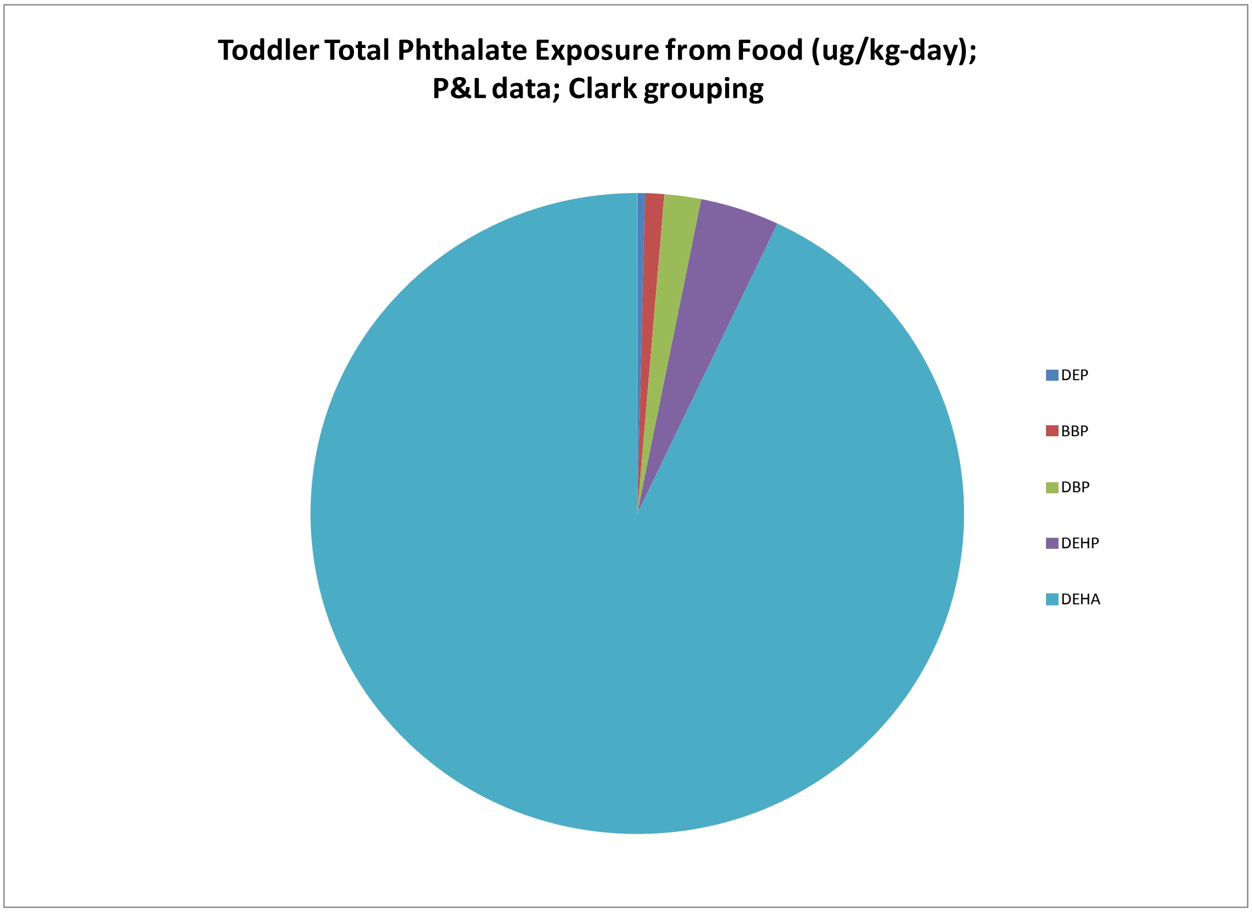
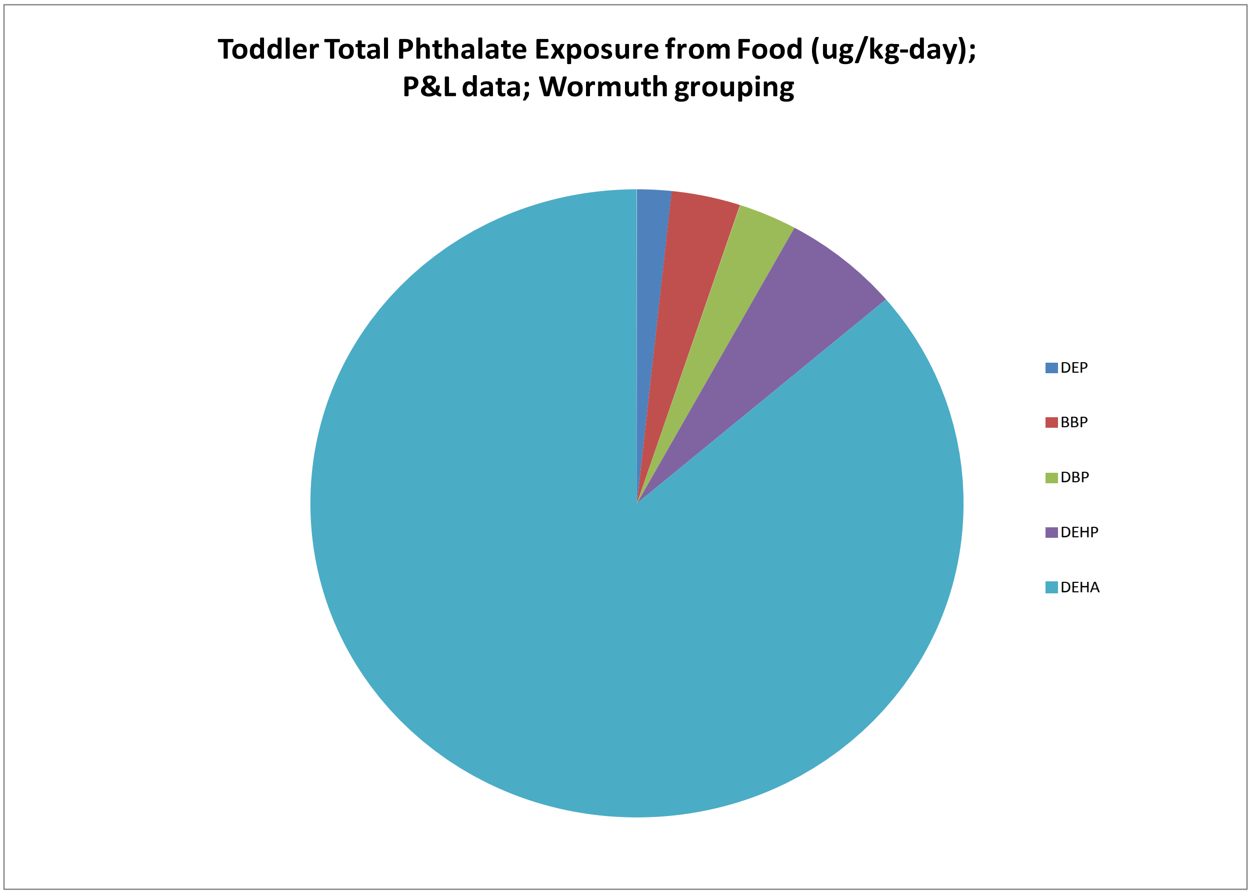


Figure E3-12 Toddler total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.3.3 Child Total Phthalate Exposure from Food, Phthalate Relative Contribution (assuming 100% phthalate absorption)

Figure E3-13 Children total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.

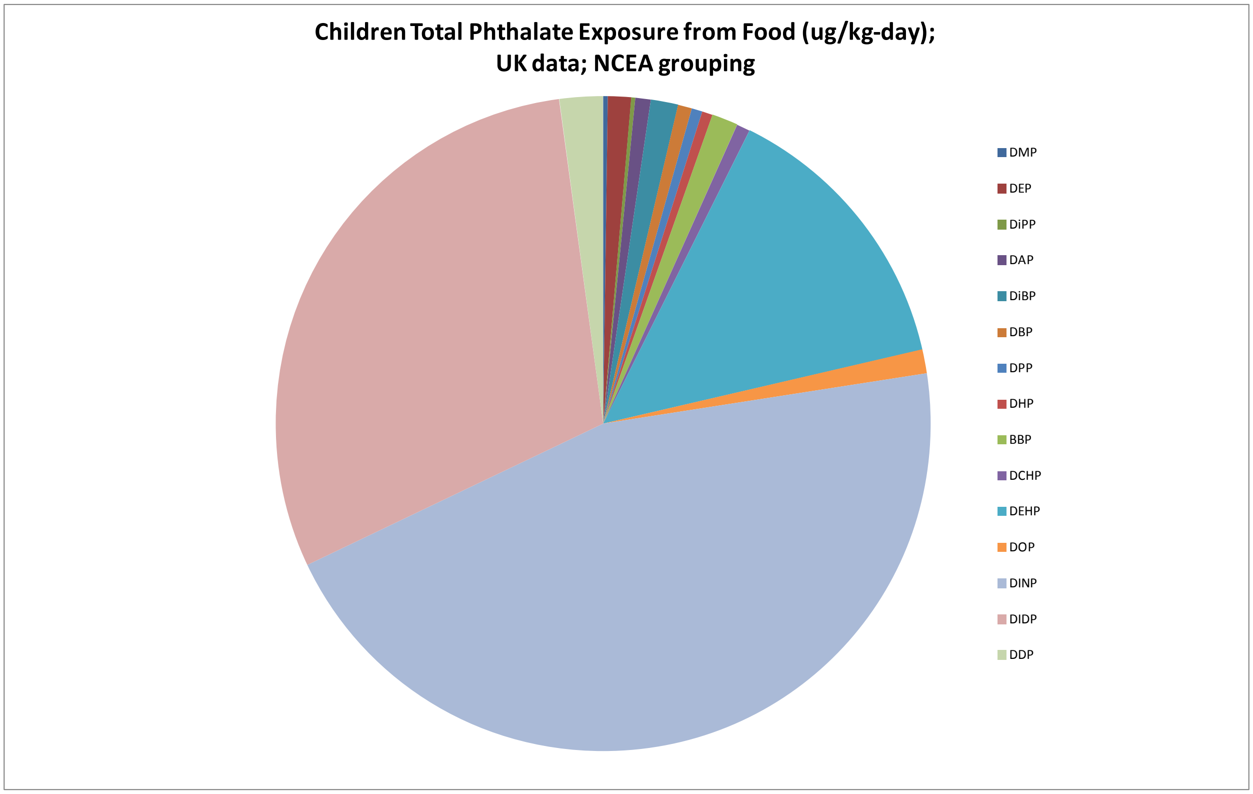


Figure E3-14 Children total phthalate exposure from food (ug/kg-day); UK data; Clark grouping.

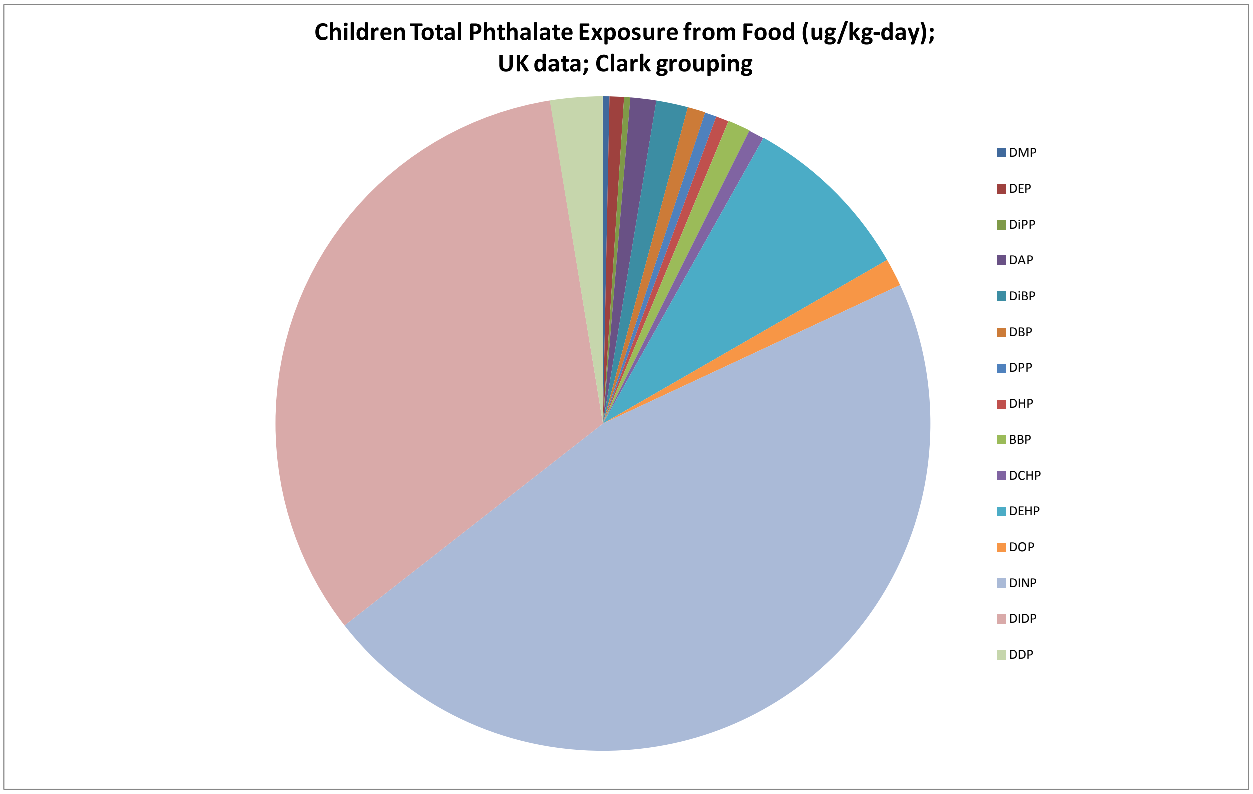


Figure E3-15 Children total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

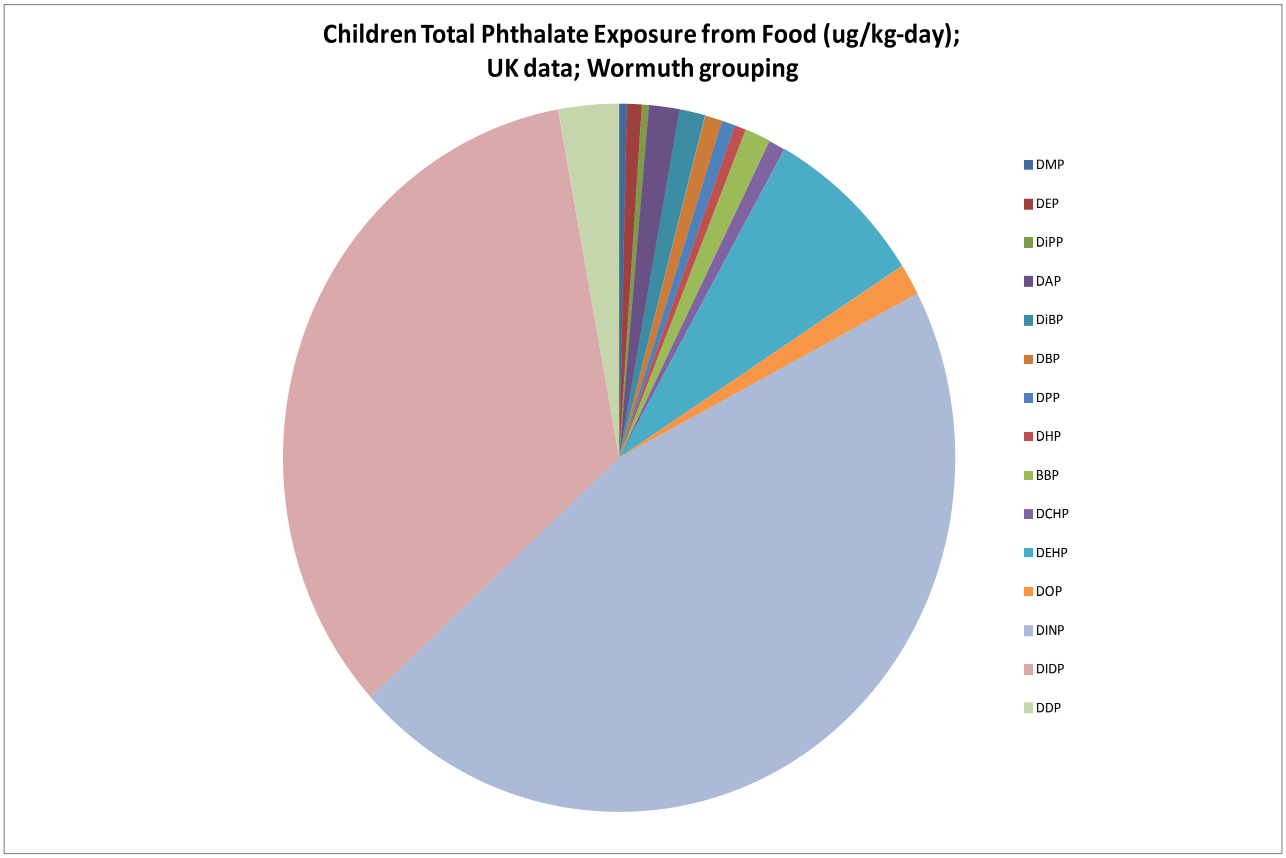


Figure E3-16 Children total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

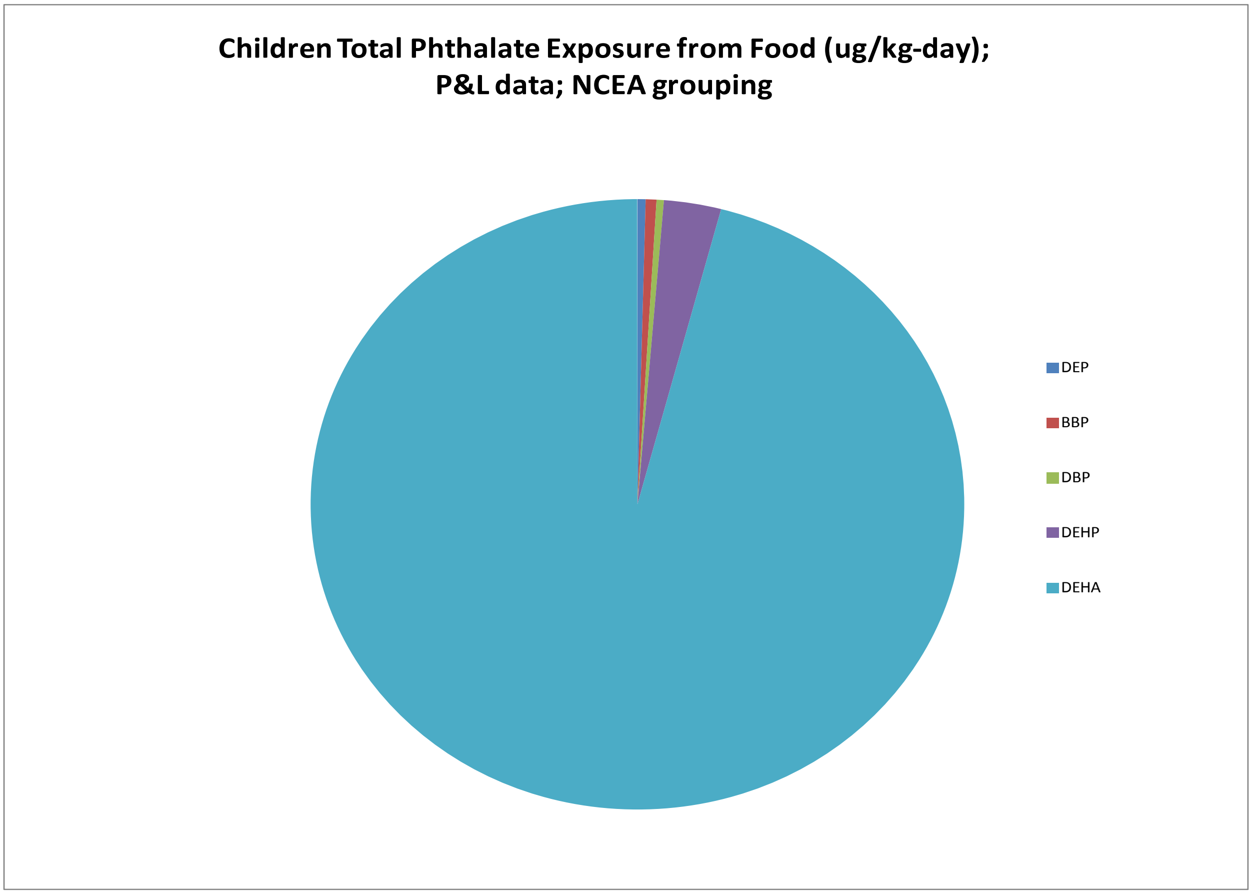


Figure E3-17 Children total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

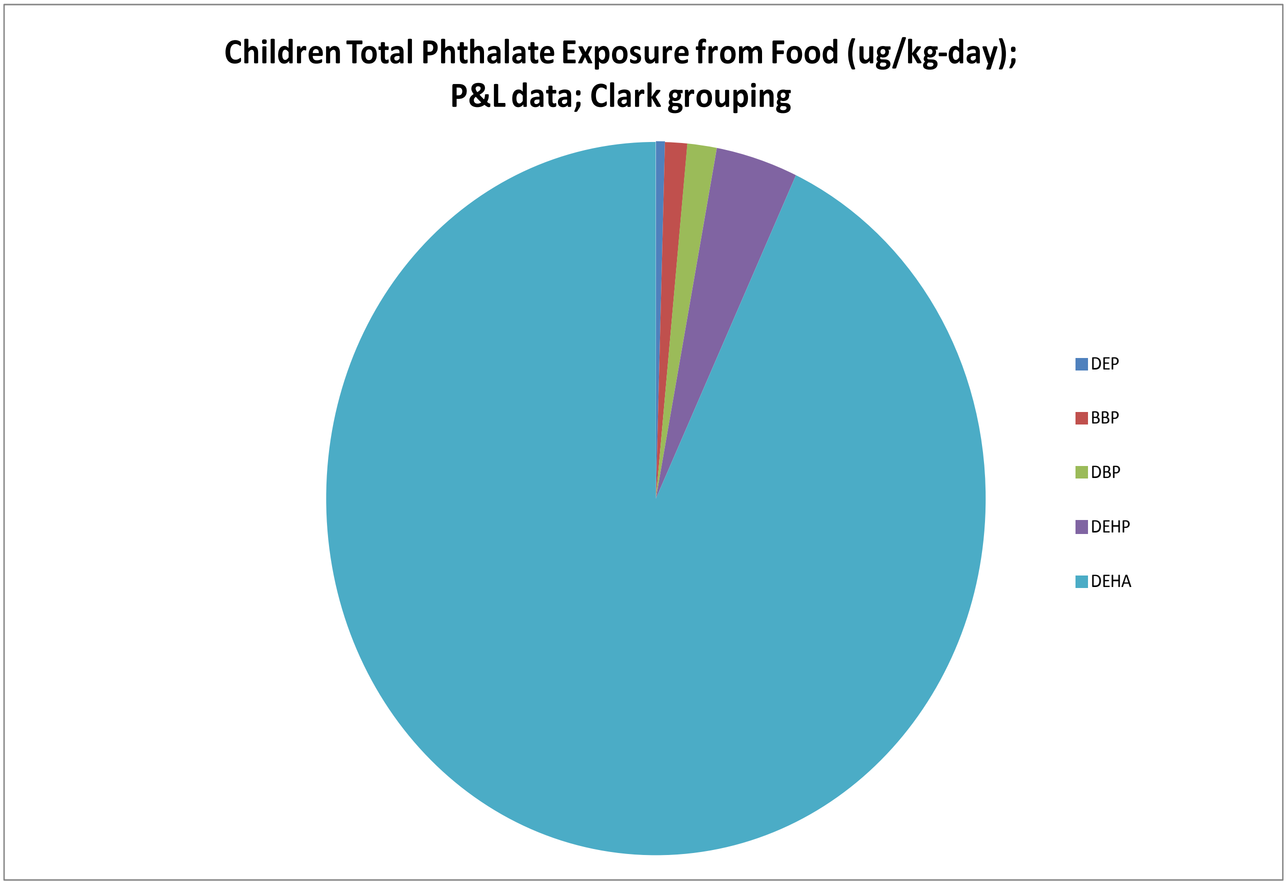
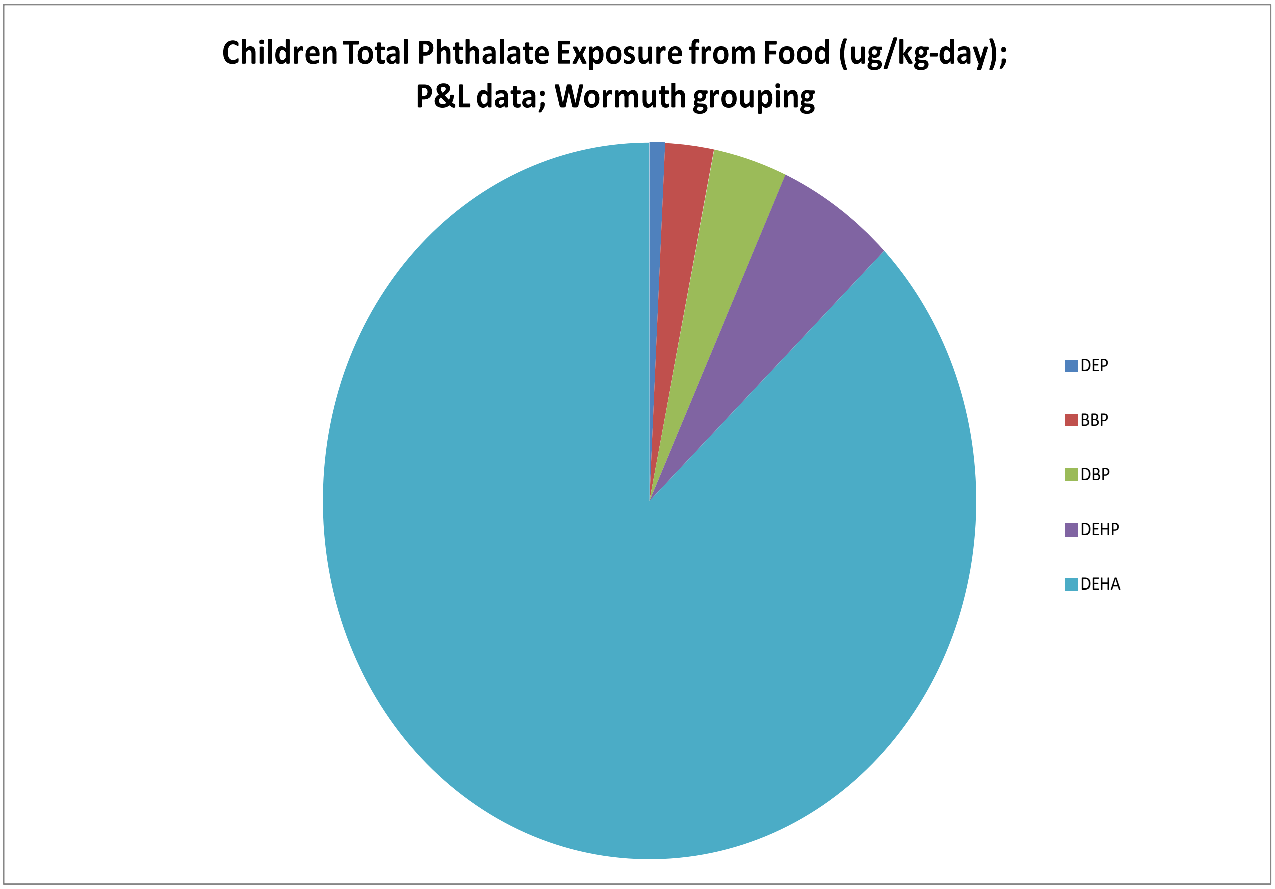


Figure E3-18 Children total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.3.4 Female Teen Total Phthalate Exposure from Food, Phthalate Relative Contribution (assuming 100% phthalate absorption)

Figure E3-19 Female teen total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.

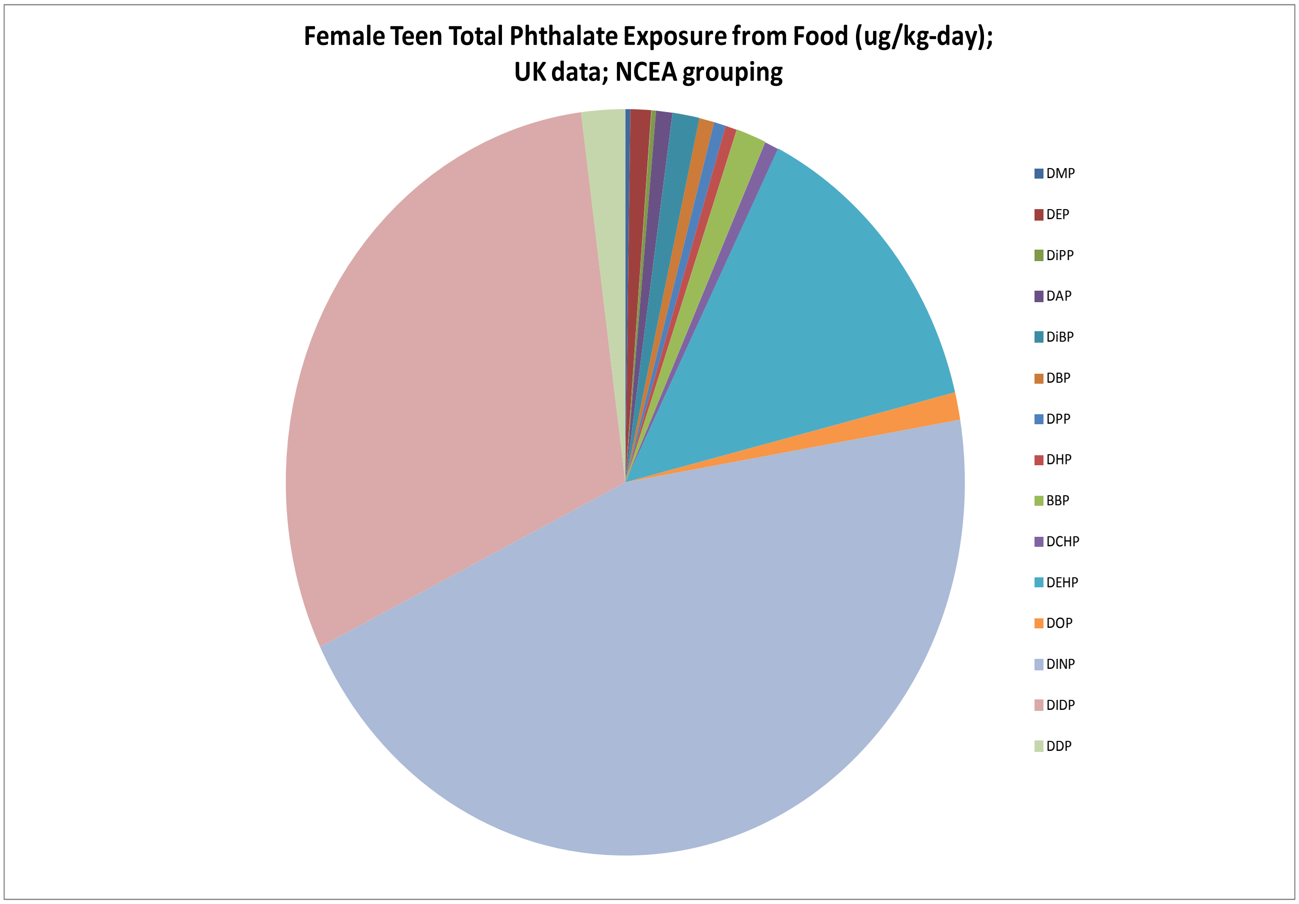


Figure E3-20 Female teen total phthalate exposure from food (ug/kg-day); UK data; Clark grouping.

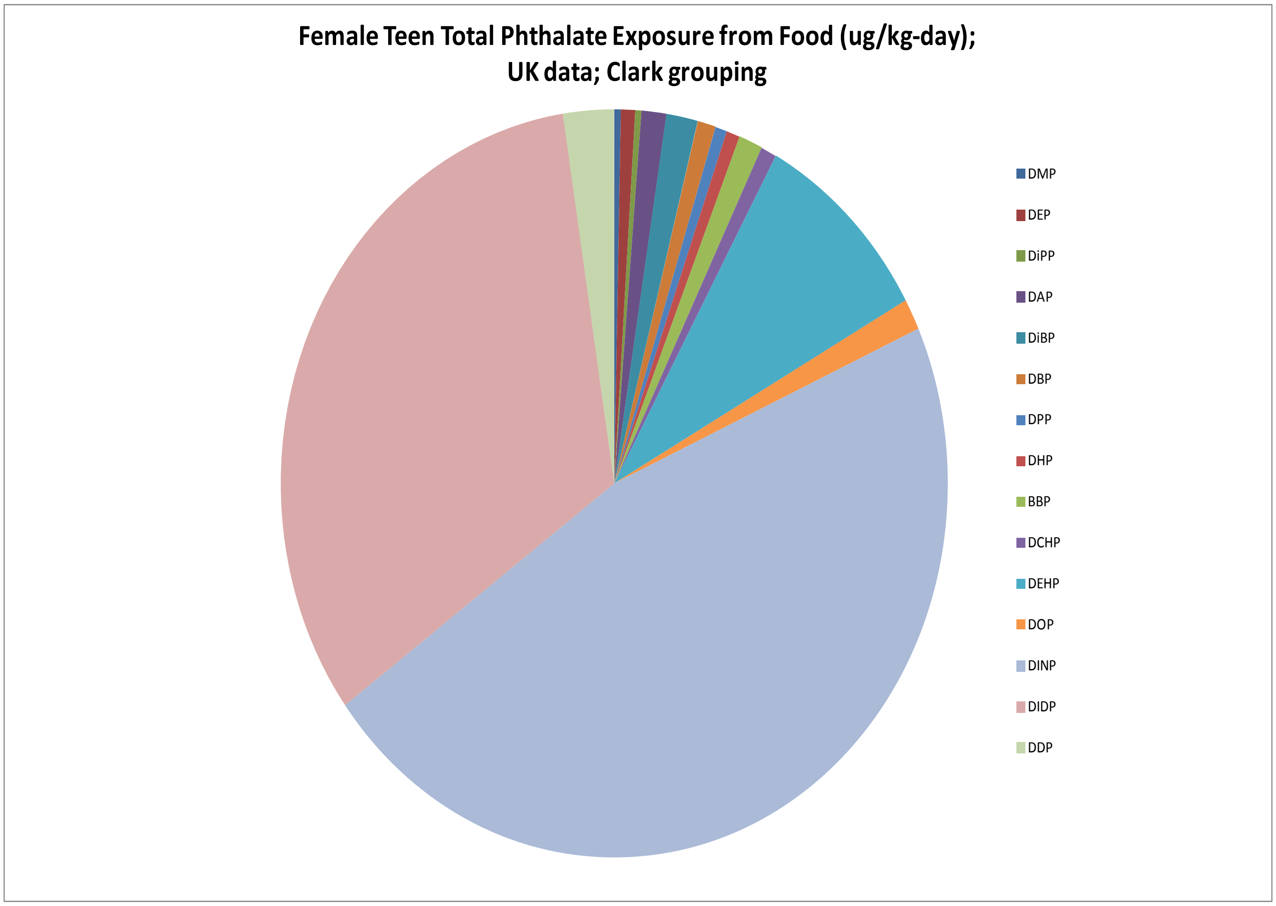


Figure E3-21 Female teen total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

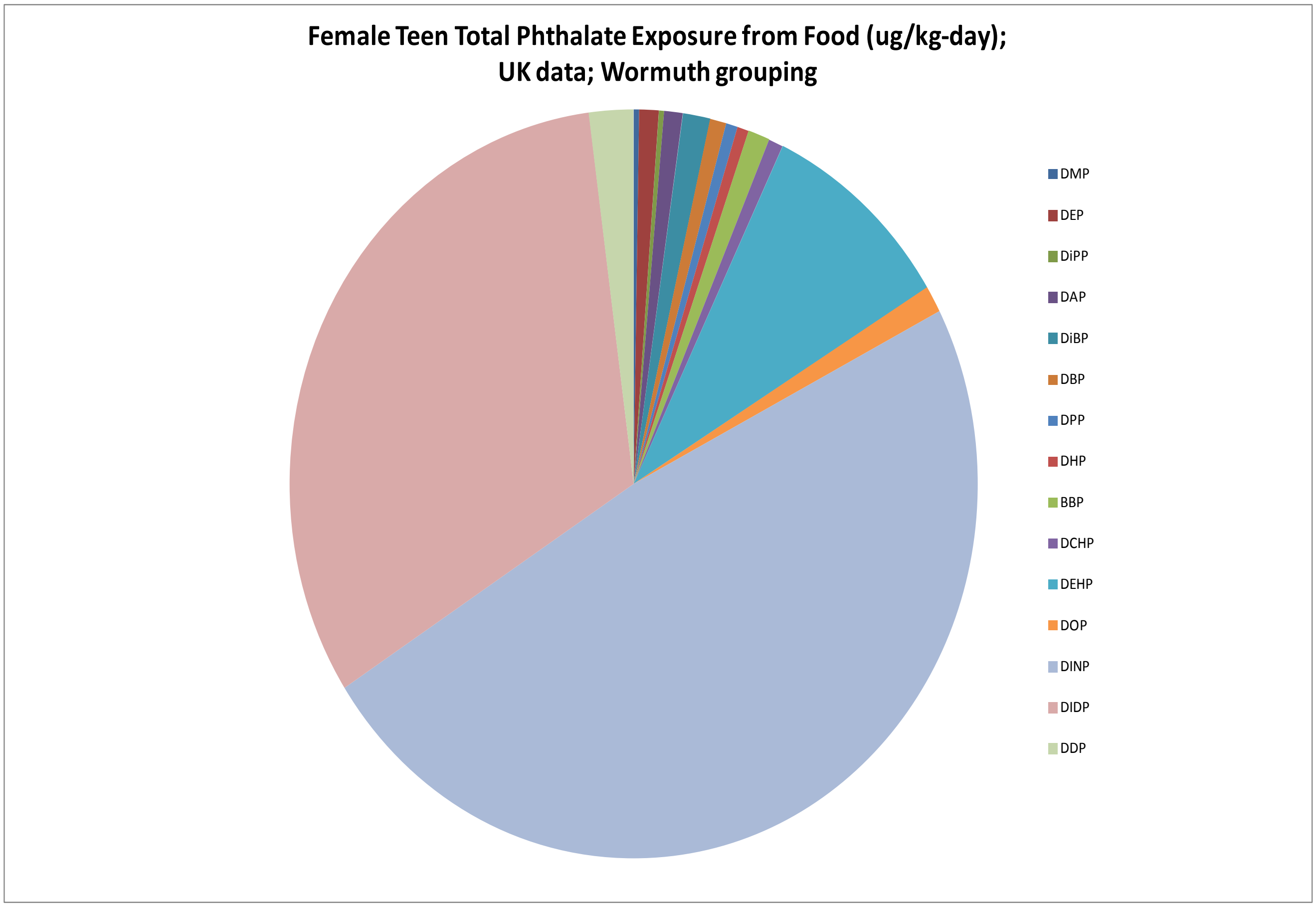


Figure E3-22 Female teen total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

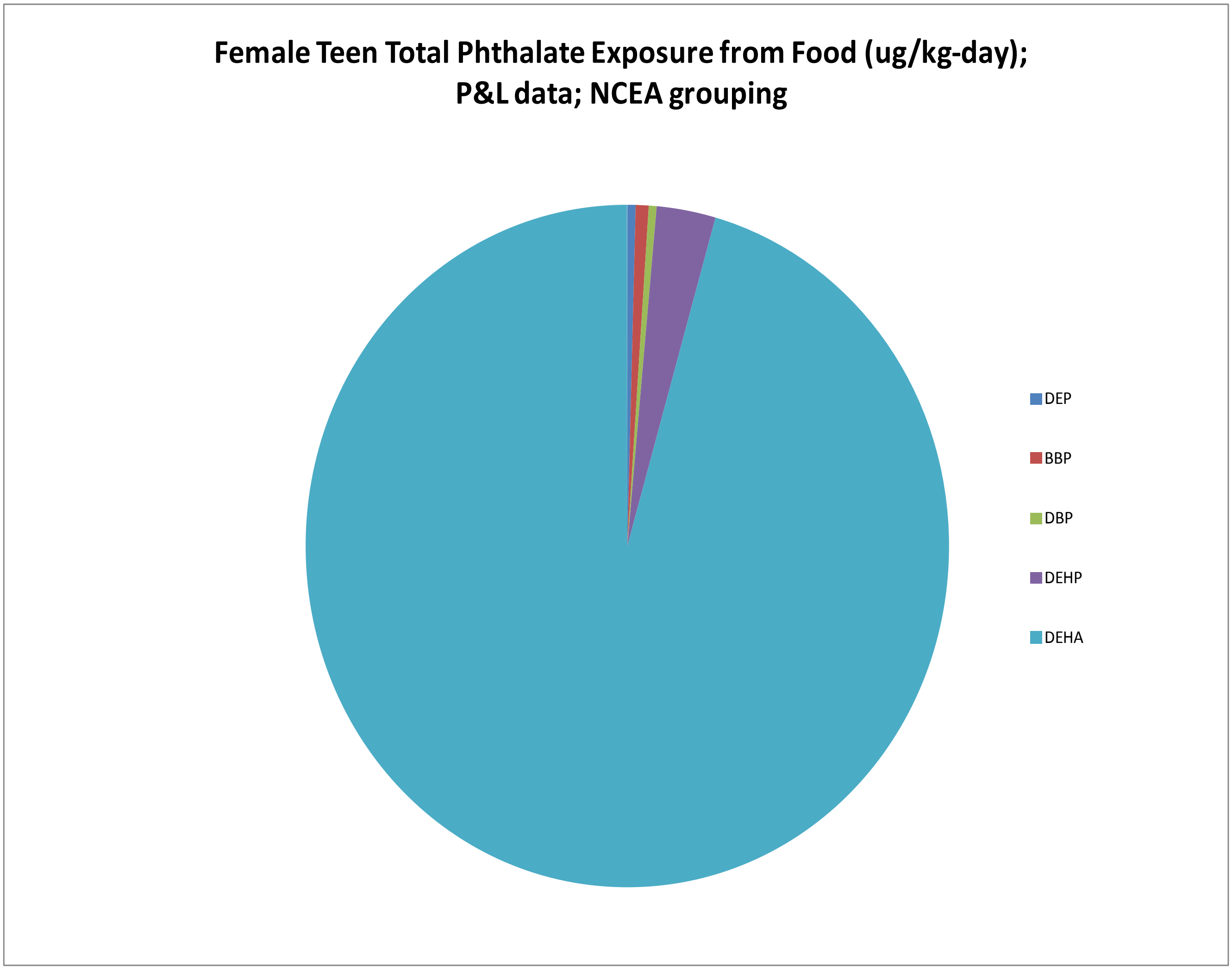


Figure E3-23 Female teen total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

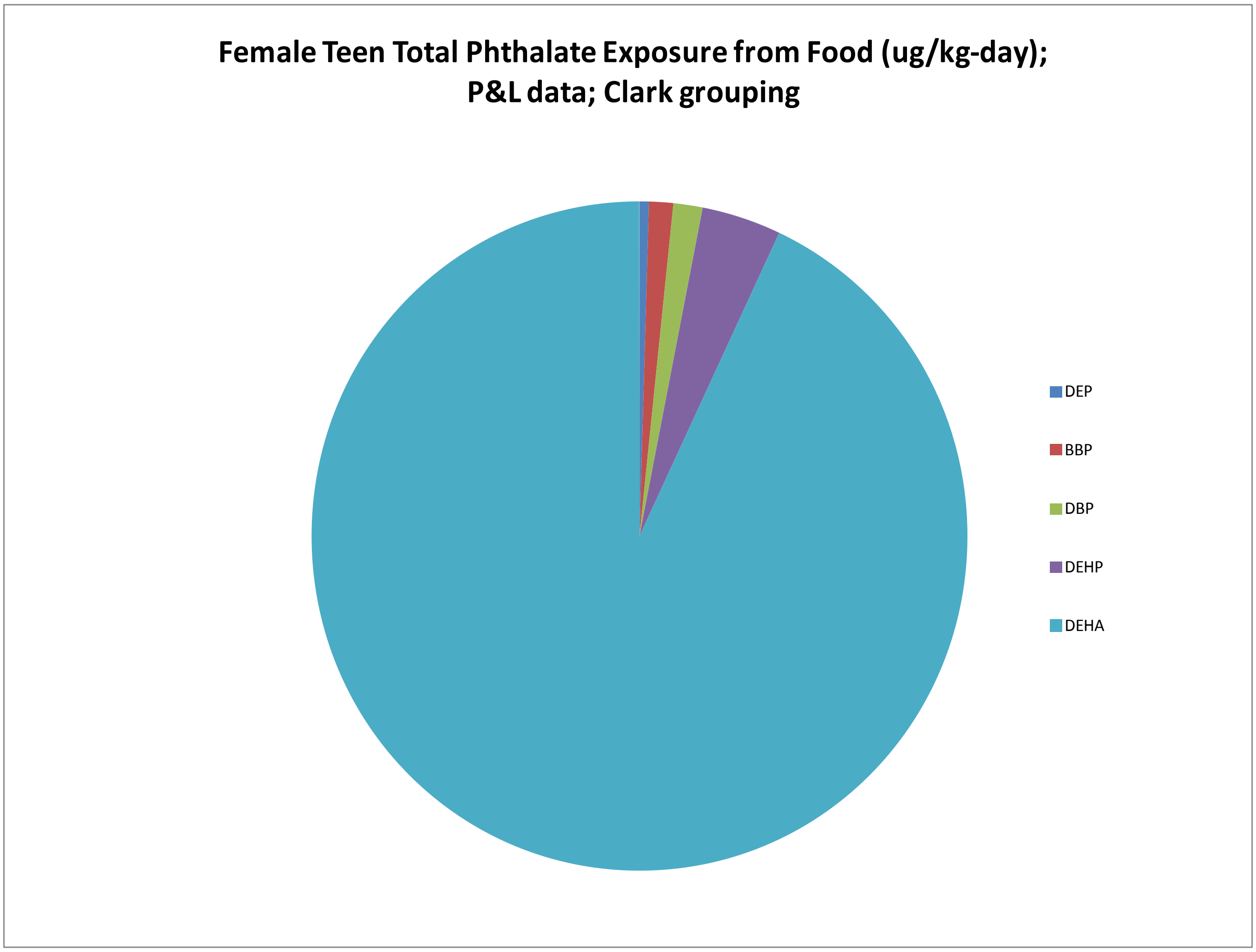
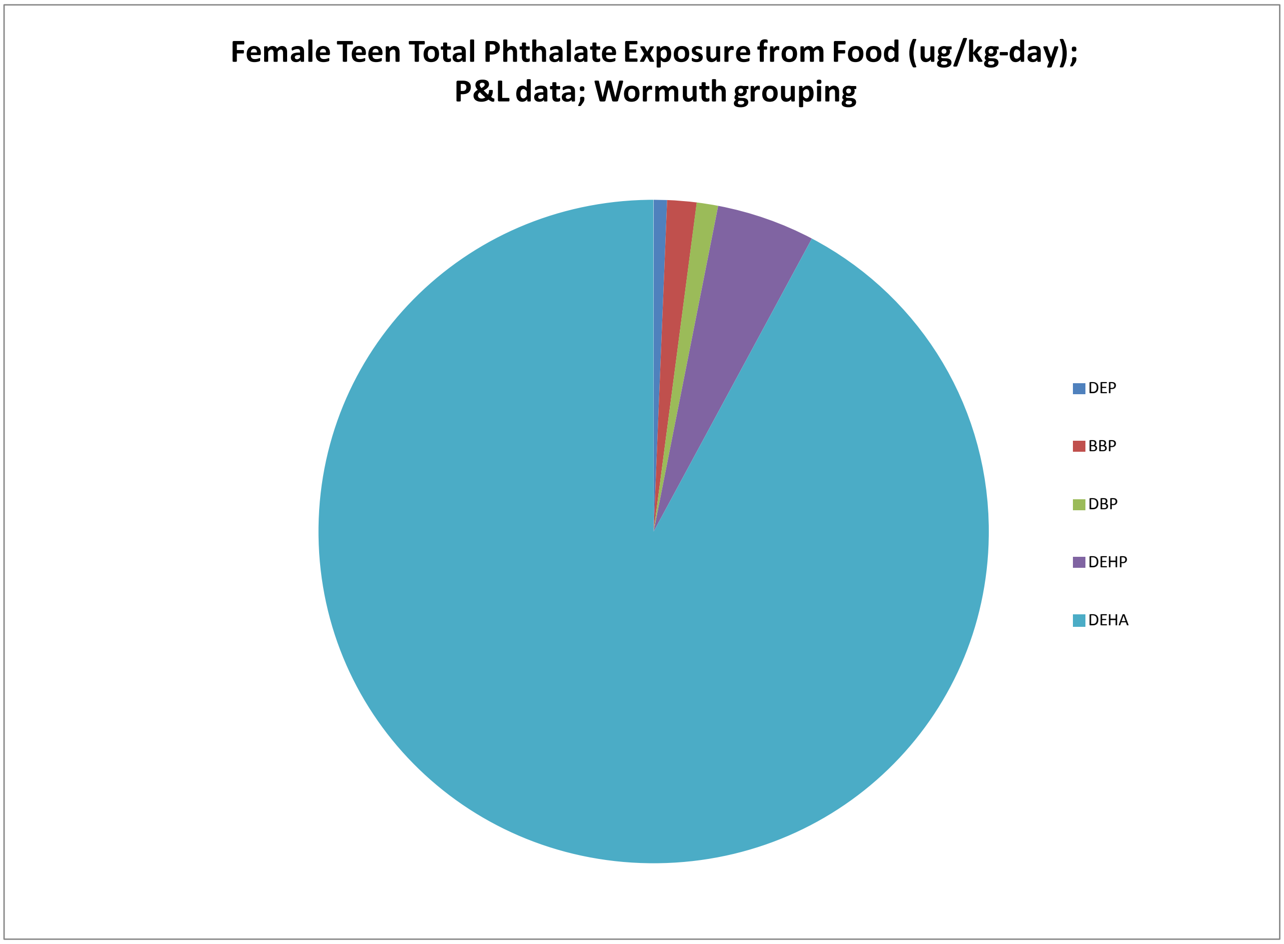


Figure E3-24 Female teen total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.3.5 Male Teen Total Phthalate Exposure from Food, Phthalate Relative Contribution (assuming 100% phthalate absorption)

Figure E3-25 Male teen total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.

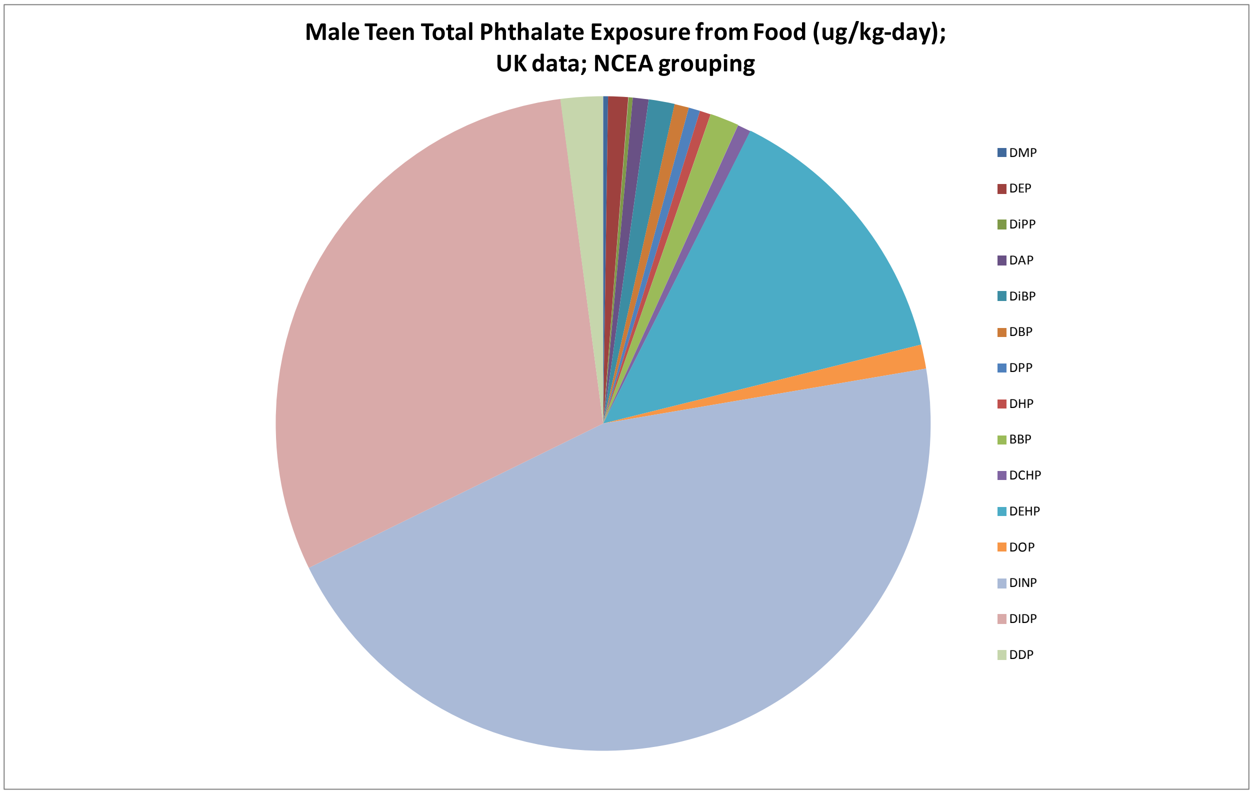


Figure E3-26 Male teen total phthalate exposure from food (ug/kg-day); UK data; Clark grouping.

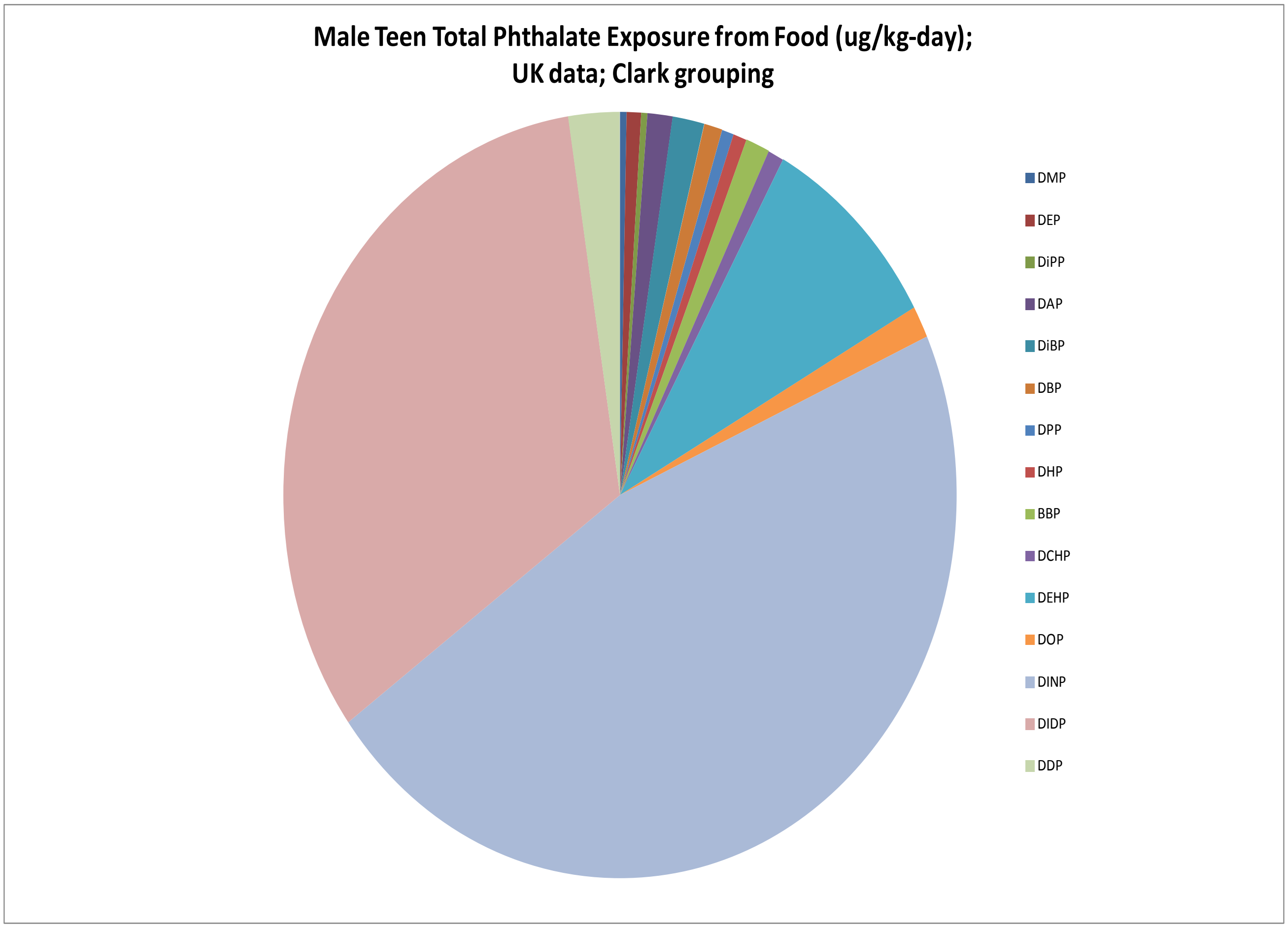


Figure E3-27 Male teen total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

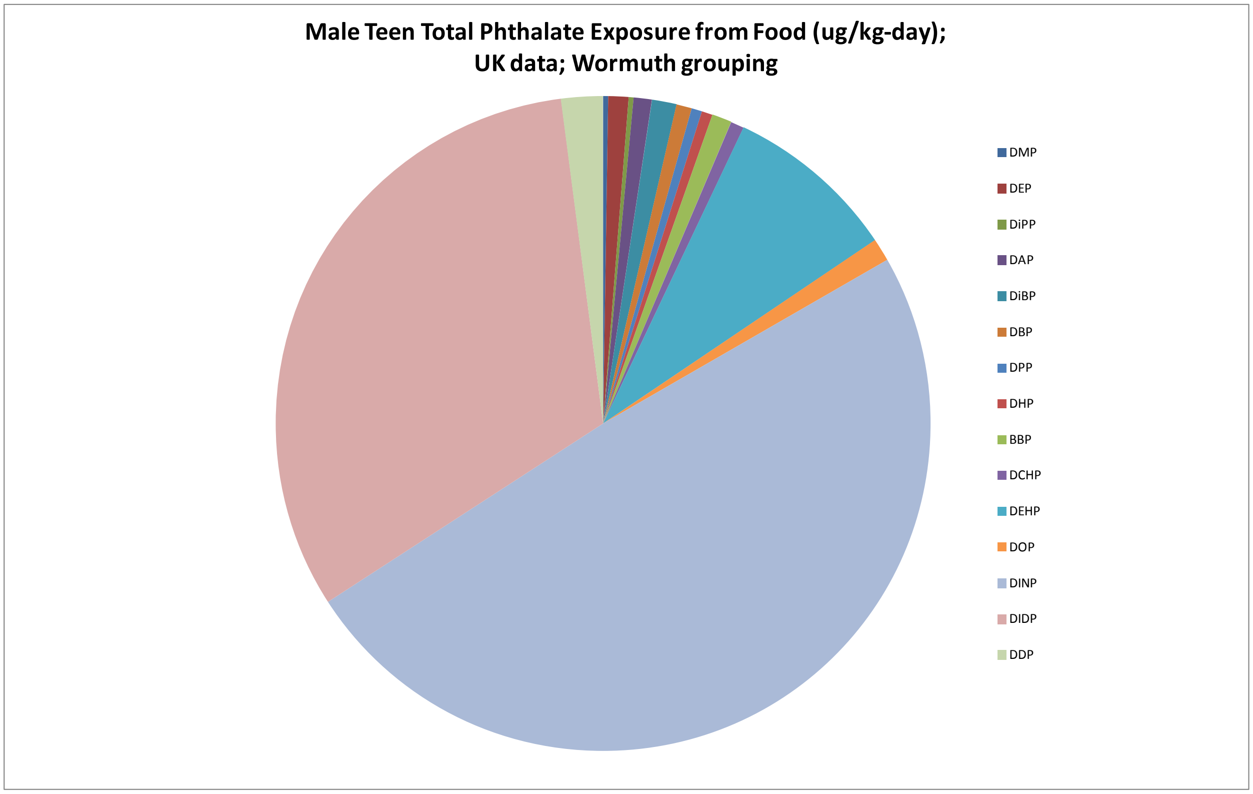


Figure E3-28 Male teen total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

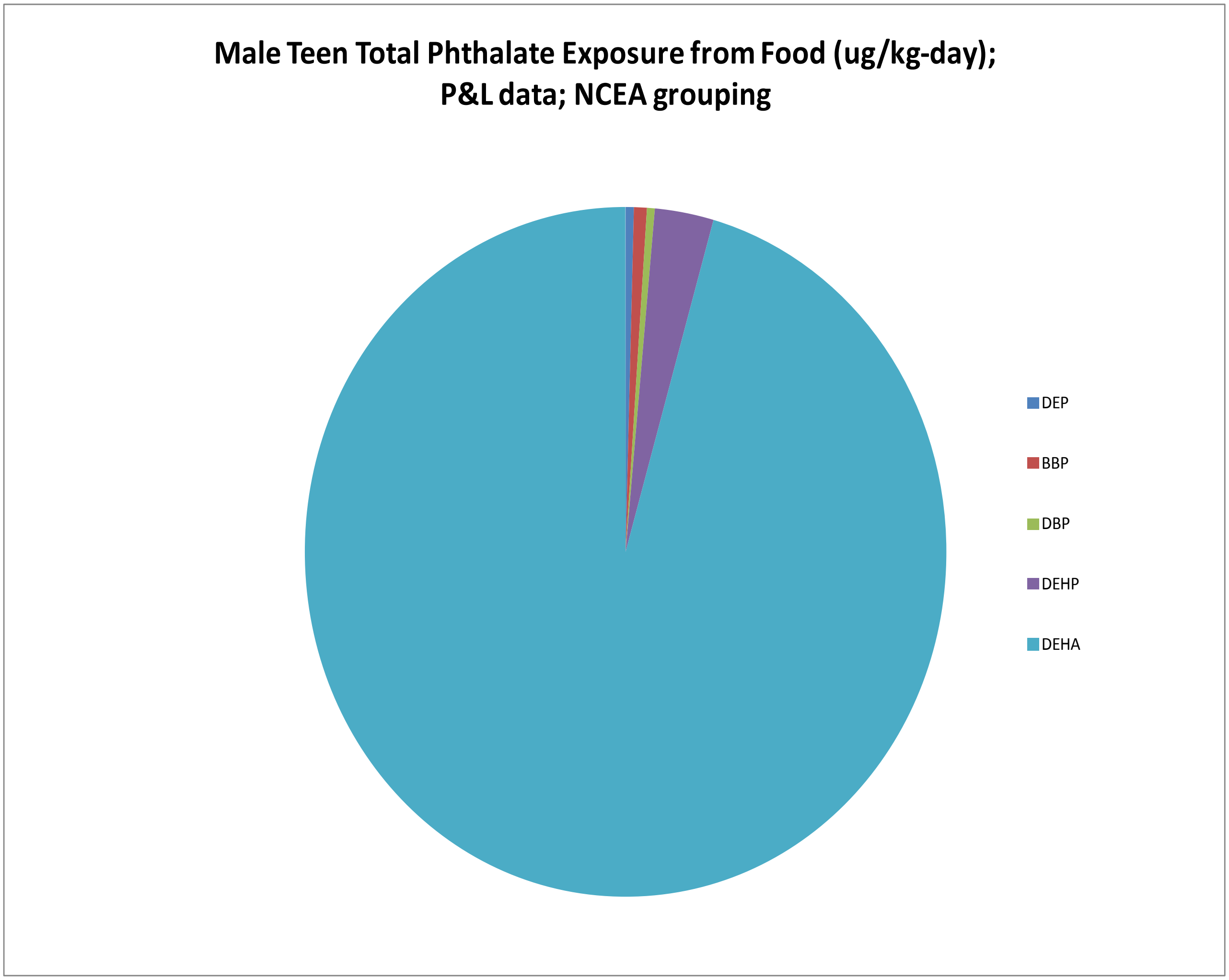


Figure E3-29 Male teen total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

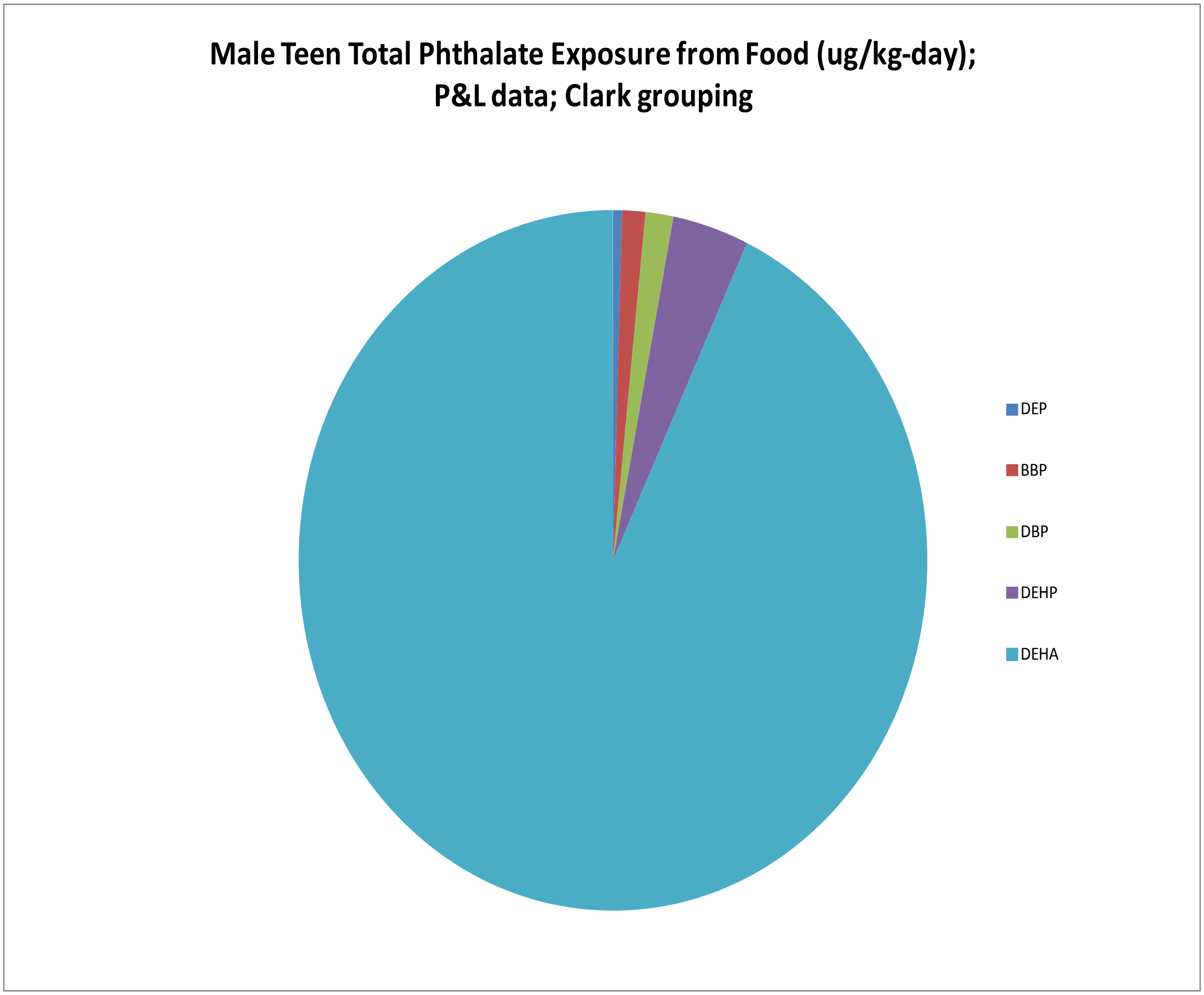
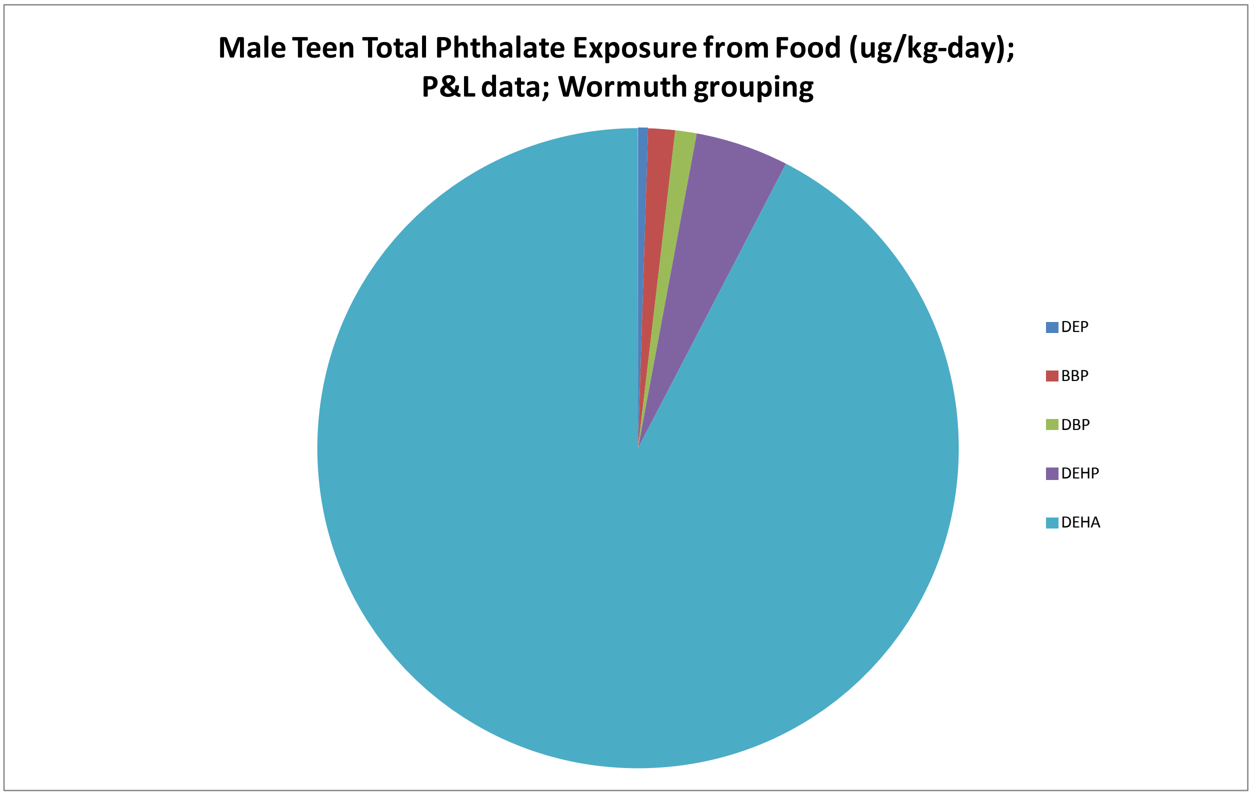
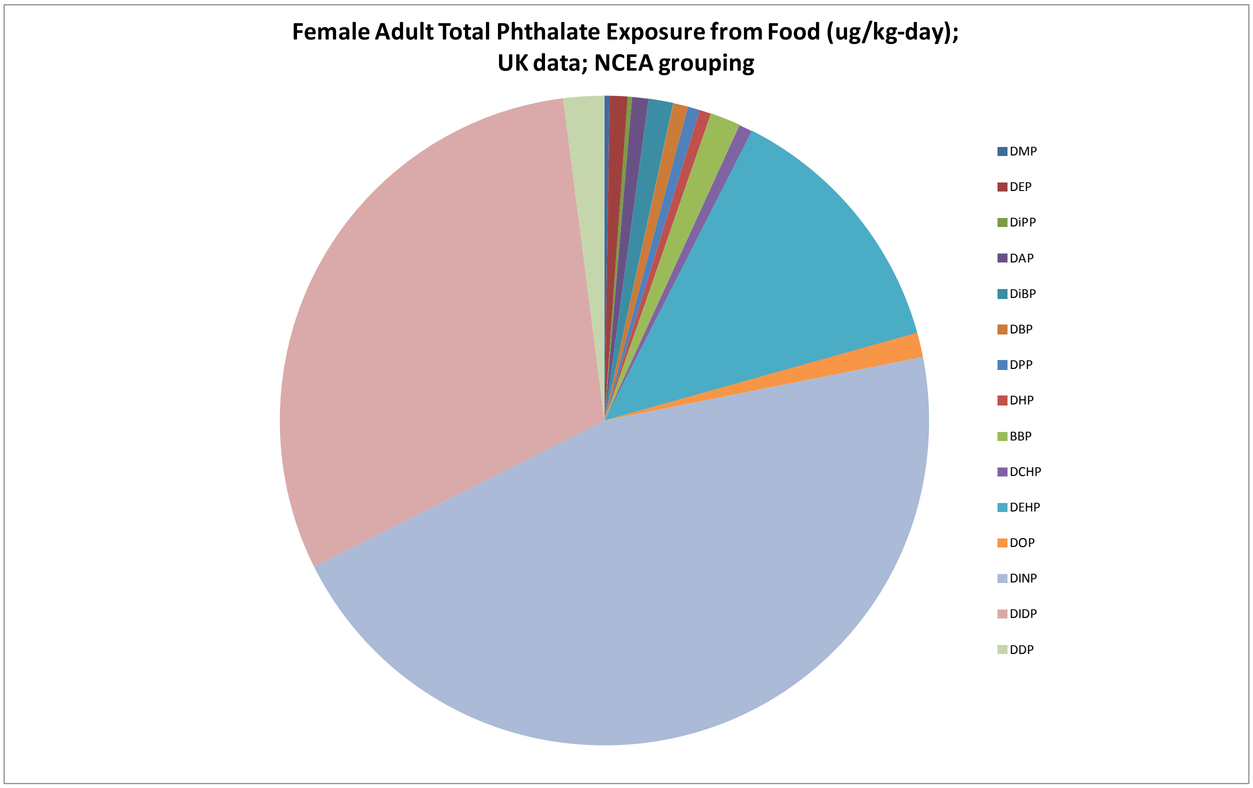


Figure E3-30 Male teen total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.3.6 Female Adult Total Phthalate Exposure from Food, Phthalate Relative Contribution (Assuming 100% Phthalate Absorption)

Figure E3-31 Female adult total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.



993 Figure E3-32 Female adult total phthalate exposure from food (ug/kg-day); UK data; Clark
994 grouping.

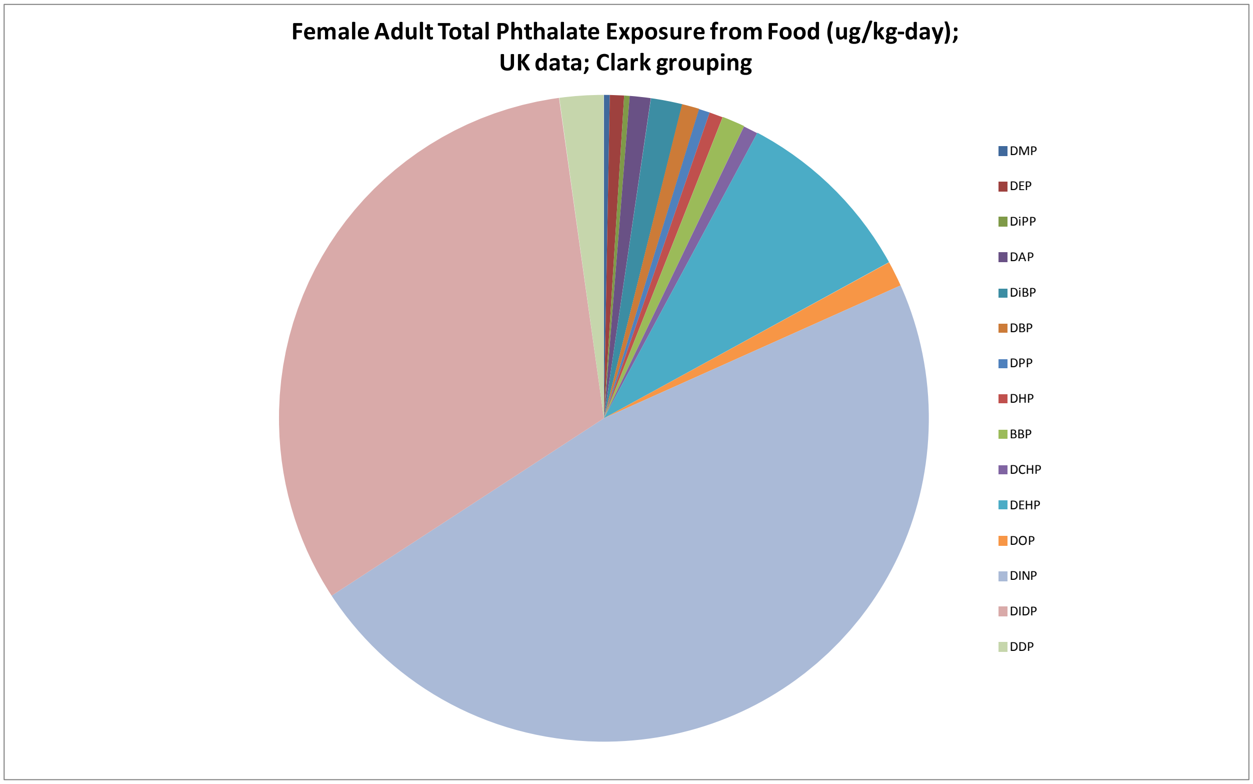


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Figure E3-33 Female adult total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

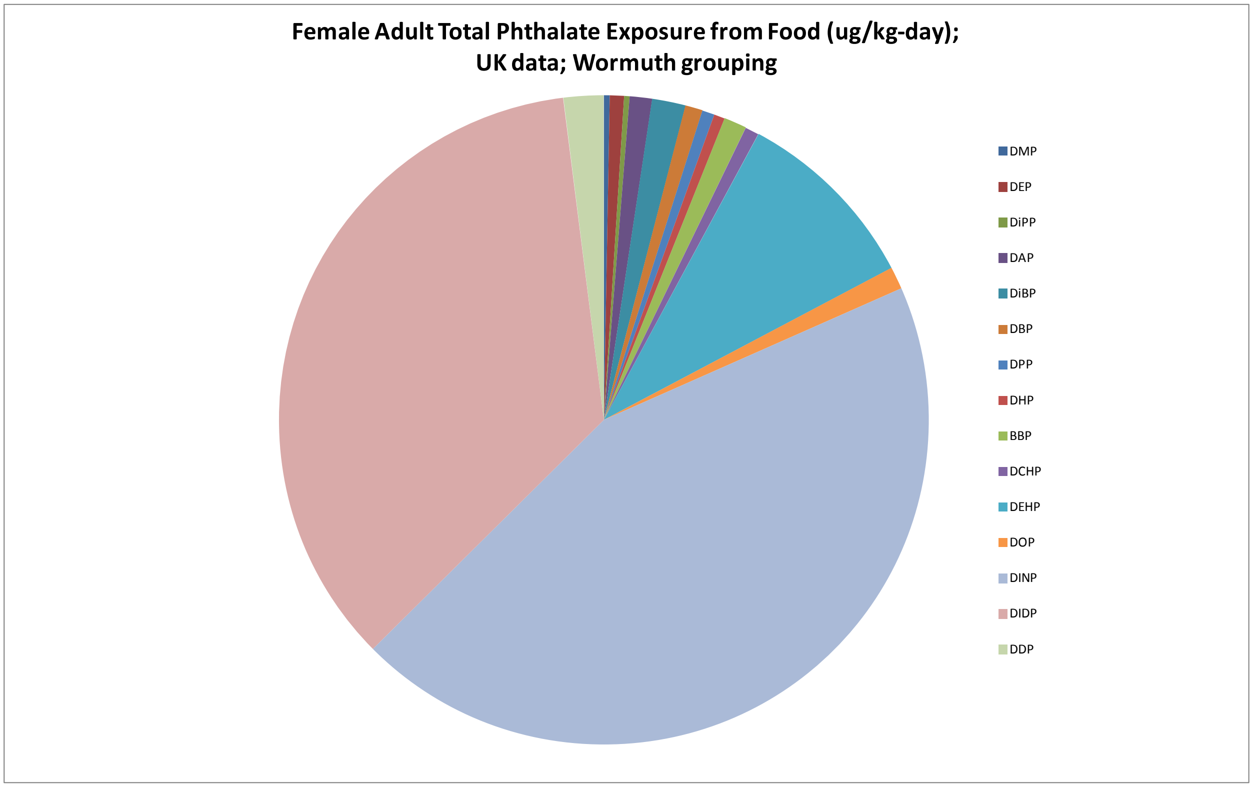


Figure E3-34 Female adult total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

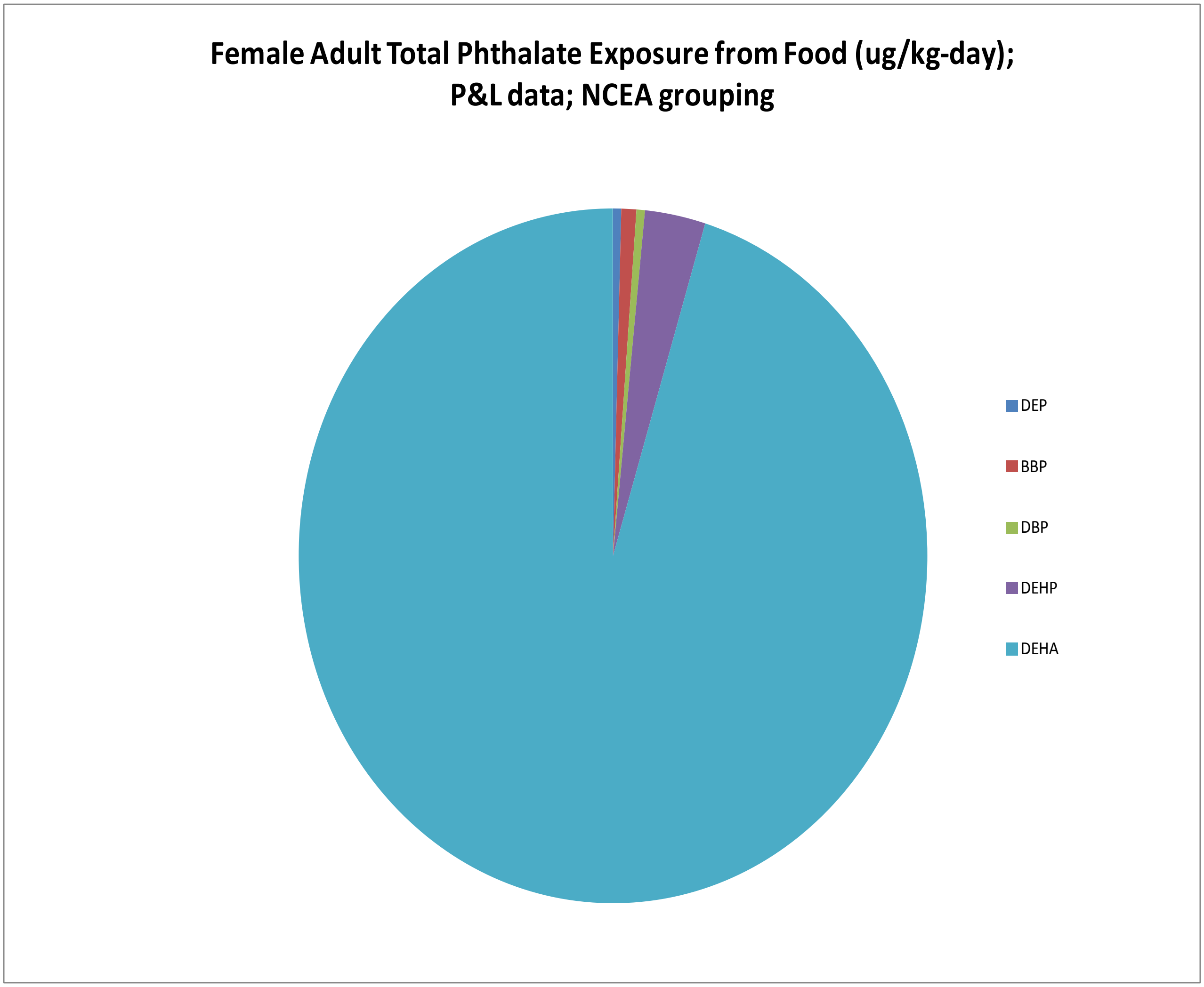


Figure E3-35 Female adult total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

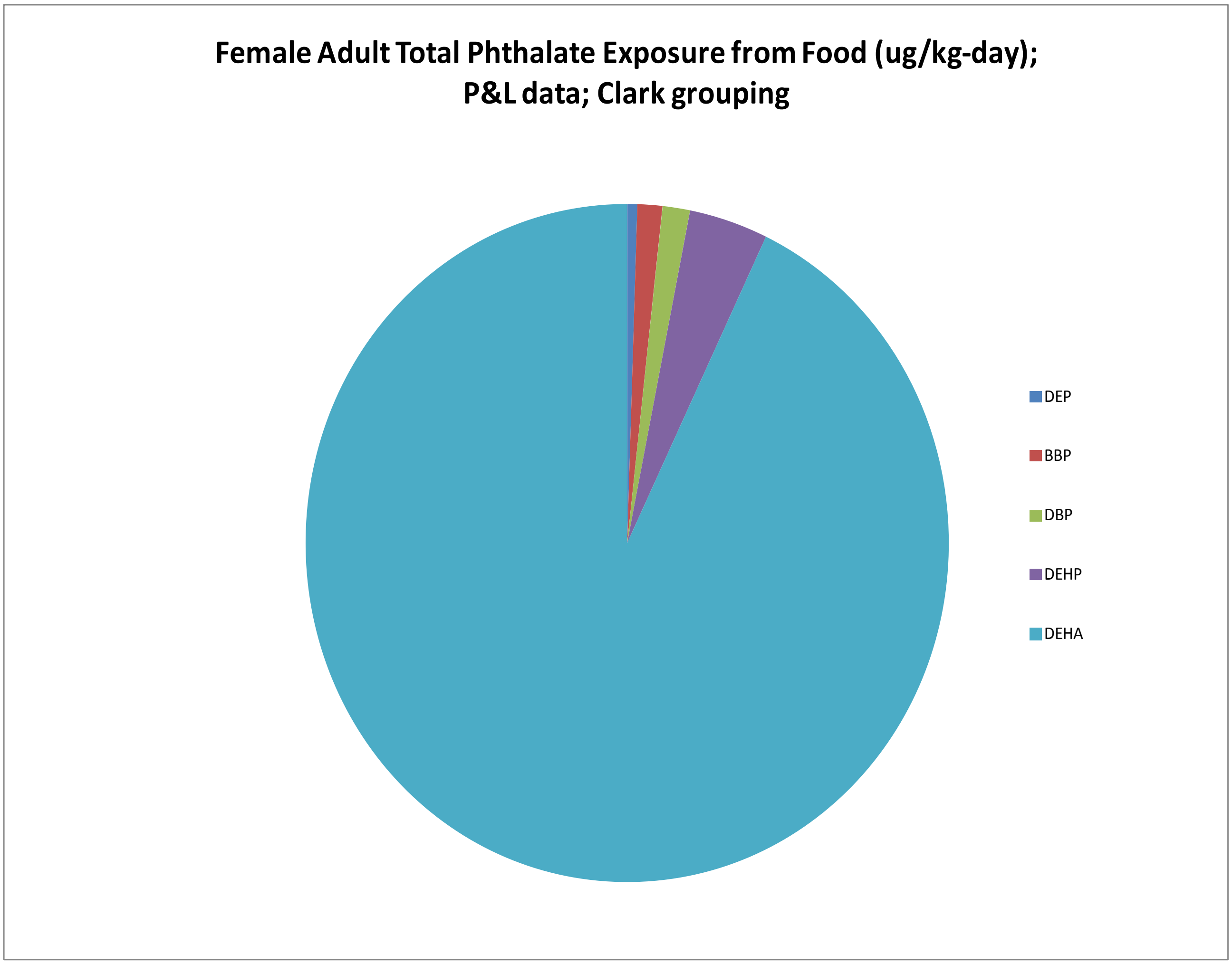
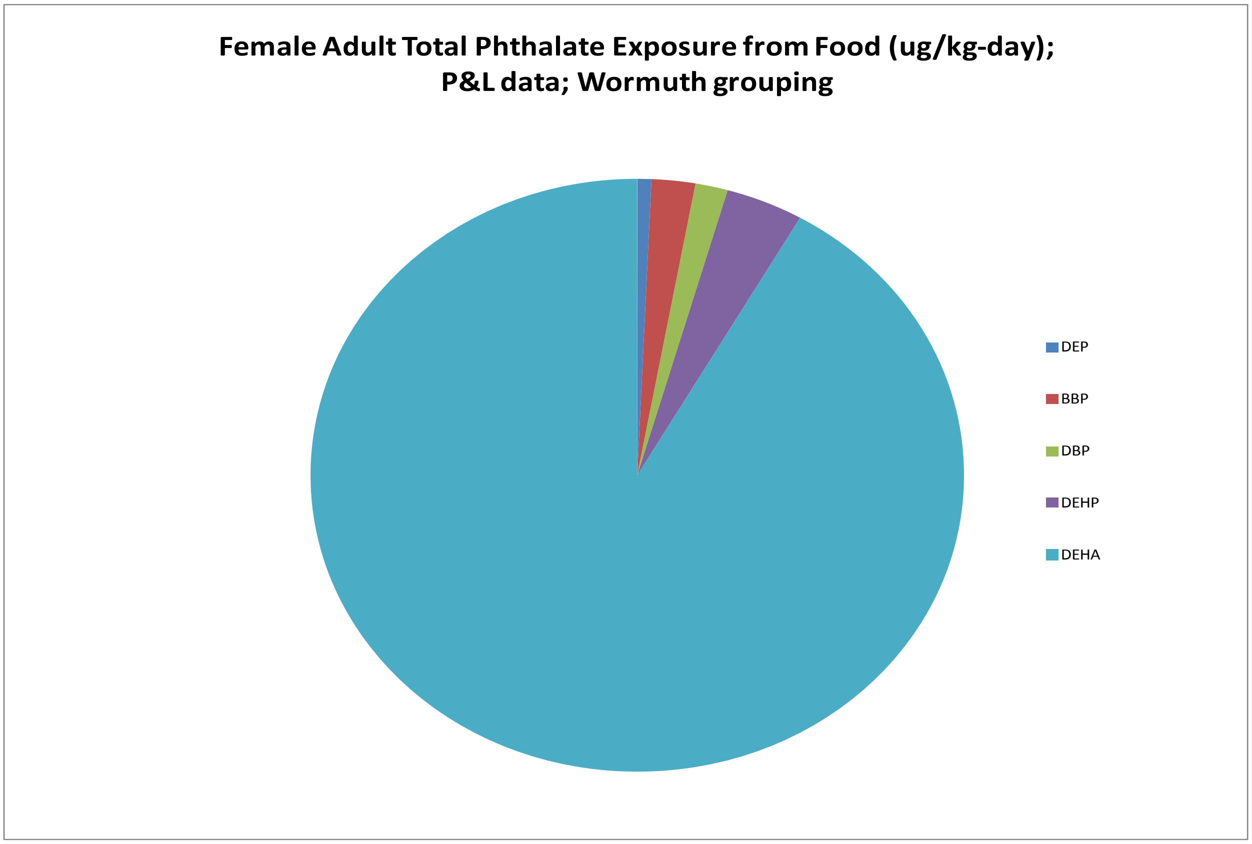


Figure E3-36 Female adult total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.3.7 Male Adult Total Phthalate Exposure from Food, Phthalate Relative Contribution (assuming 100% phthalate absorption)

Figure E3-37 Male adult total phthalate exposure from food (ug/kg-day); UK data; NCEA grouping.

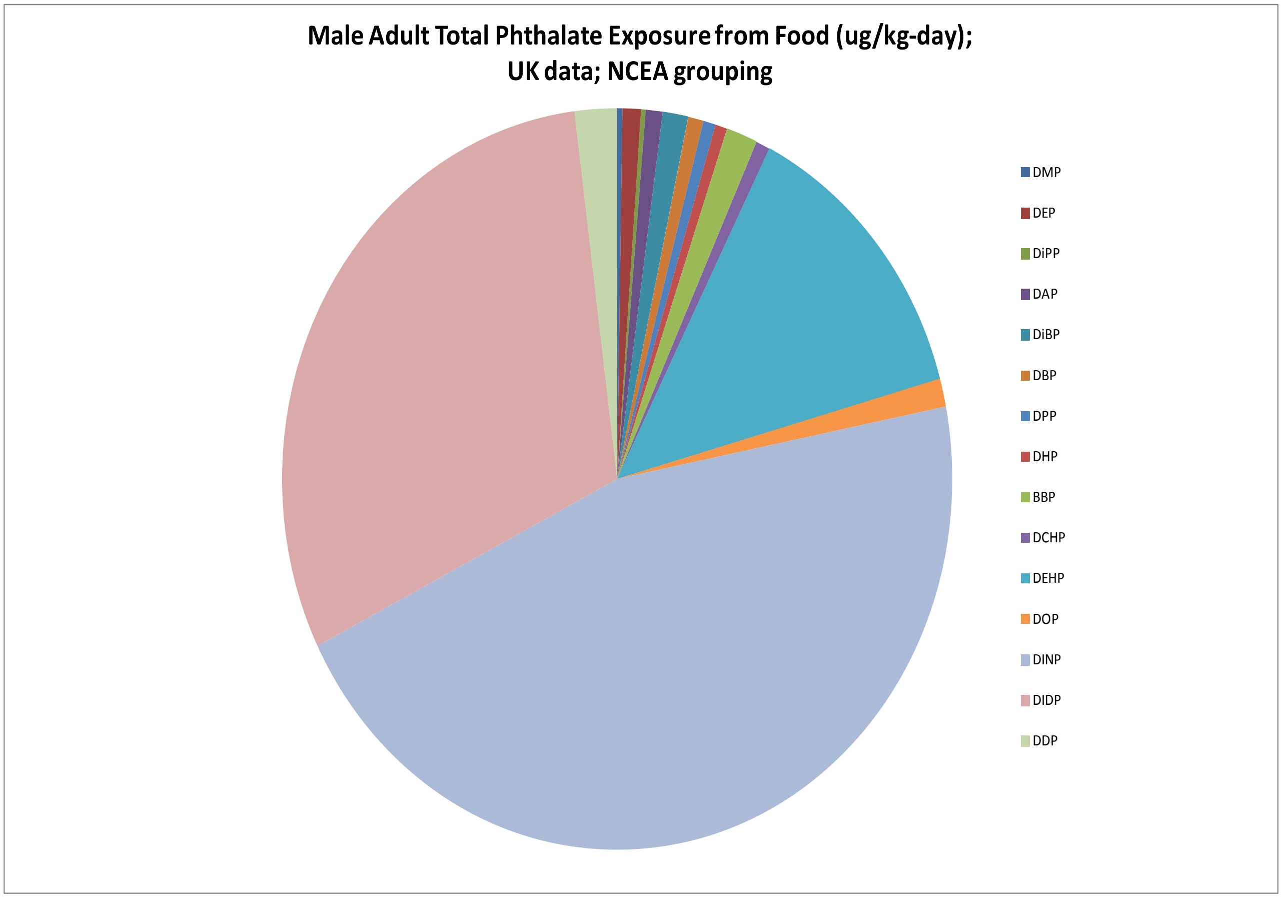


Figure E3-38 Male adult total phthalate exposure from food (ug/kg-day); UK data; Clark grouping.

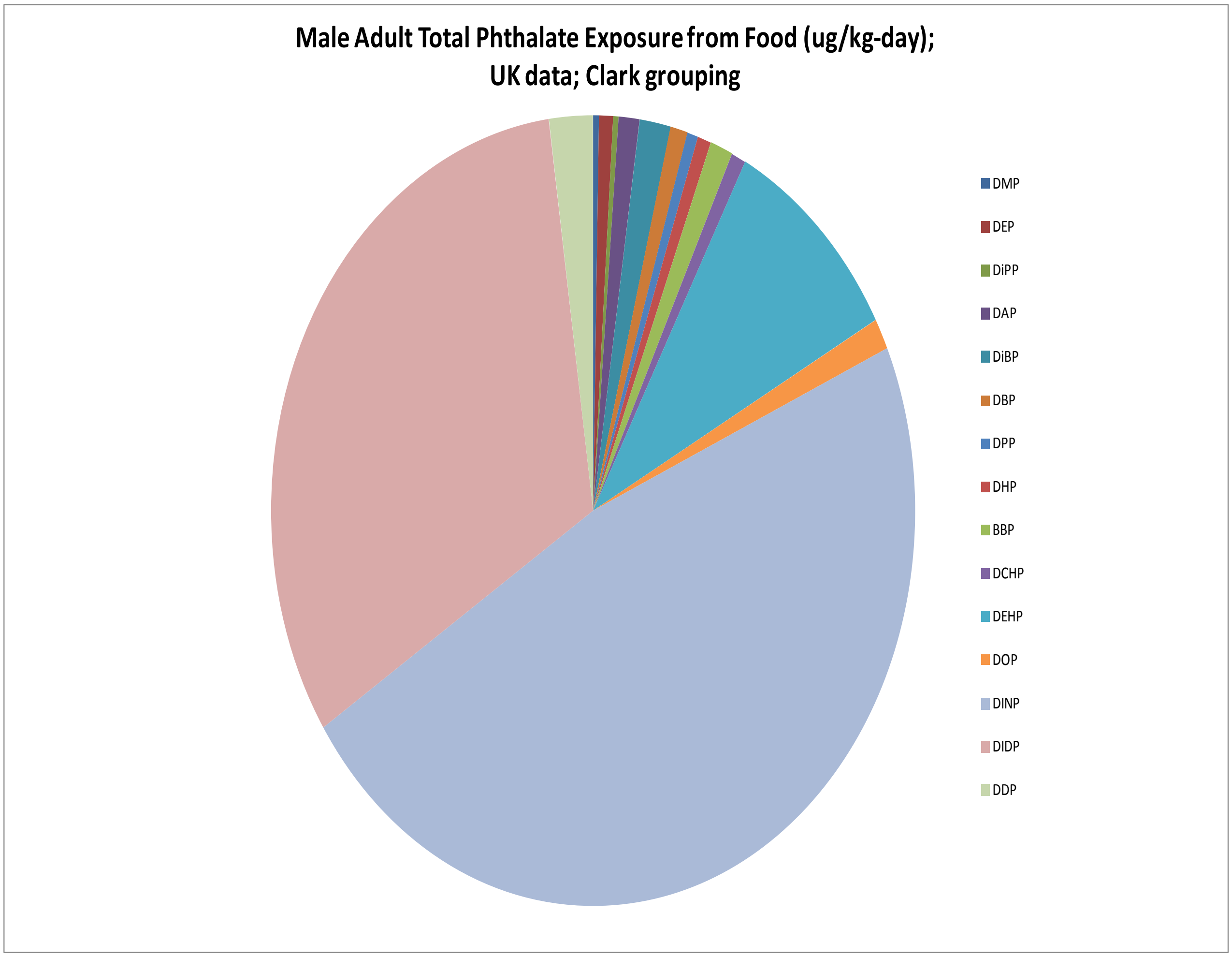


Figure E3-39 Male adult total phthalate exposure from food (ug/kg-day); UK data; Wormuth grouping.

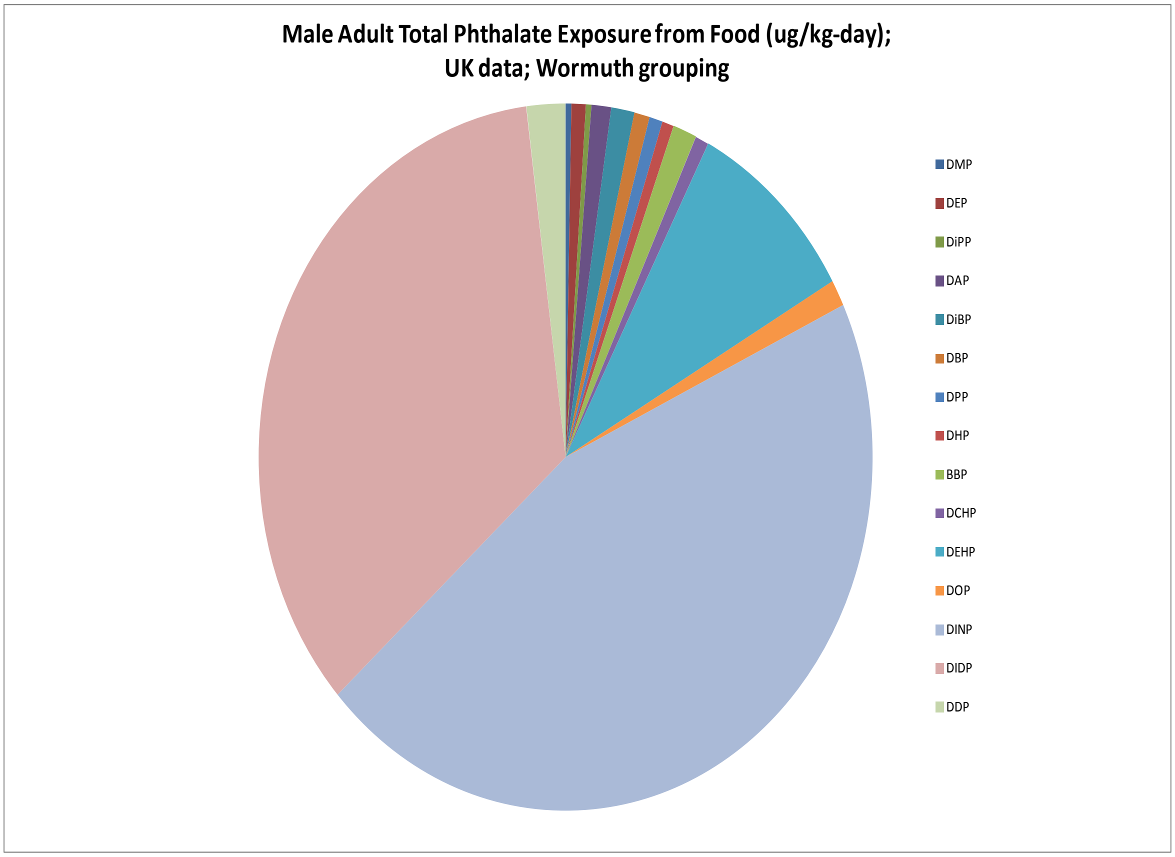


Figure E3-40 Male adult total phthalate exposure from food (ug/kg-day); P&L data; NCEA grouping.

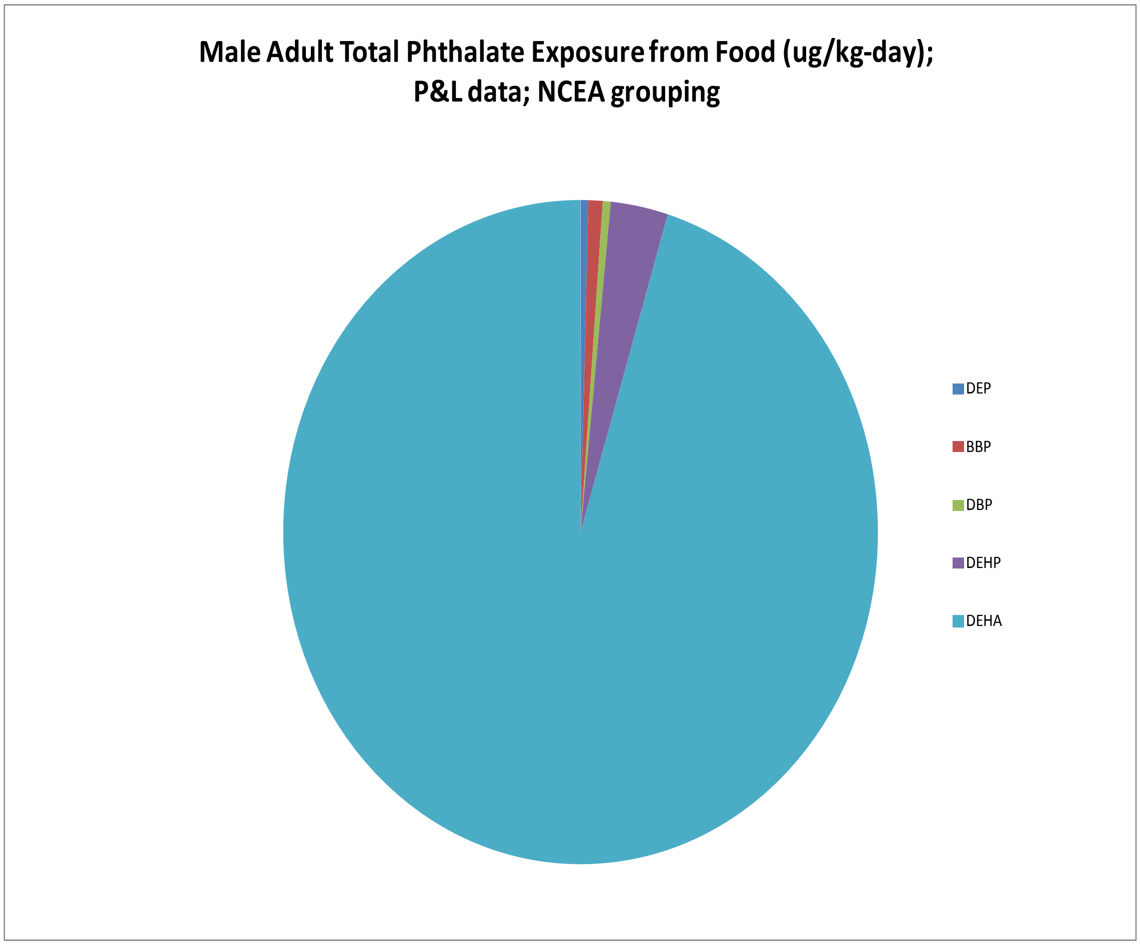


Figure E3-41 Male adult total phthalate exposure from food (ug/kg-day); P&L data; Clark grouping.

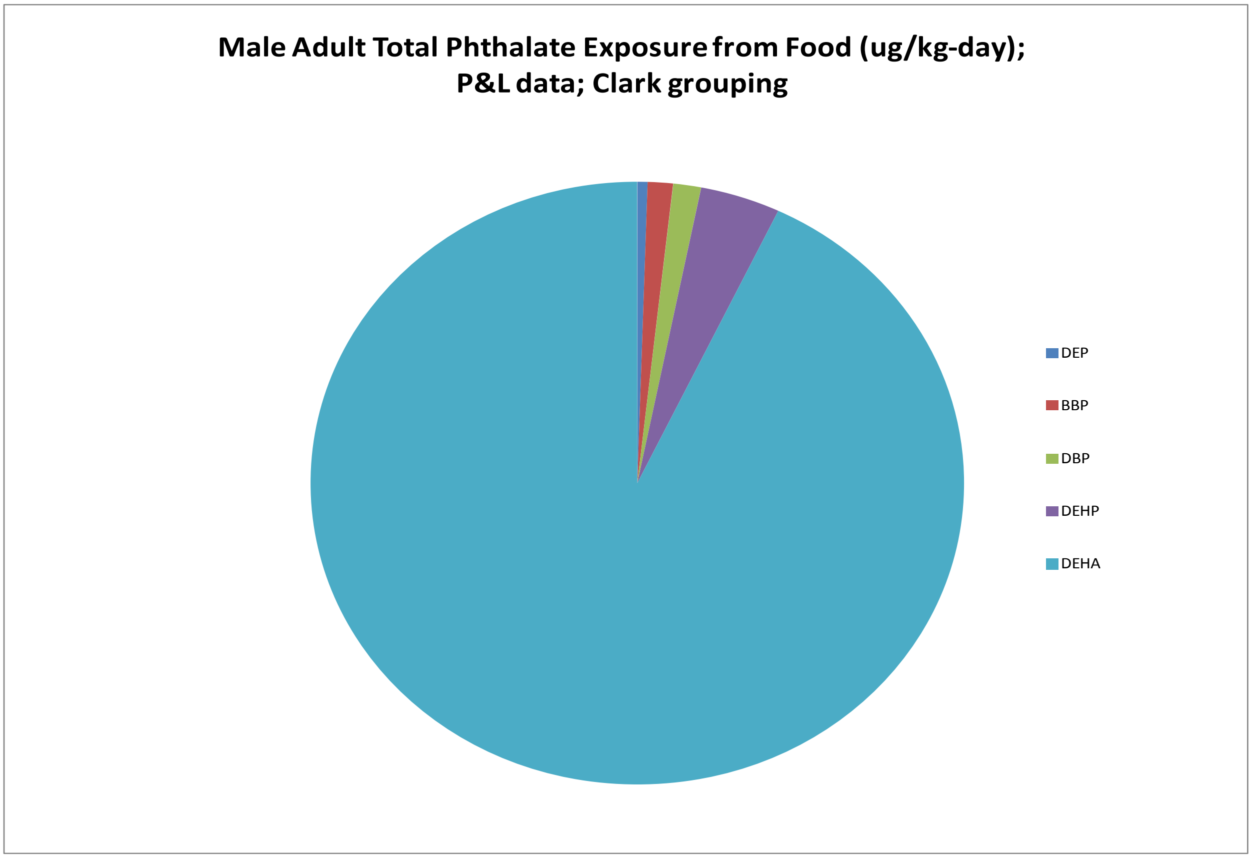
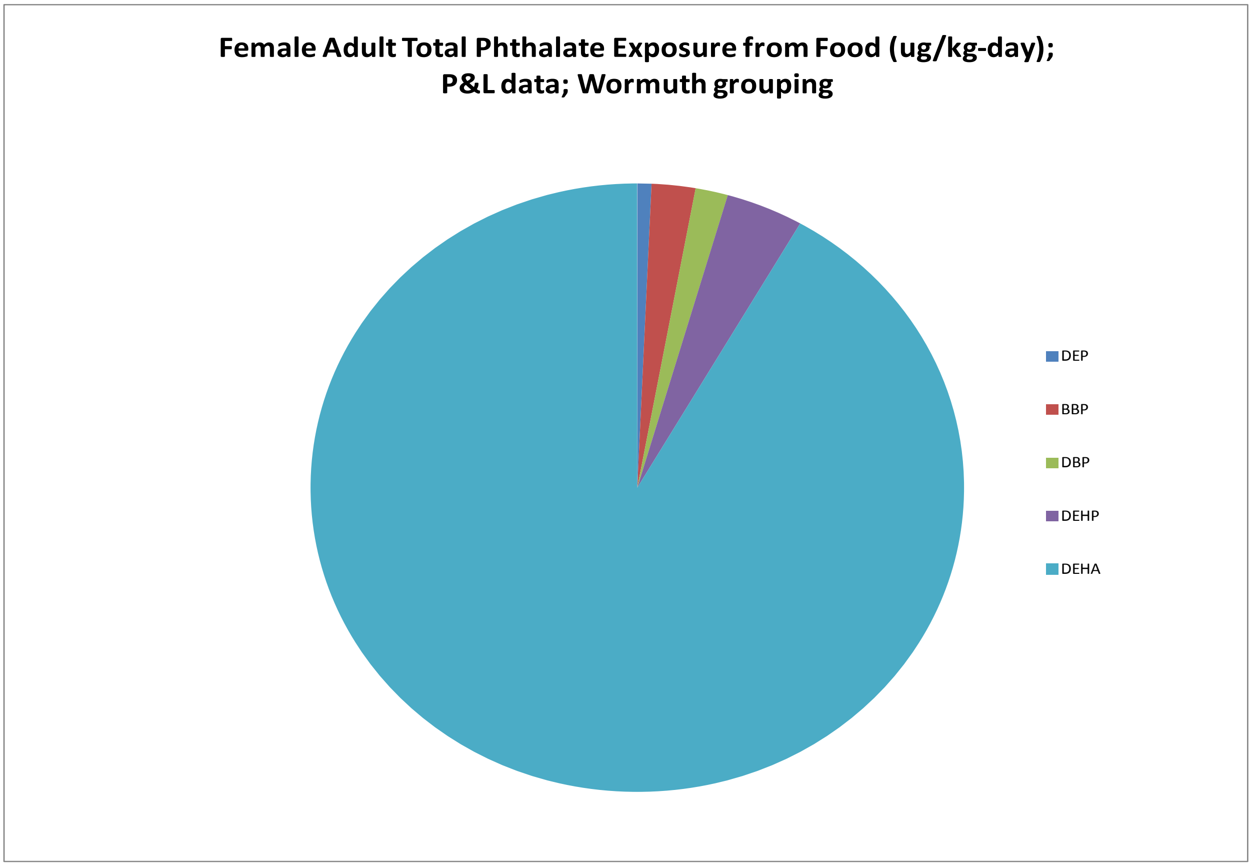


Figure E3-42 Female adult total phthalate exposure from food (ug/kg-day); P&L data; Wormuth grouping.



4.4 Population-based Average Dietary Exposures and the Relative Contribution of Various Phthalates

4.5

4.5.1 Infant Average Dietary Exposures and the Relative Contribution of Various Phthalates

Figure E3-43 Infant average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.

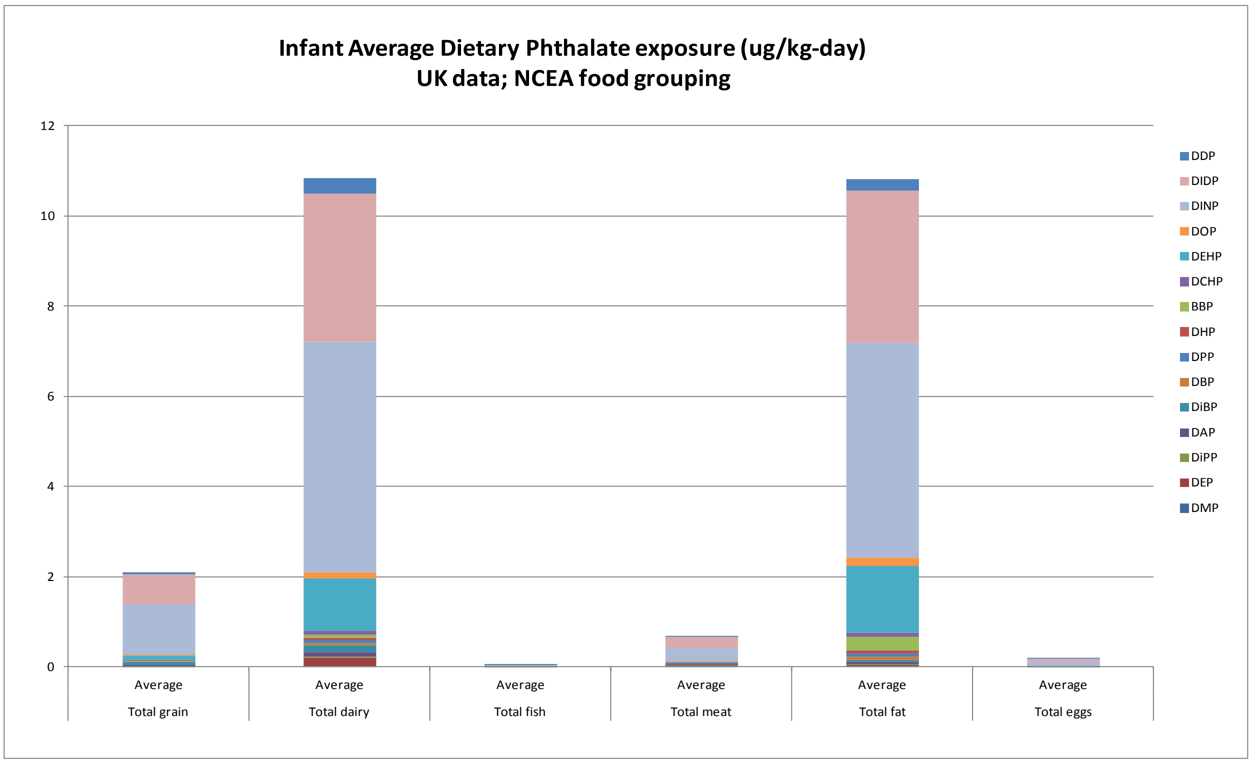


Figure E3-44 Infant average dietary phthalate exposure (ug/kg-day); P&L data; NCEA food grouping.

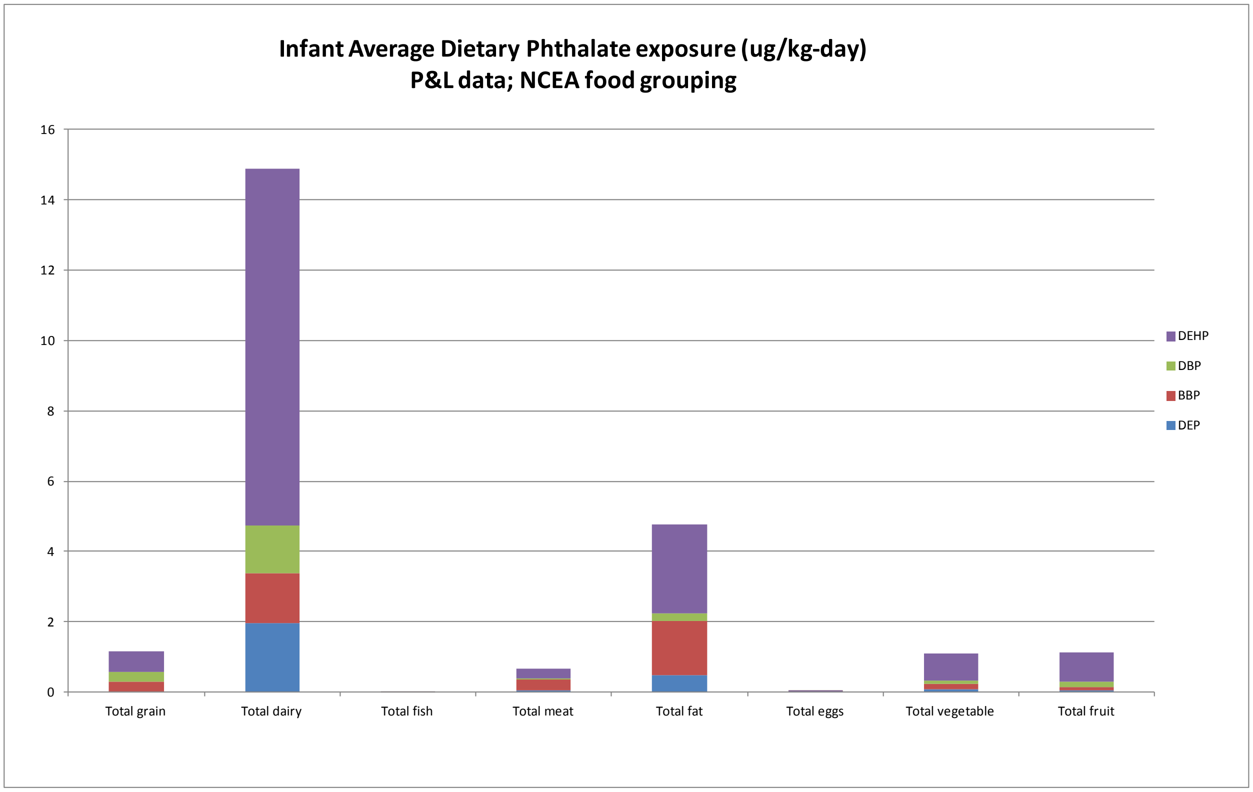


Figure E3-45 Infant average dietary phthalate exposure (ug/kg-day); UK data, Clark food grouping.

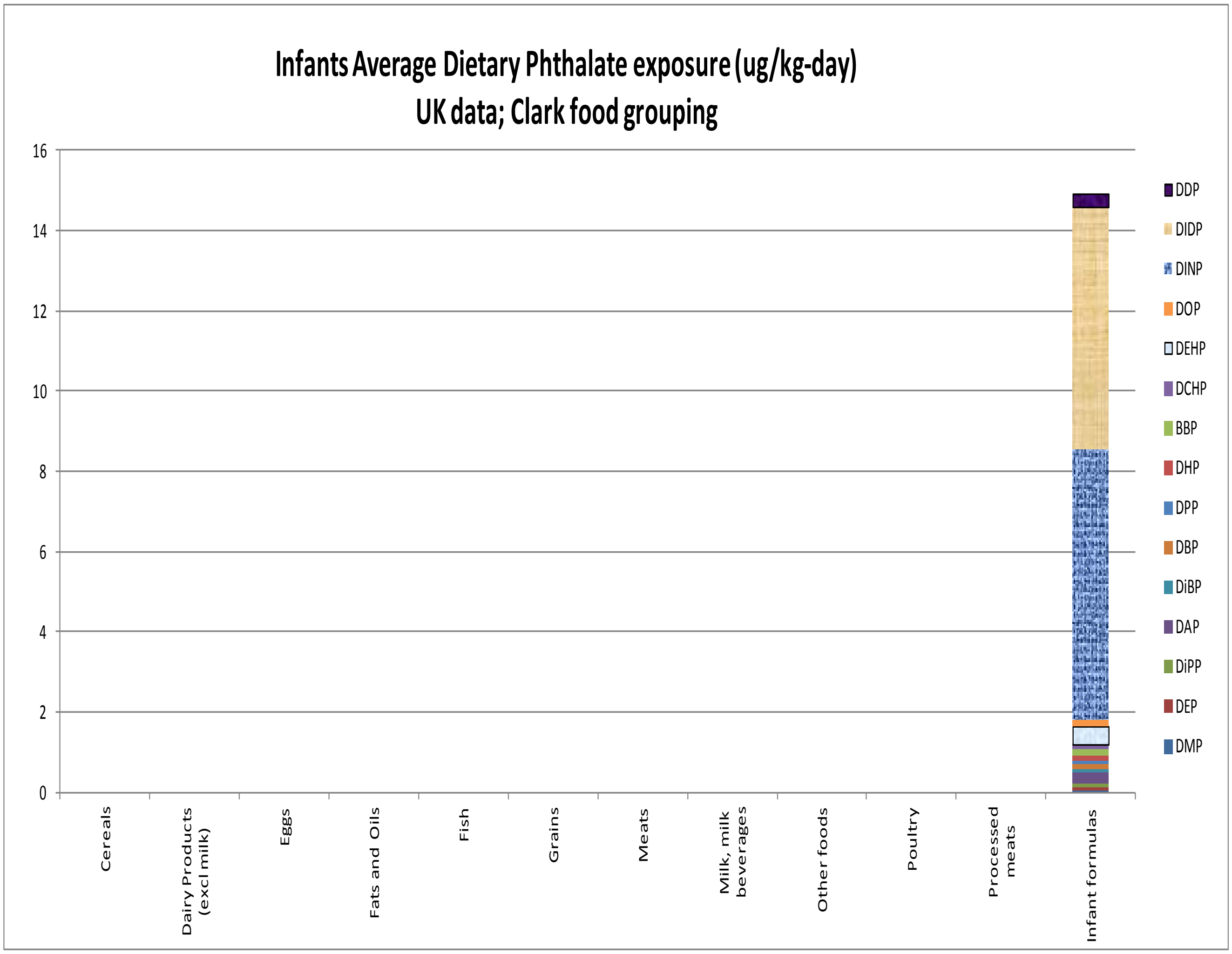
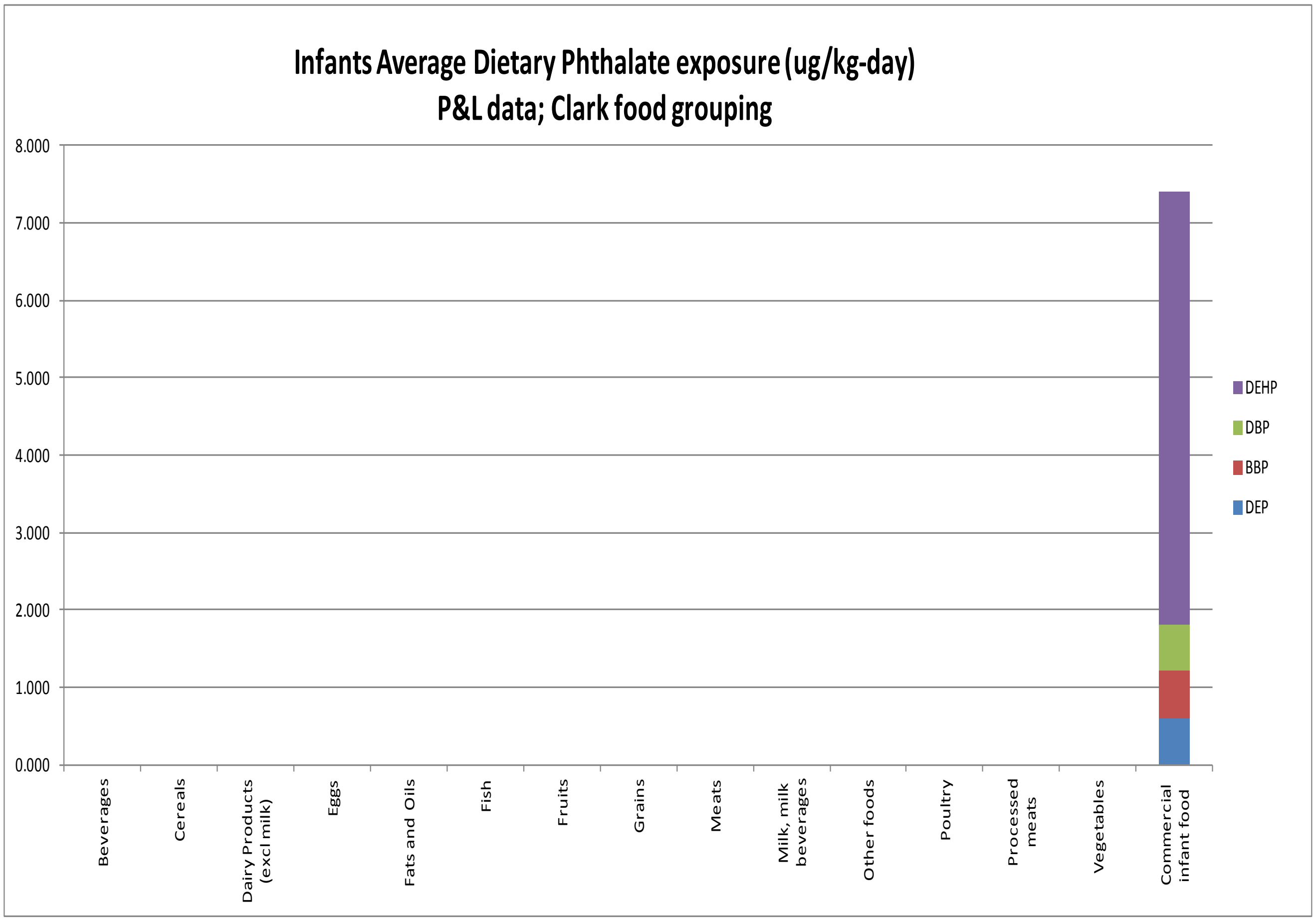


Figure E3-46 Infants average dietary phthalate exposure (ug/kg-day); P&L data; Clark food grouping.



1058 Figure E3-47 Infants average dietary phthalate exposure (ug/kg-day); UK data; Wormuth food
1059 grouping.

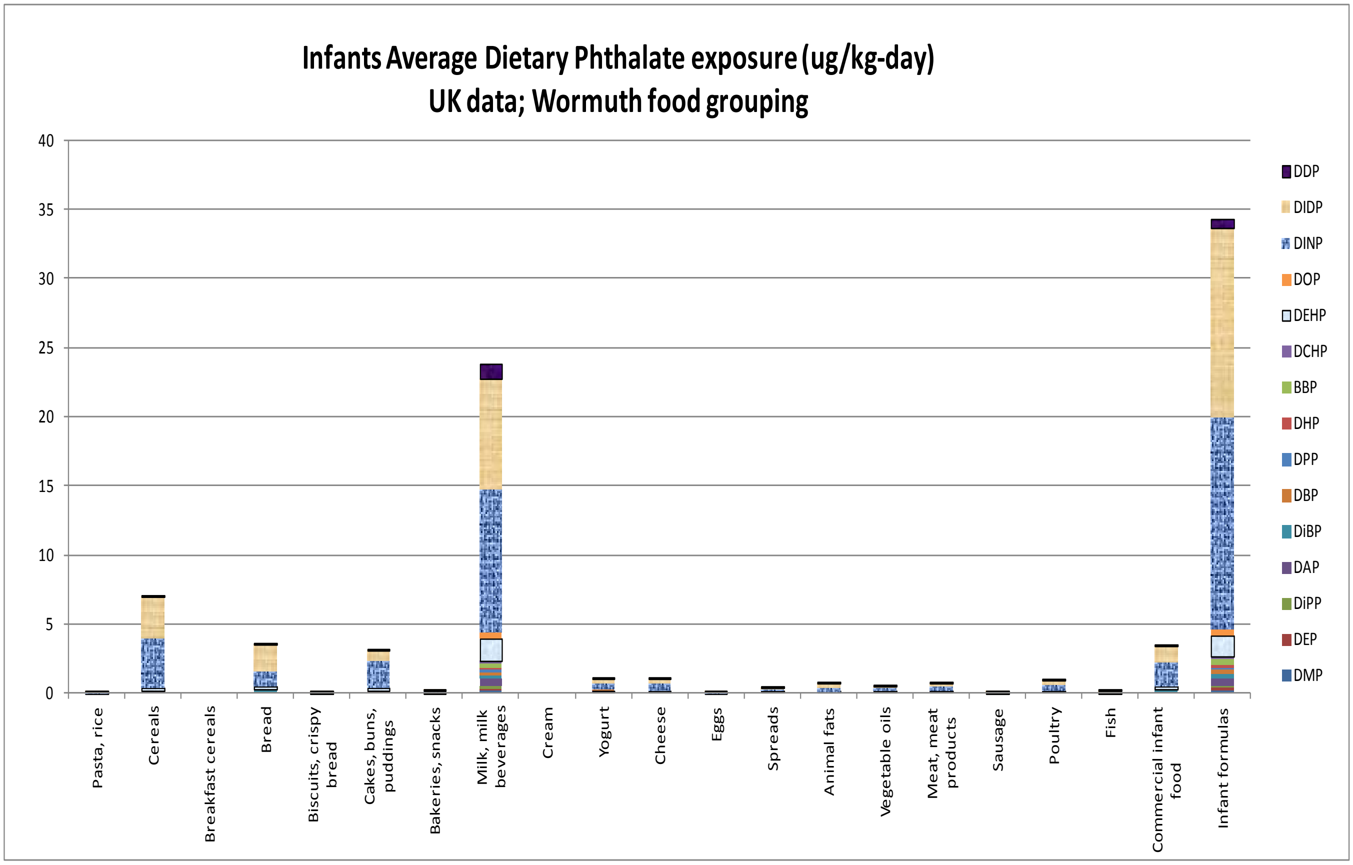


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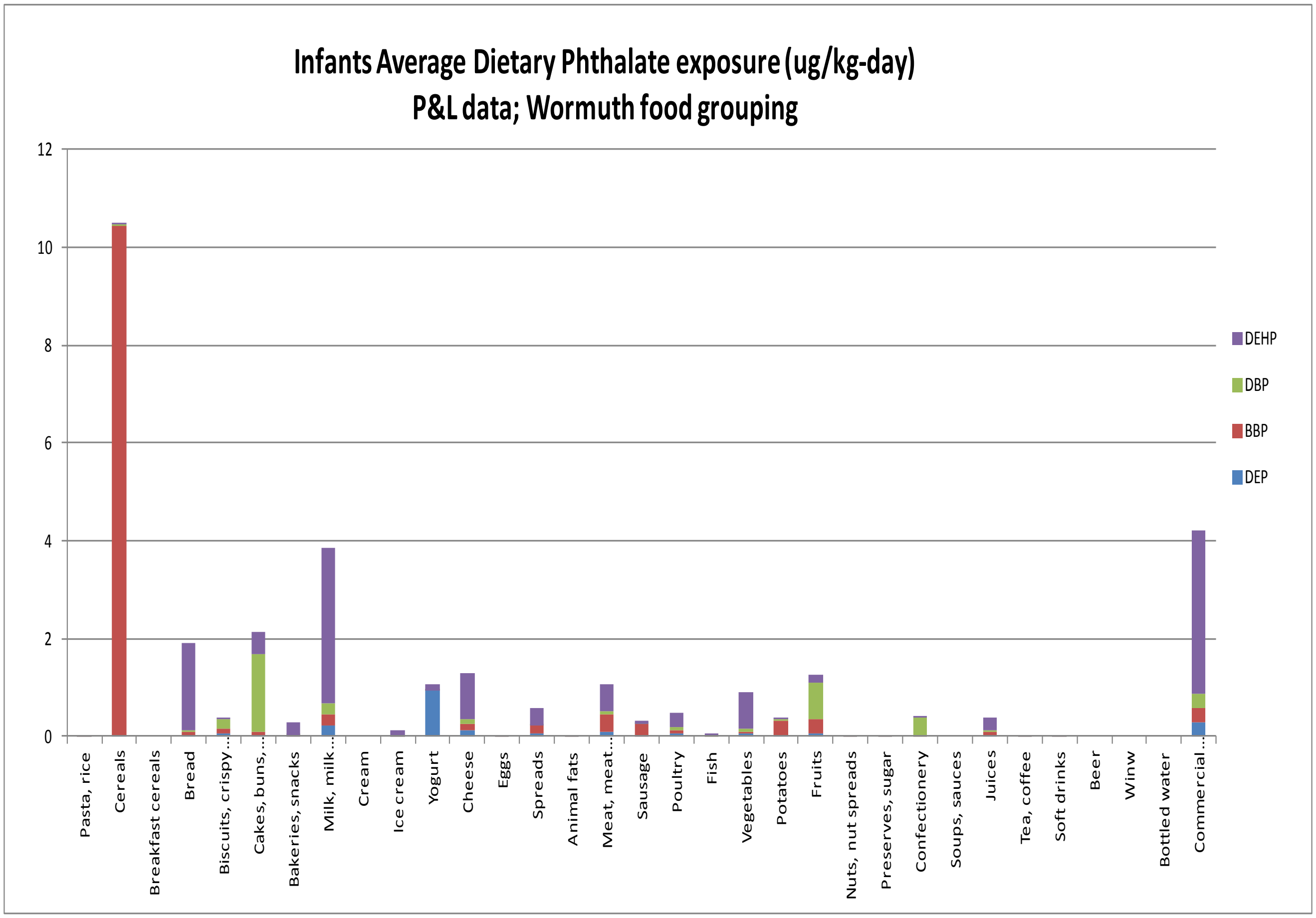
Figure E3-48 Infants average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth food grouping.



4.5.2 Toddler Average Dietary Exposures and the Relative Contribution of Various Phthalates

Figure E3-49 Toddler average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.

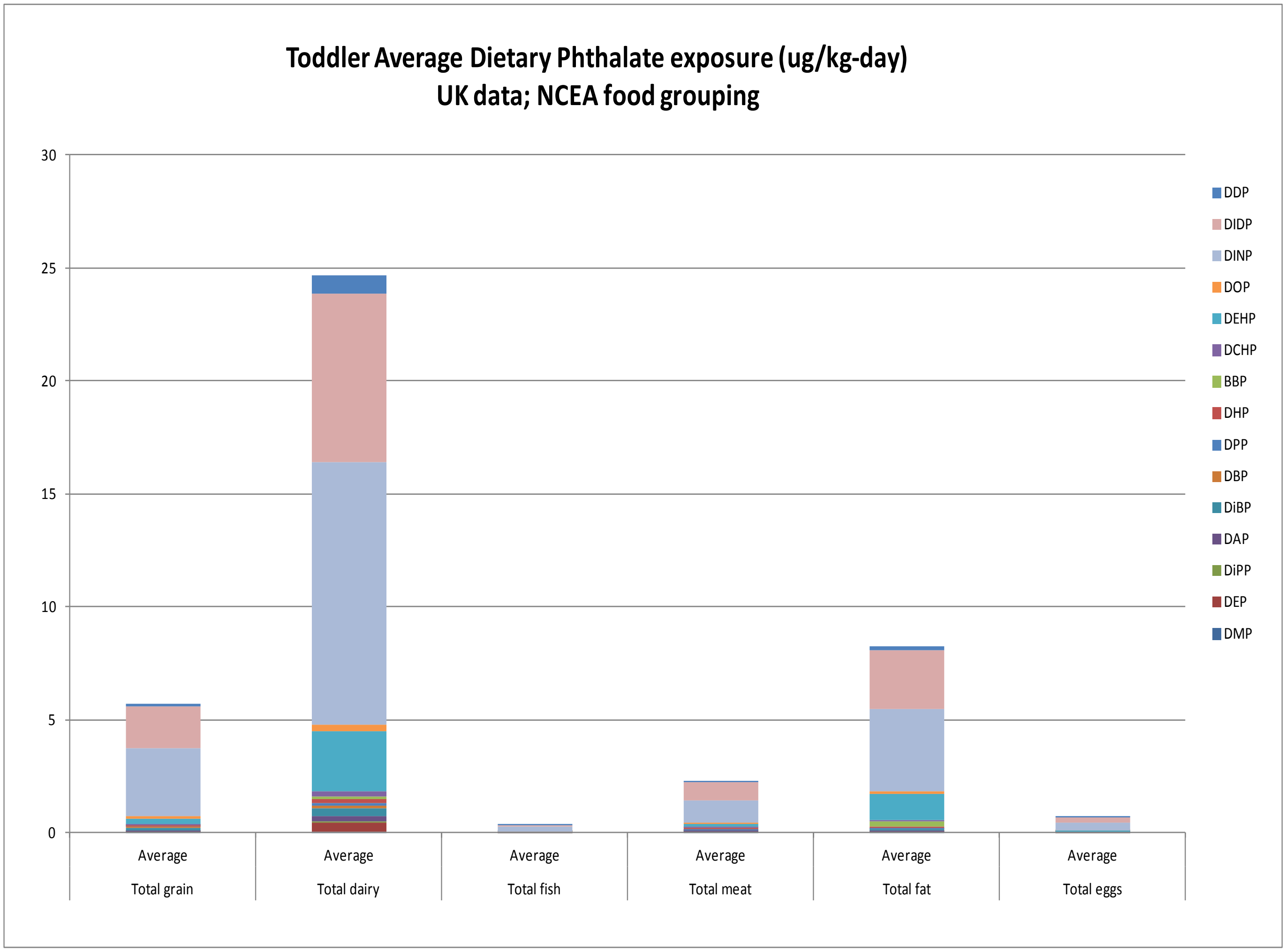


Figure E3-50 Toddler average dietary phthalate exposure (ug/kg-day); P&L data; NCEA food grouping.

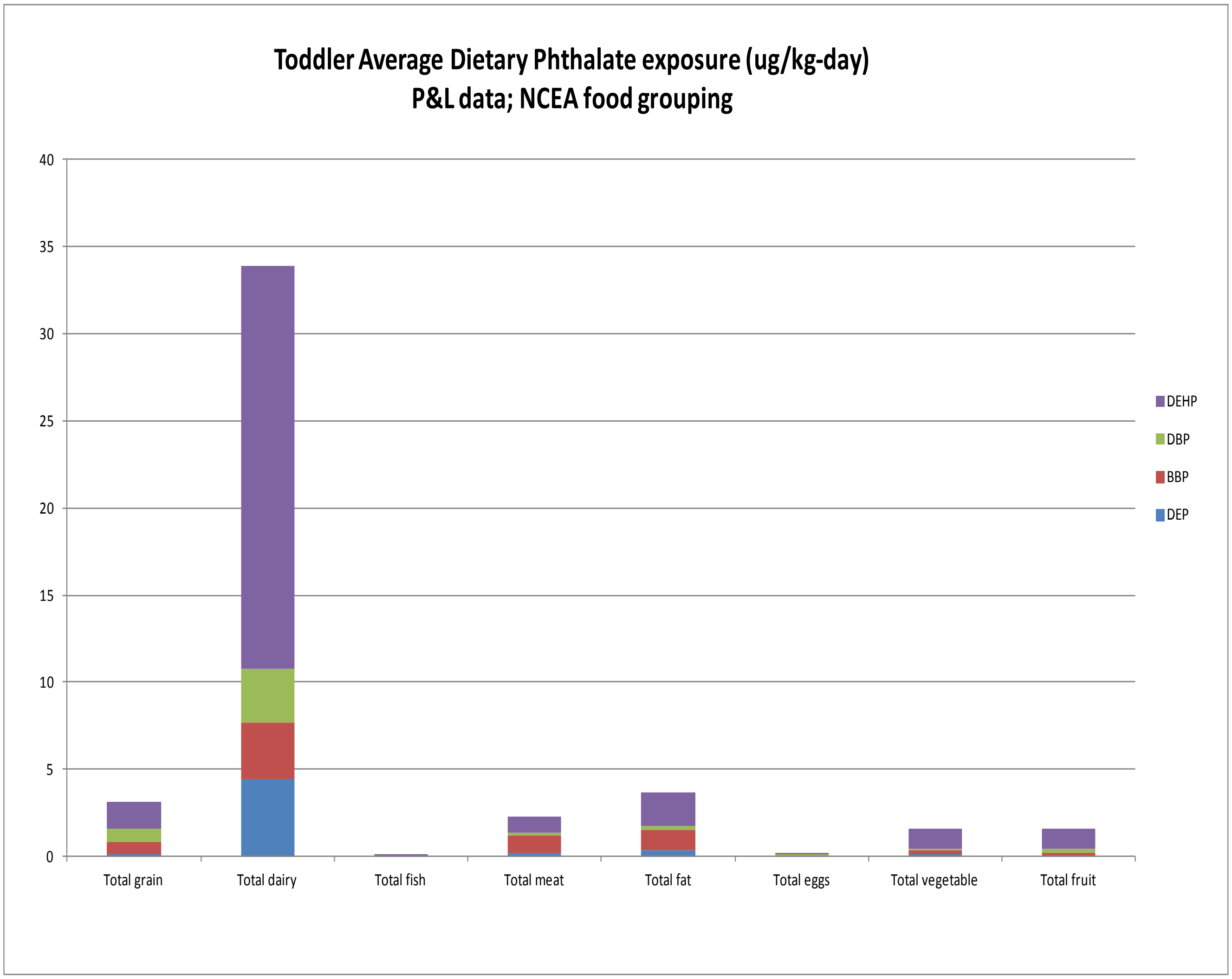
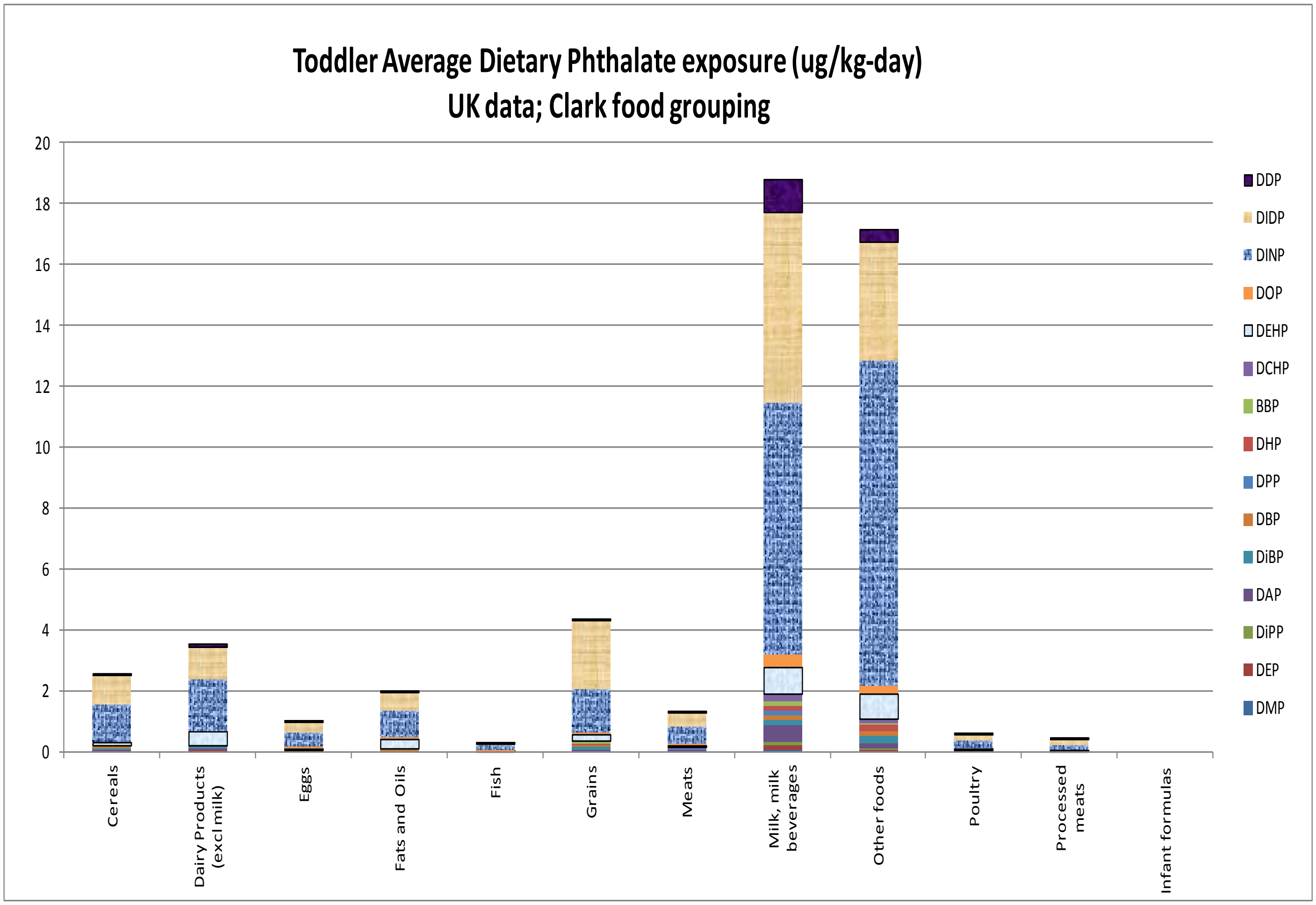


Figure E3-51 Toddler average dietary phthalate exposure (ug/kg-day); UK data; Clark food grouping.



1080 Figure E3-52 Toddler average dietary phthalate exposure (ug/kg-day); P&L data; Clark food
1081 grouping.

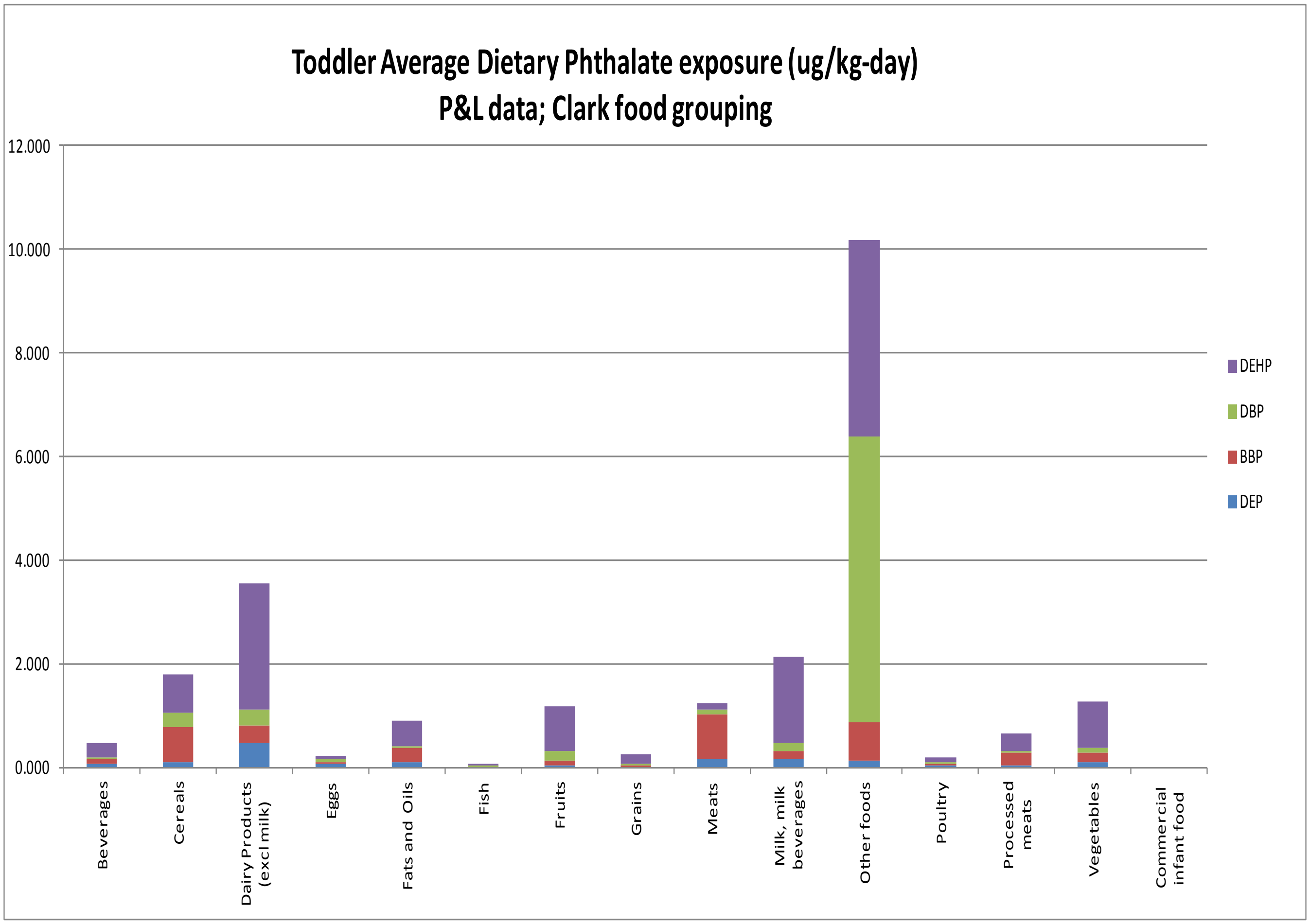


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Figure E3-53 Toddler average dietary phthalate exposure (ug/kg-day); UK data; Wormuth food grouping.

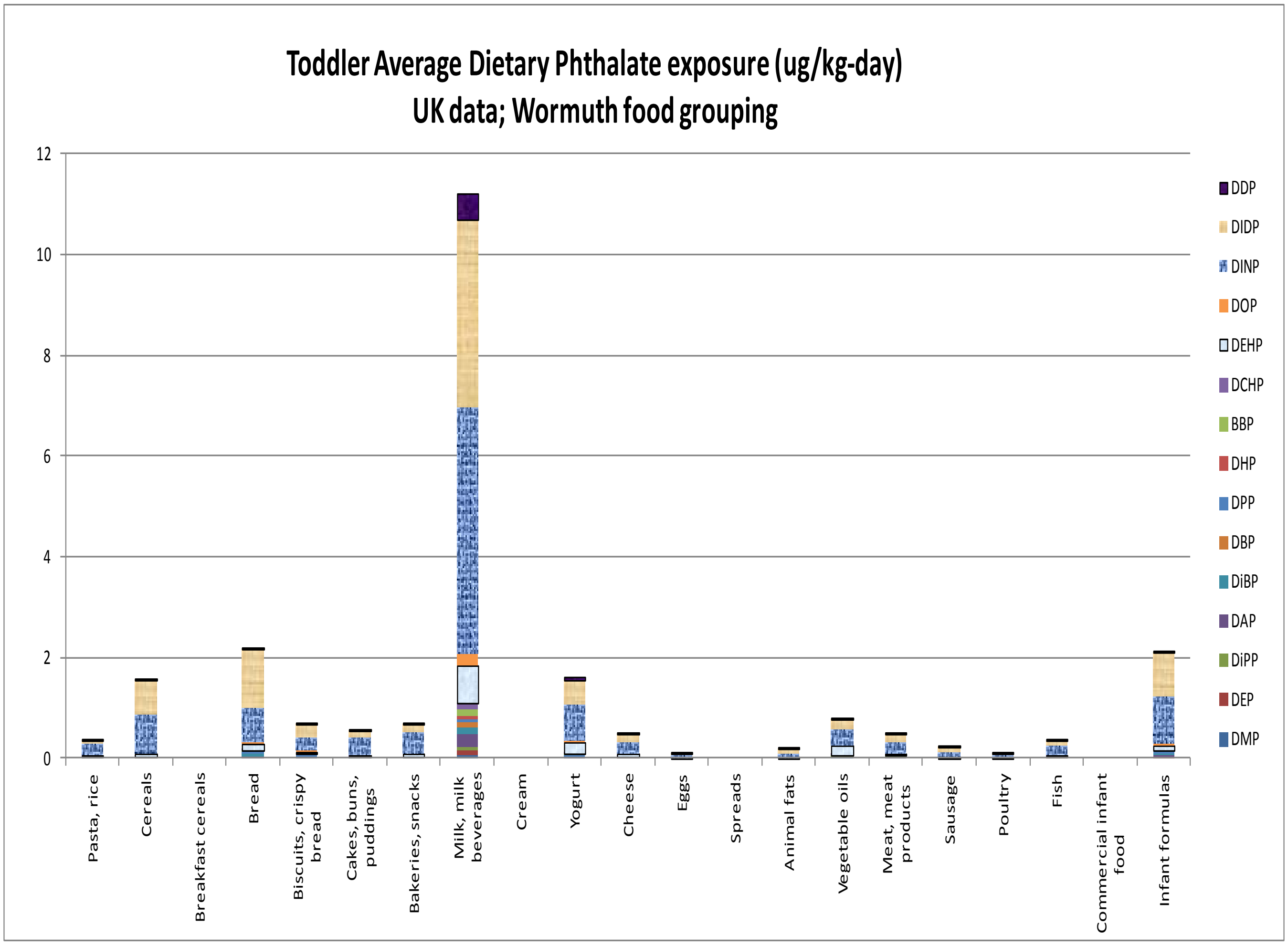
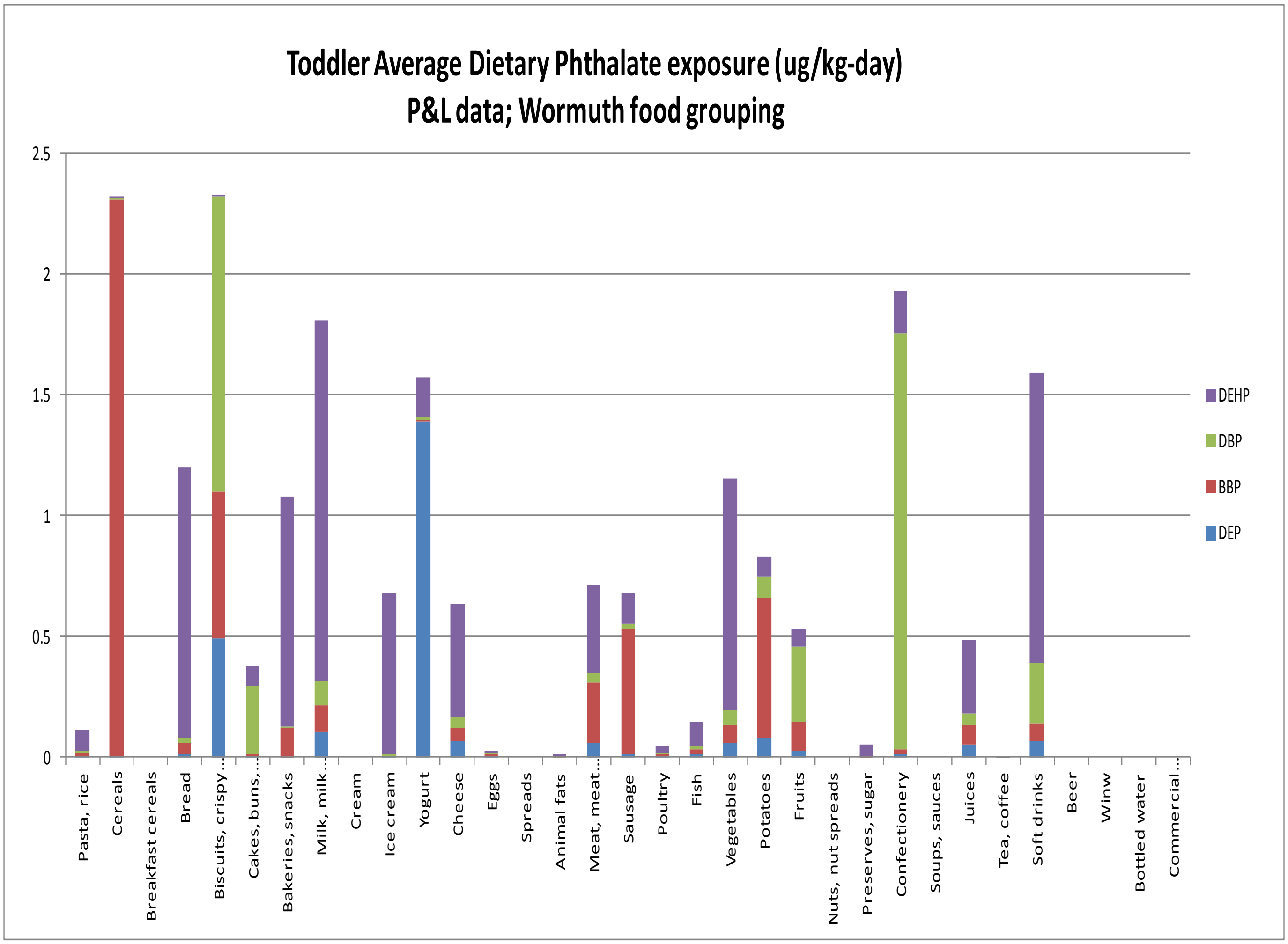
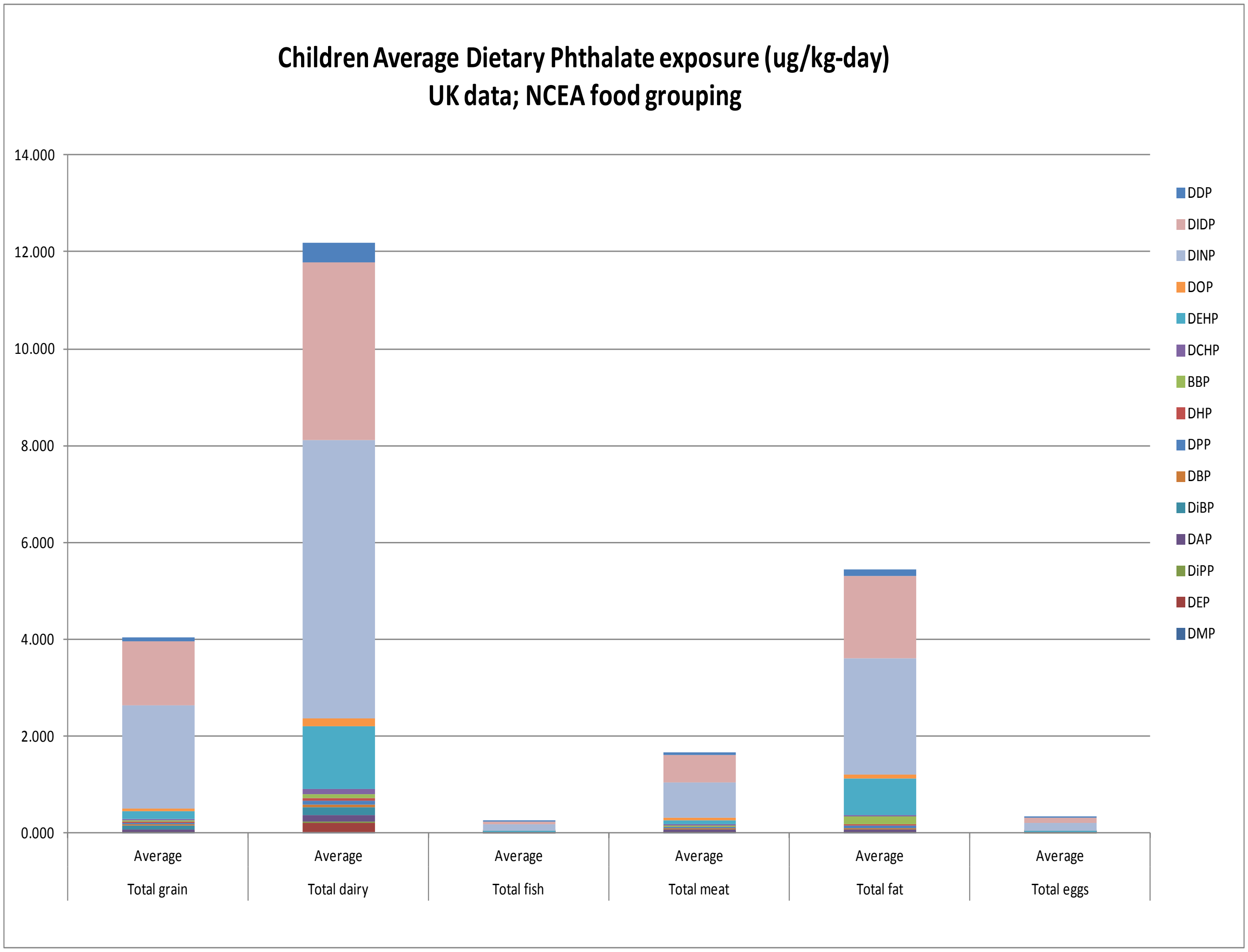


Figure E3-54 Toddler average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth food grouping.



4.5.3 Children Average Exposures and the Relative Contribution of Various Phthalates

Figure E3-55 Children average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.



1098 **Figure E3-56** Children average dietary phthalate exposure (ug/kg-day); P&L data; NCEA food
1099 grouping.

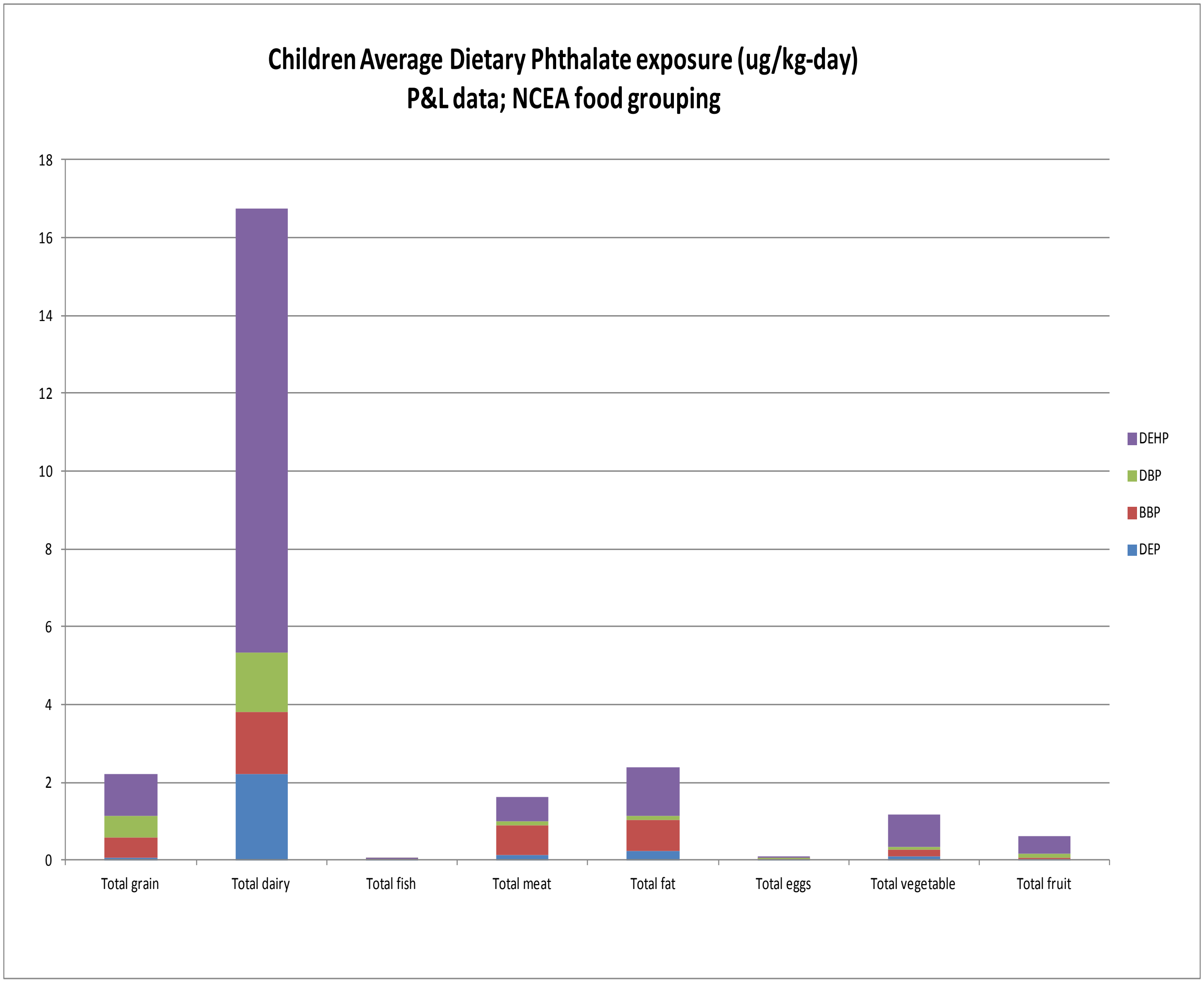


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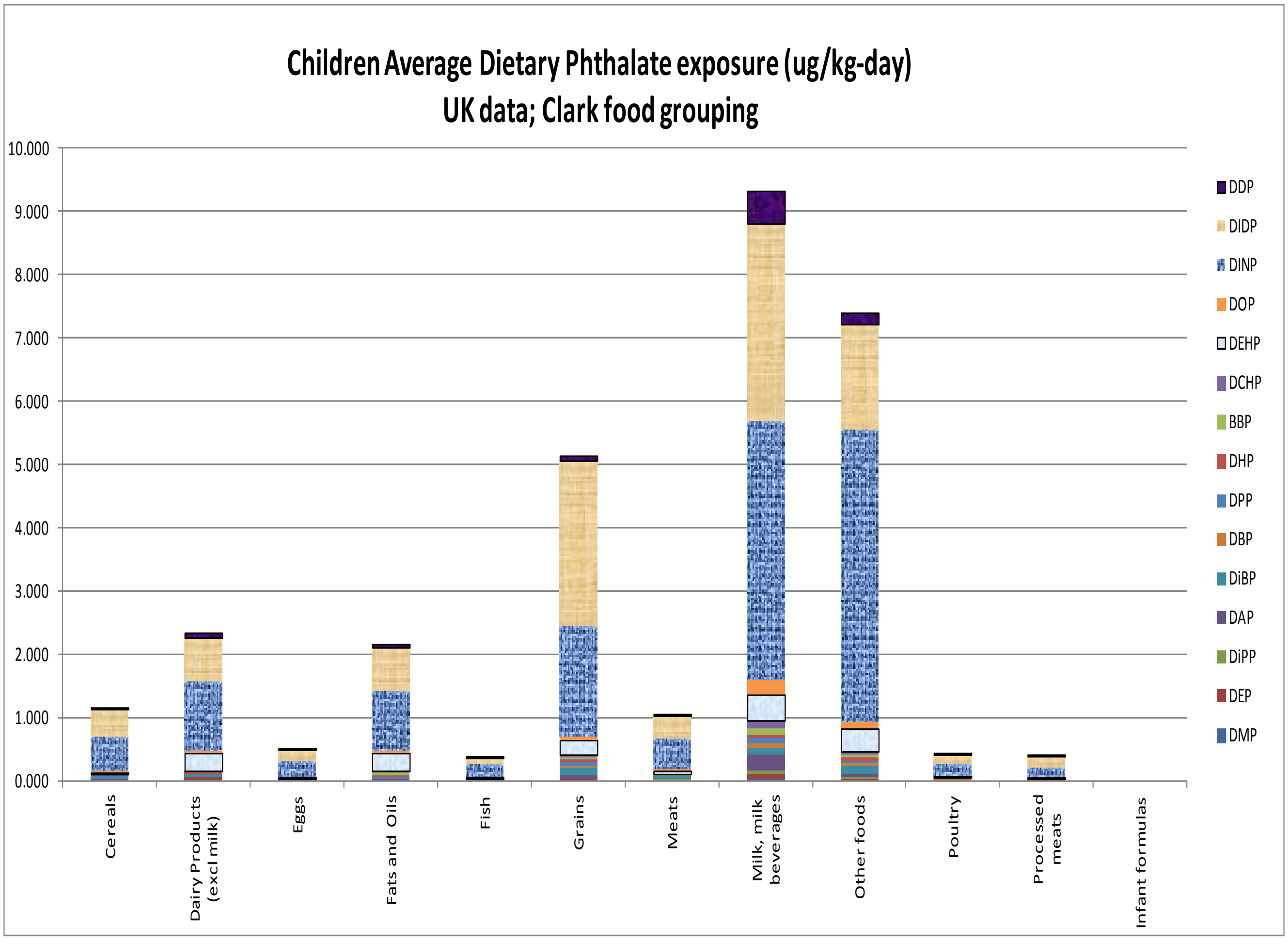
Figure E3-57 Children average dietary phthalate exposure (ug/kg-day); UK data; Clark food grouping.



1106 Figure E3-58 Children average dietary phthalate exposure (ug/kg-day); P&L data; Clark food
1107 grouping

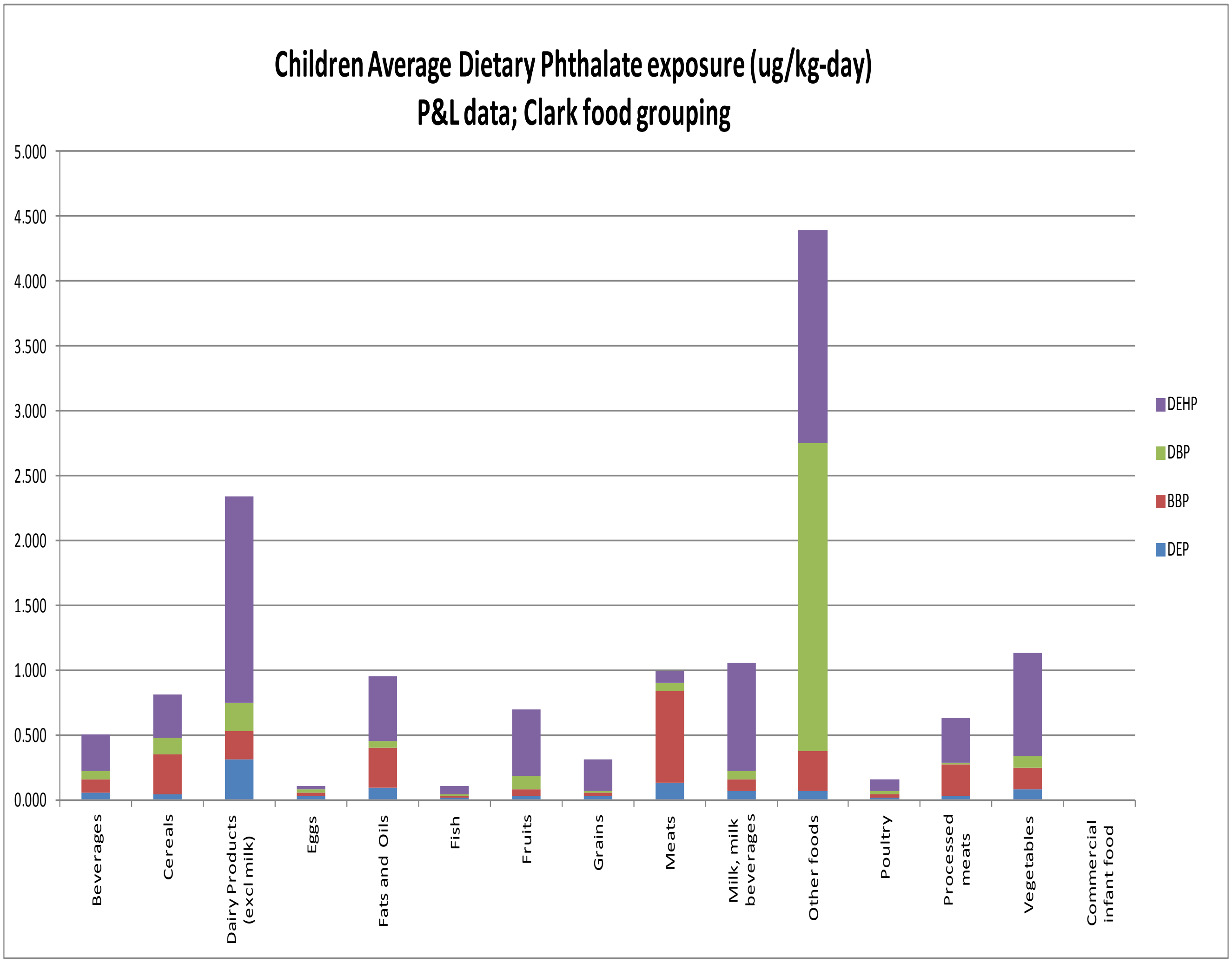


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Figure E3-59 Children average dietary phthalate exposure (ug/kg-day); UK data; Wormuth food grouping.

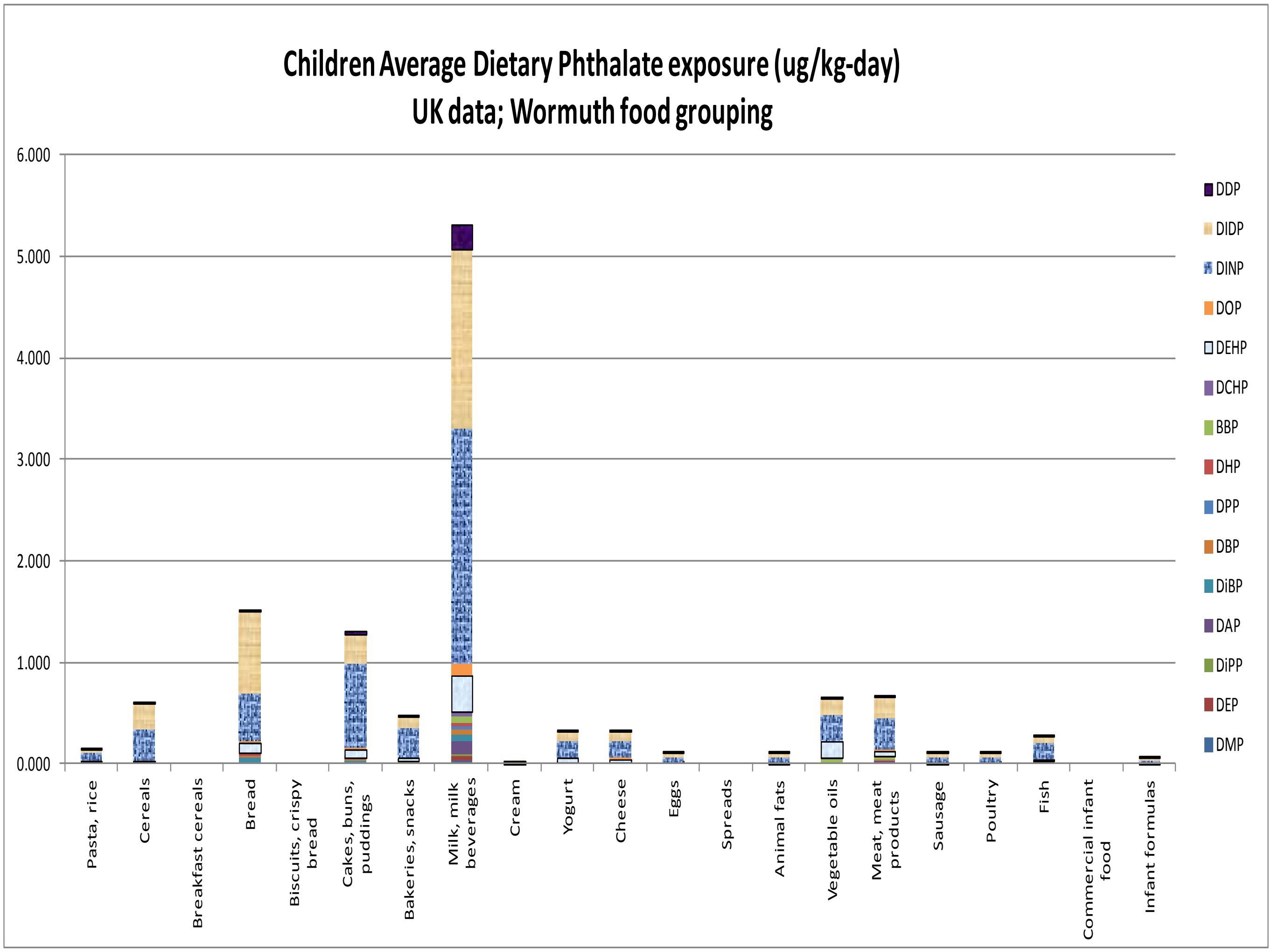
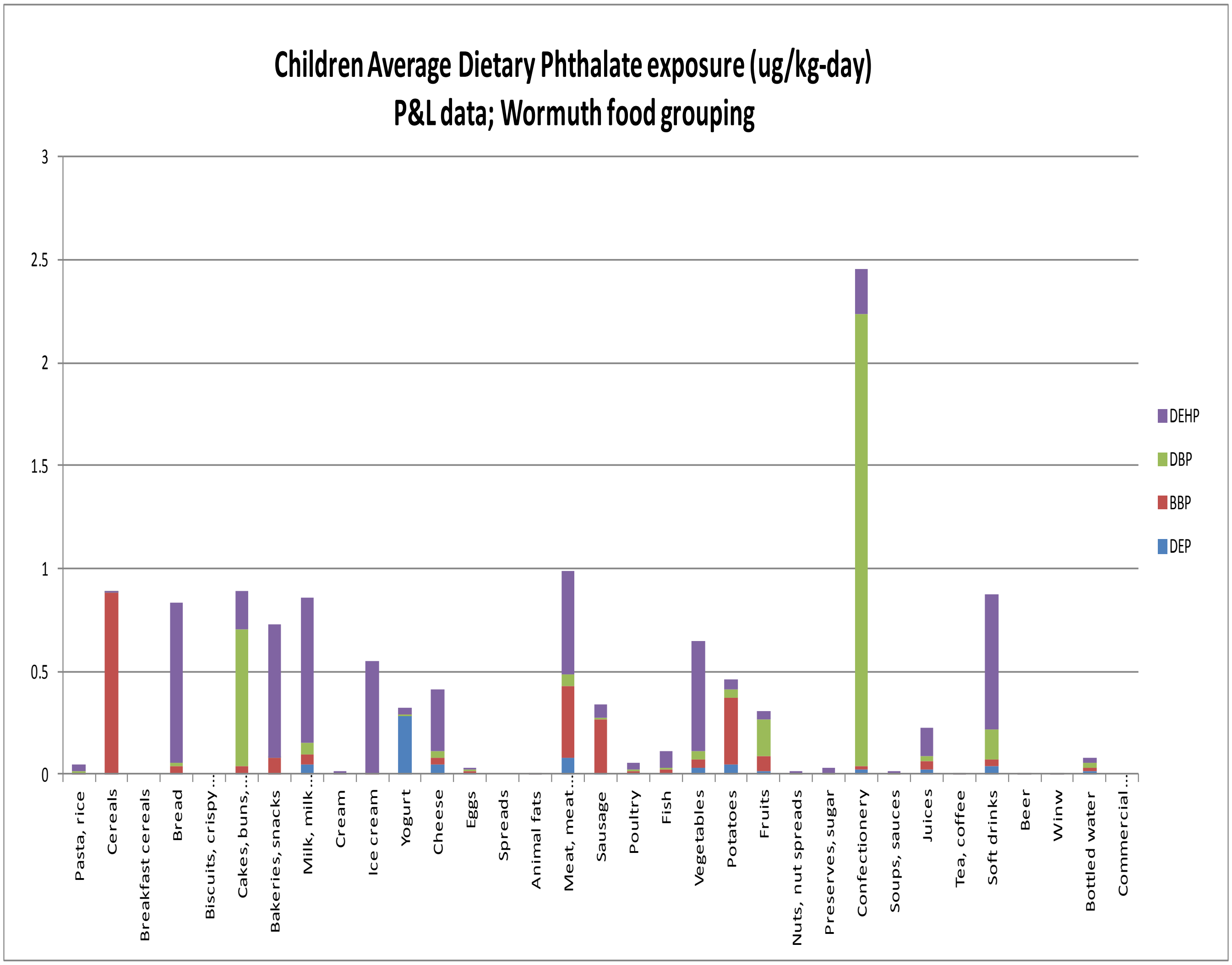
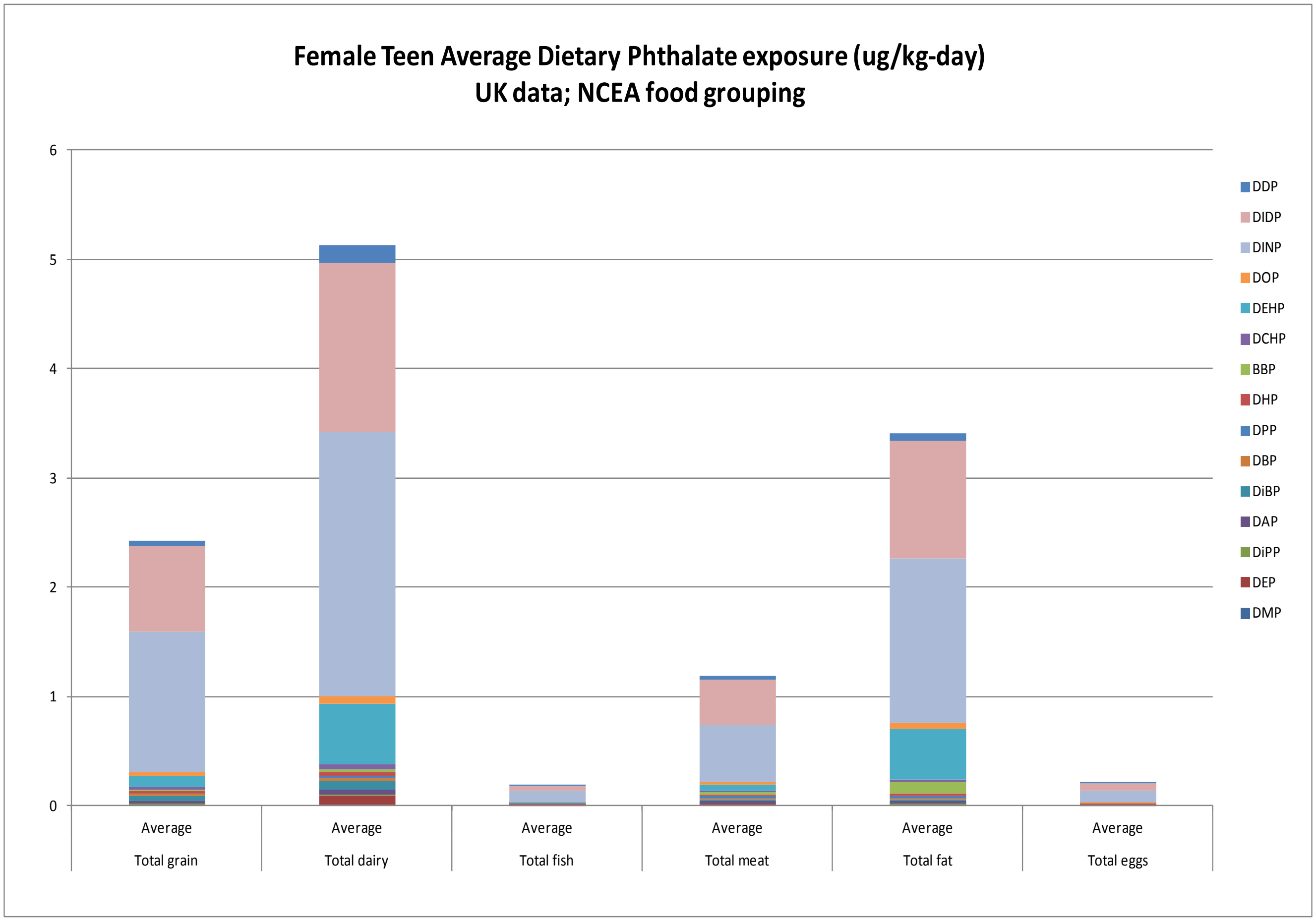


Figure E3-60 Children average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth food grouping.



4.5.4 Female Teen Average Dietary Exposures and the Relative Contribution of Various Phthalates

Figure E3-61 Female teen average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.



1125 Figure E3-62 Female teen average dietary phthalate exposure (ug/kg-day); P&L data; NCEA
1126 food grouping.

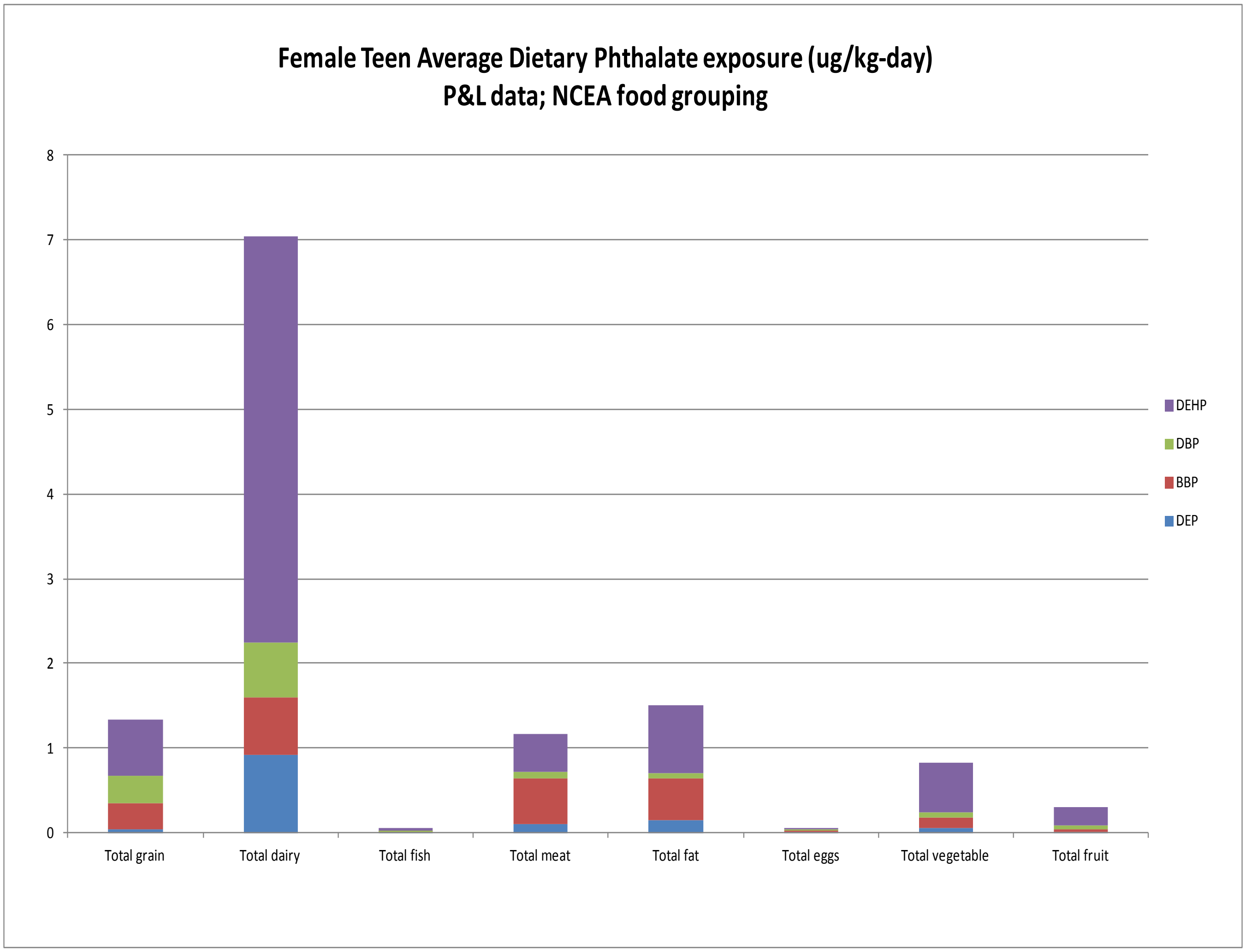


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Figure E3-63 Female teen average dietary phthalate exposure (ug/kg-day); UK data; Clark food grouping.

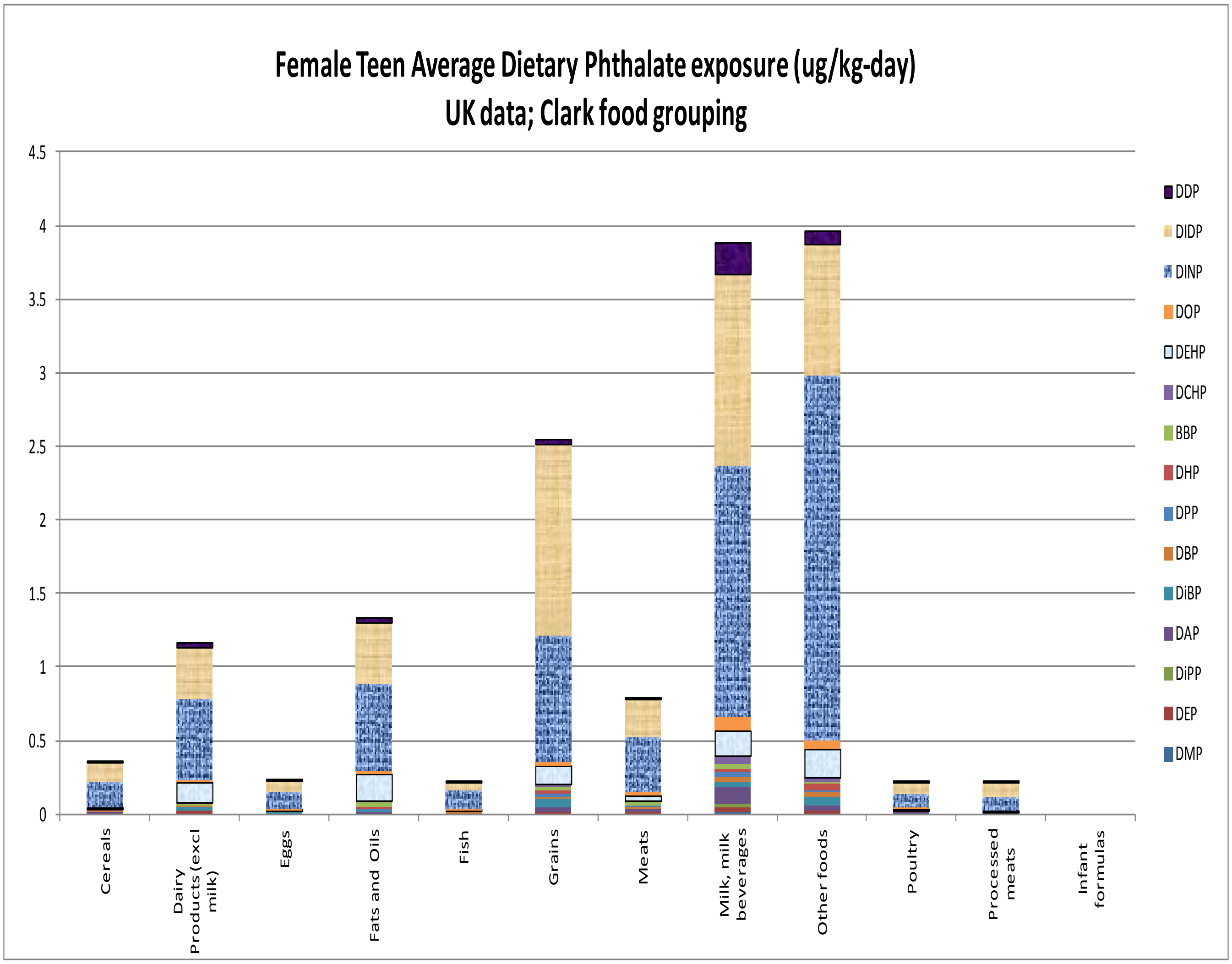


Figure E3-64 Female teen average dietary phthalate exposure (ug/kg-day); P&L data; Clark food grouping.

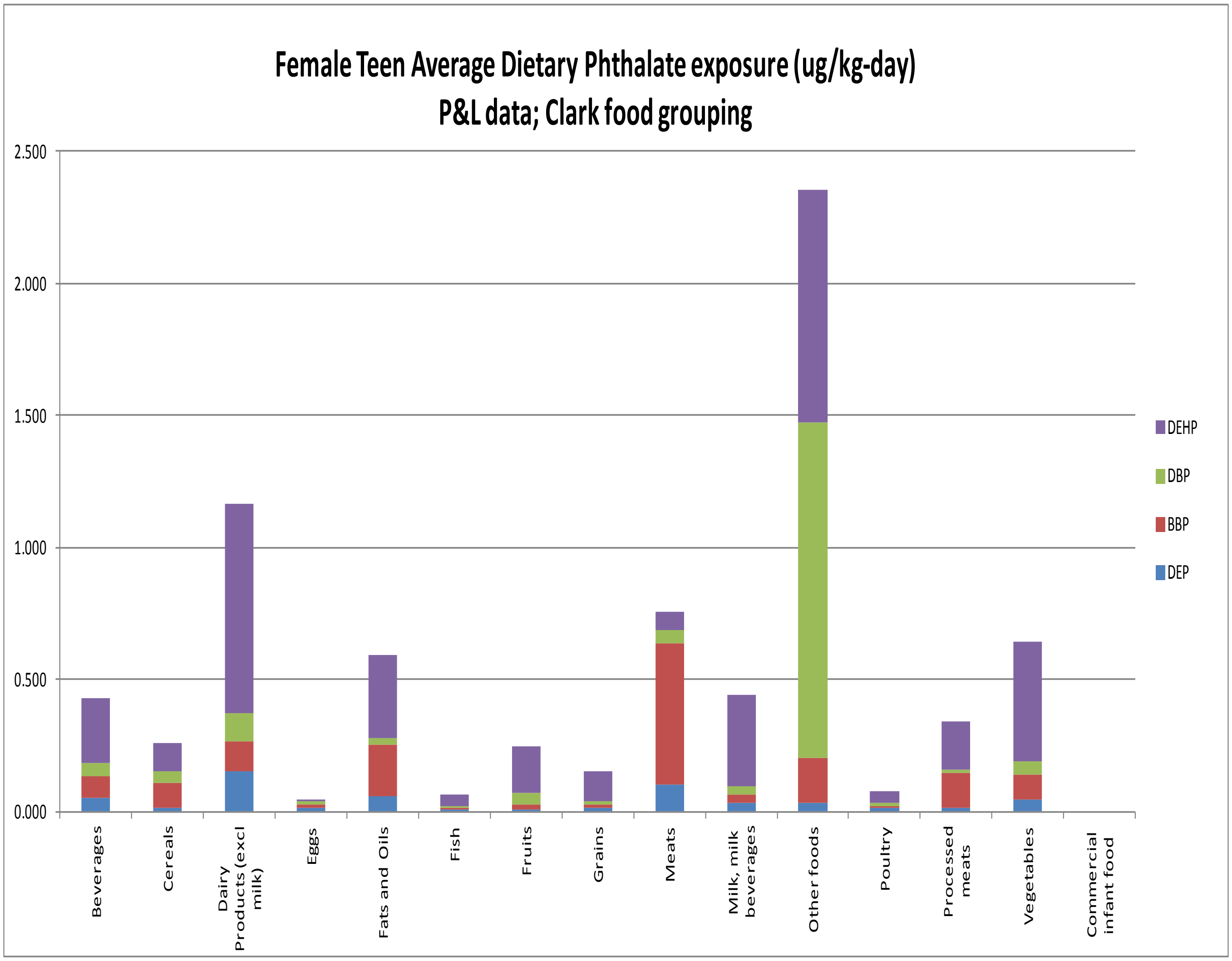


Figure E3-65 Female teen average dietary phthalate exposure (ug/kg-day); UK data; Wormuth food grouping.

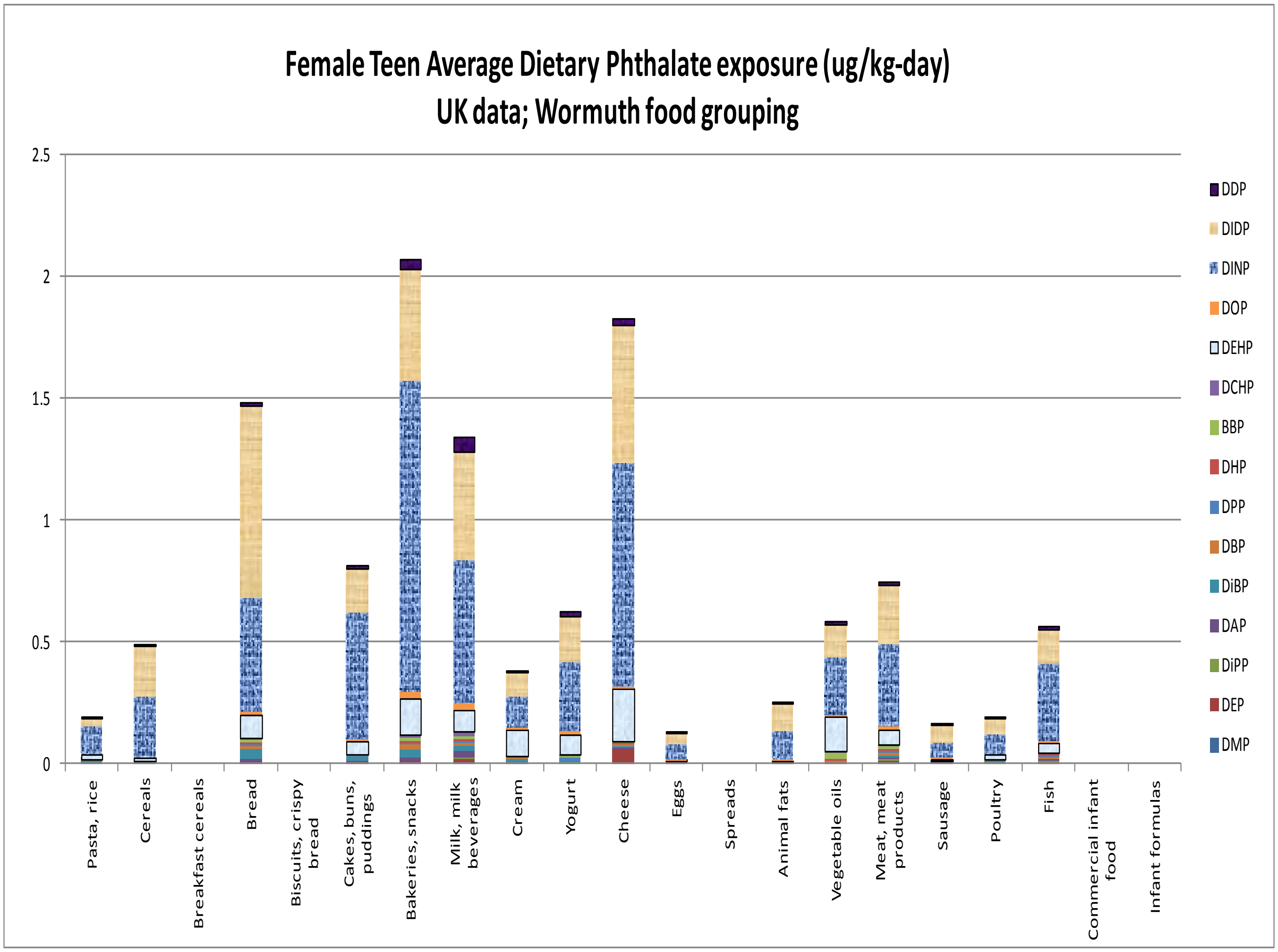
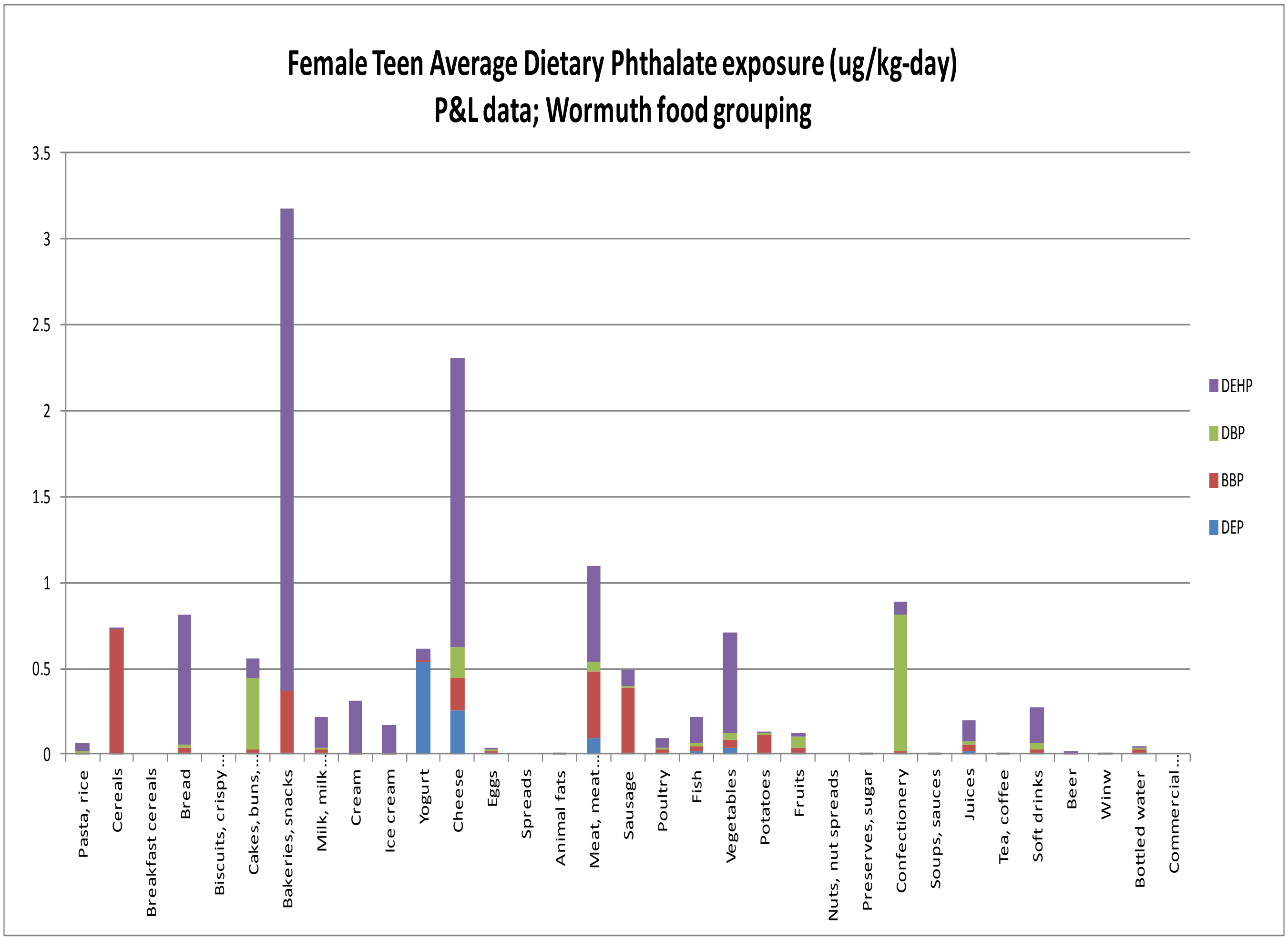
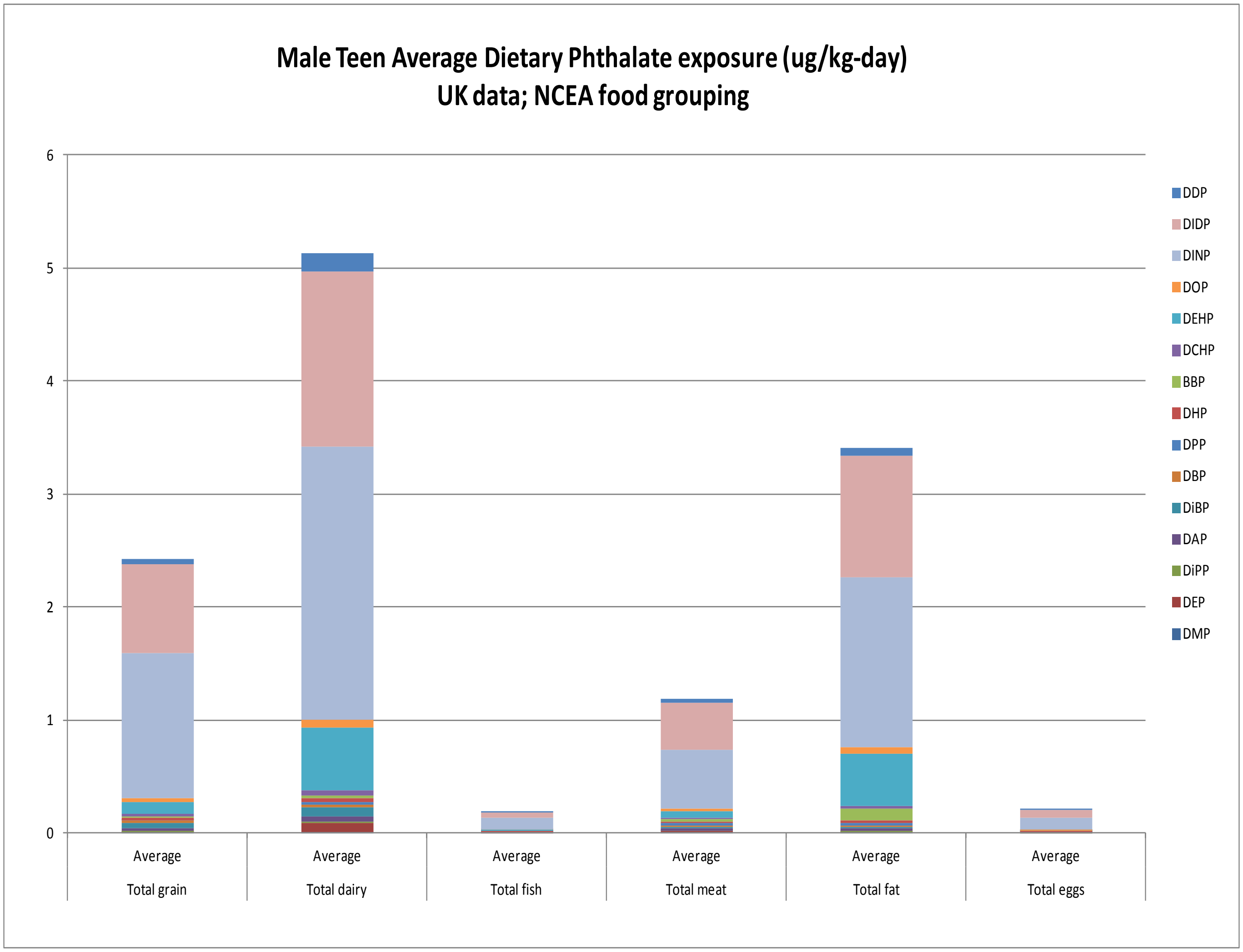


Figure E3-66 Female teen average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth food grouping.

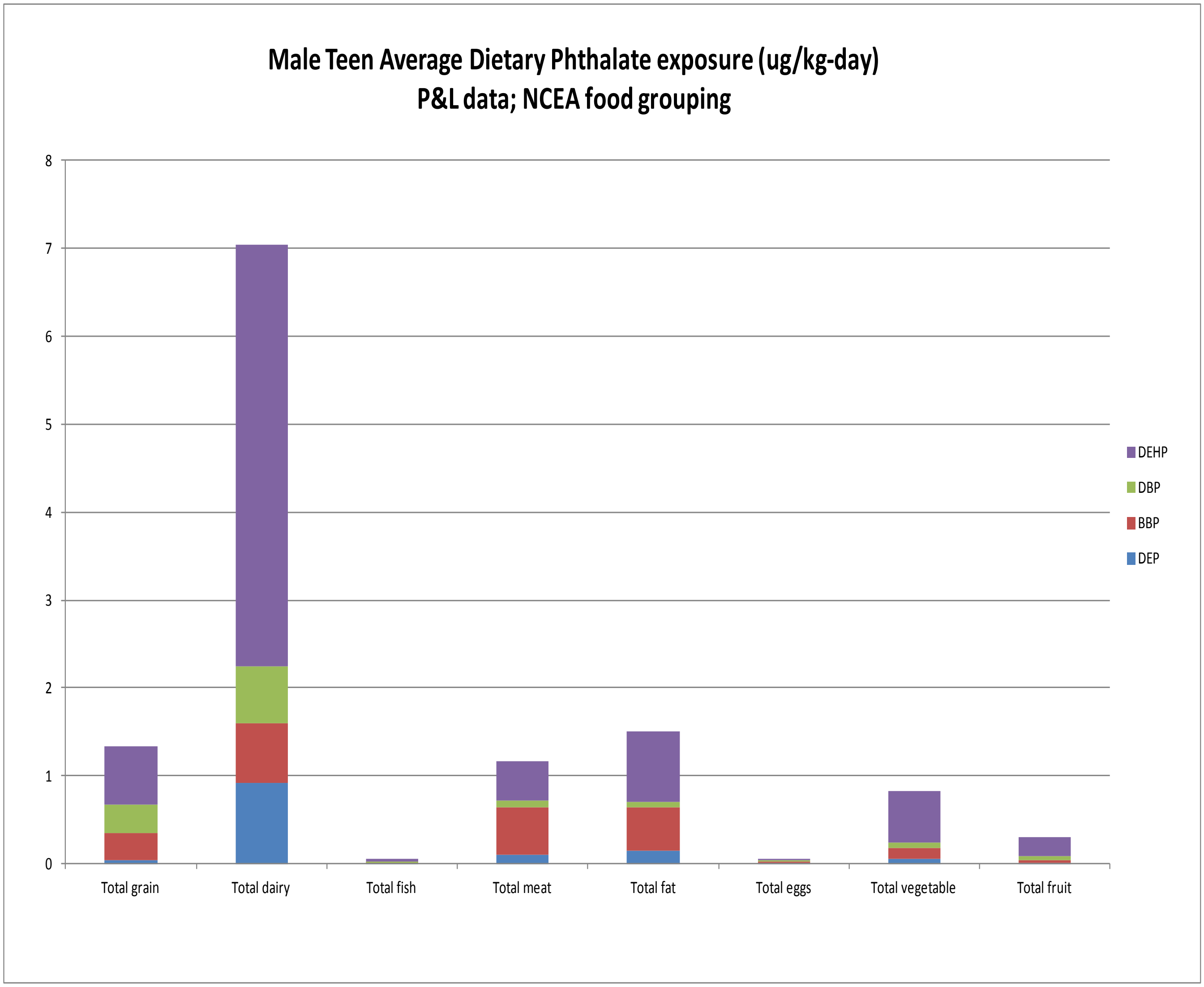


4.5.5 Male Teen Average Dietary Exposures and the Relative Contribution of Various Phthalates

Figure E3-67 Male teen average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.



1152 **Figure E3-68** Male teen average dietary phthalate exposure (ug/kg-day); P&L data; NCEA food
1153 grouping.



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1156 **Figure E3-69** Male teen average dietary phthalate exposure (ug/kg-day); UK data; Clark food
1157 grouping.

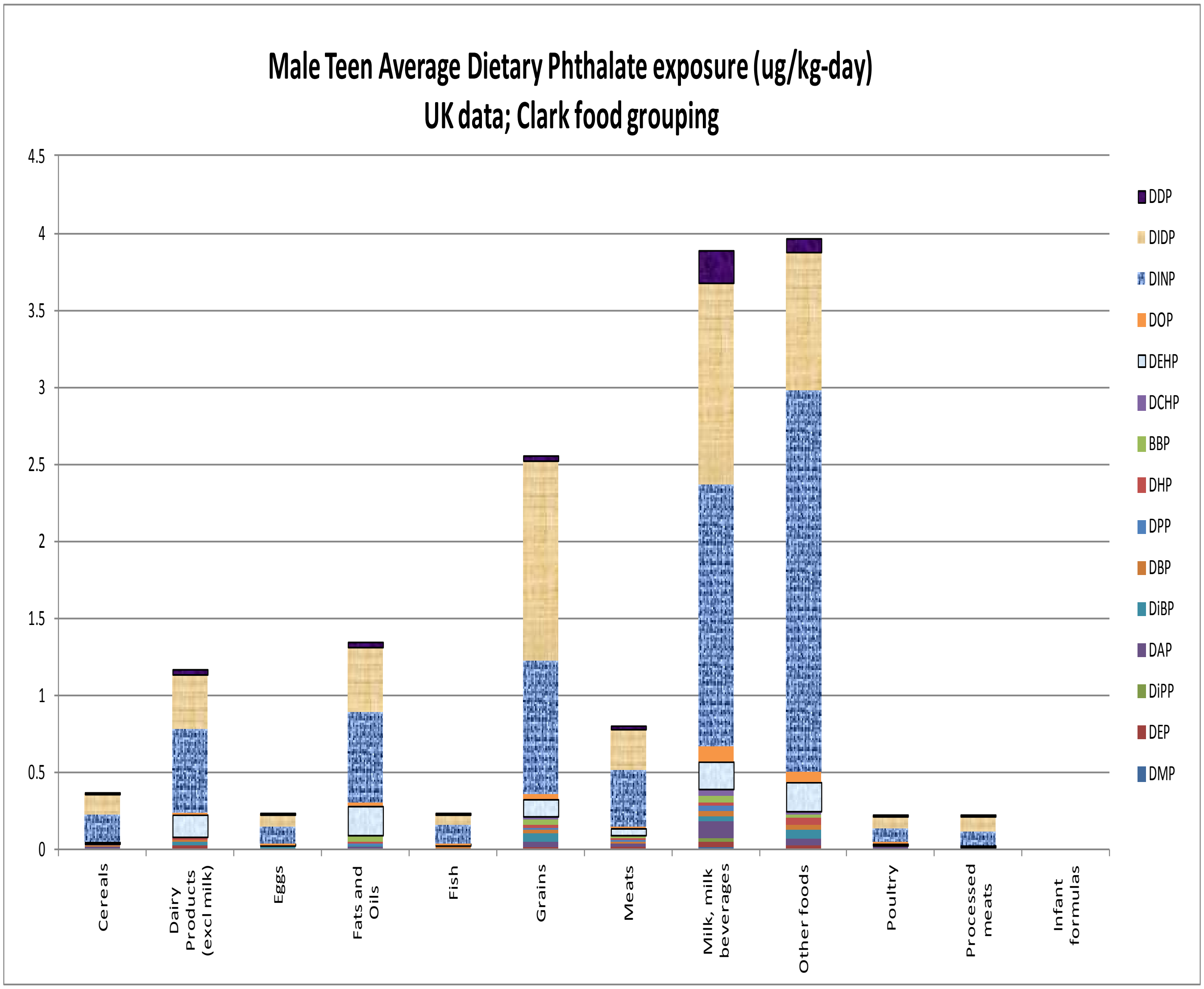

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Figure E3-70 Male teen average dietary phthalate exposure (ug/kg-day); P&L data; Clark food grouping.

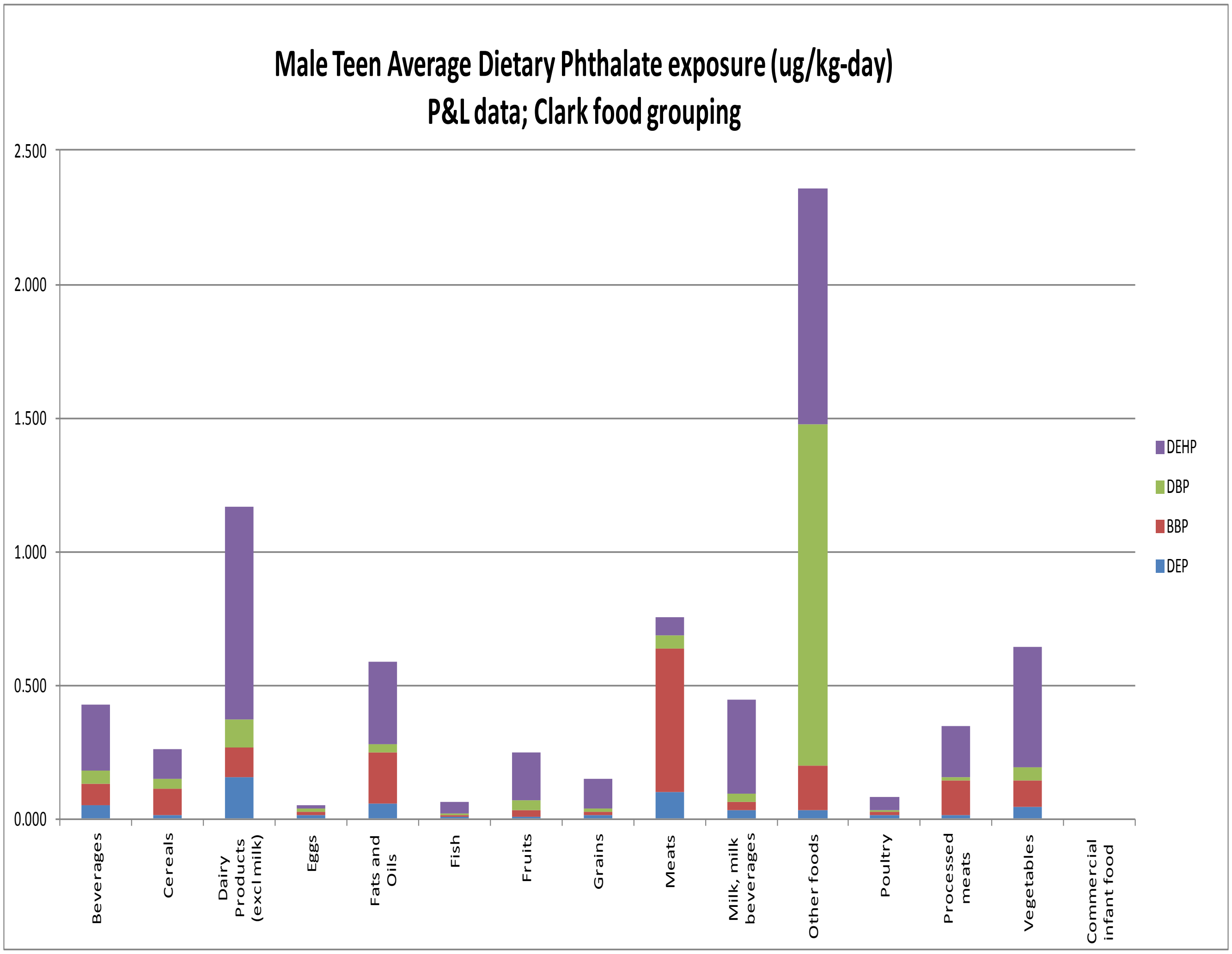
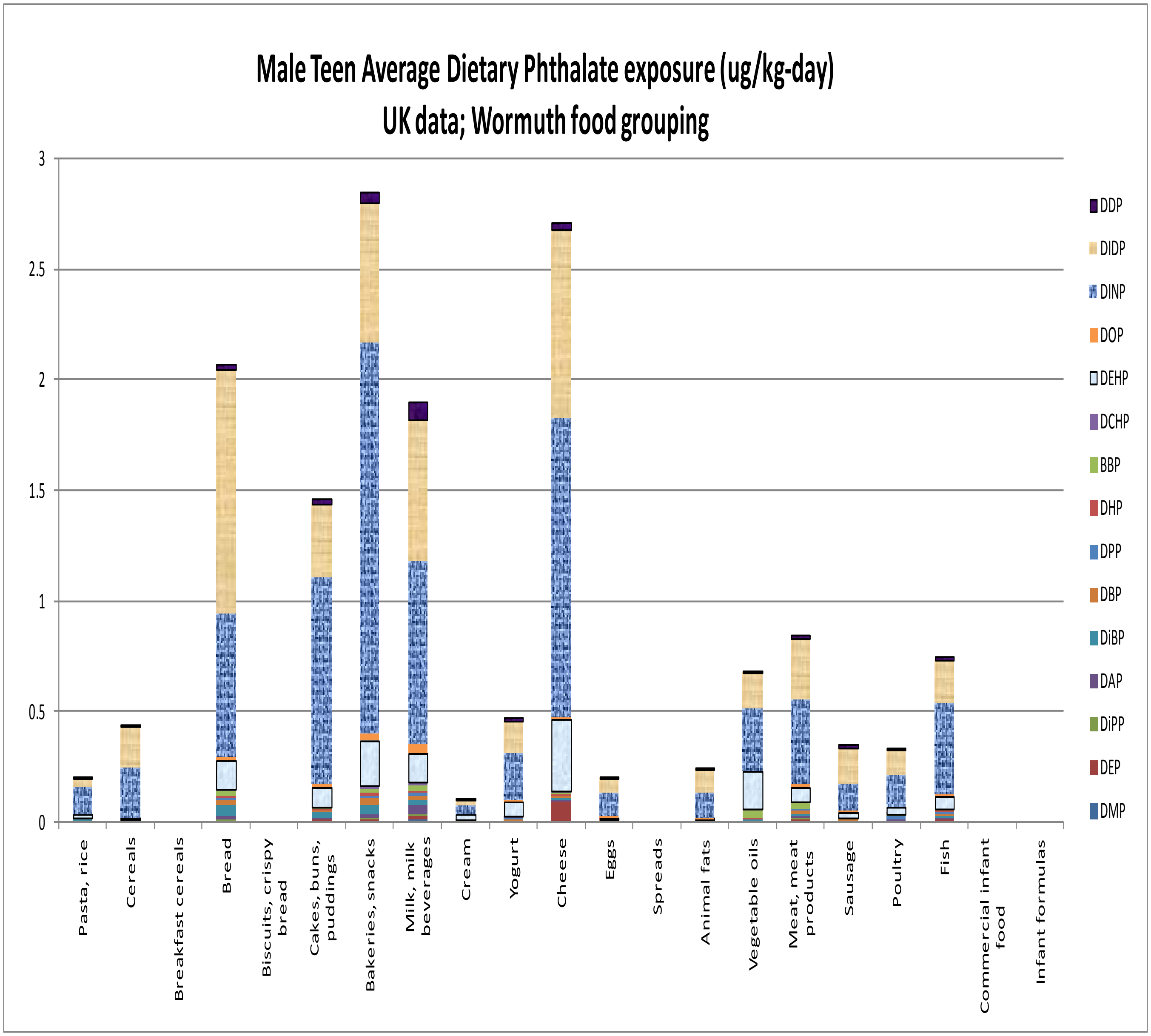
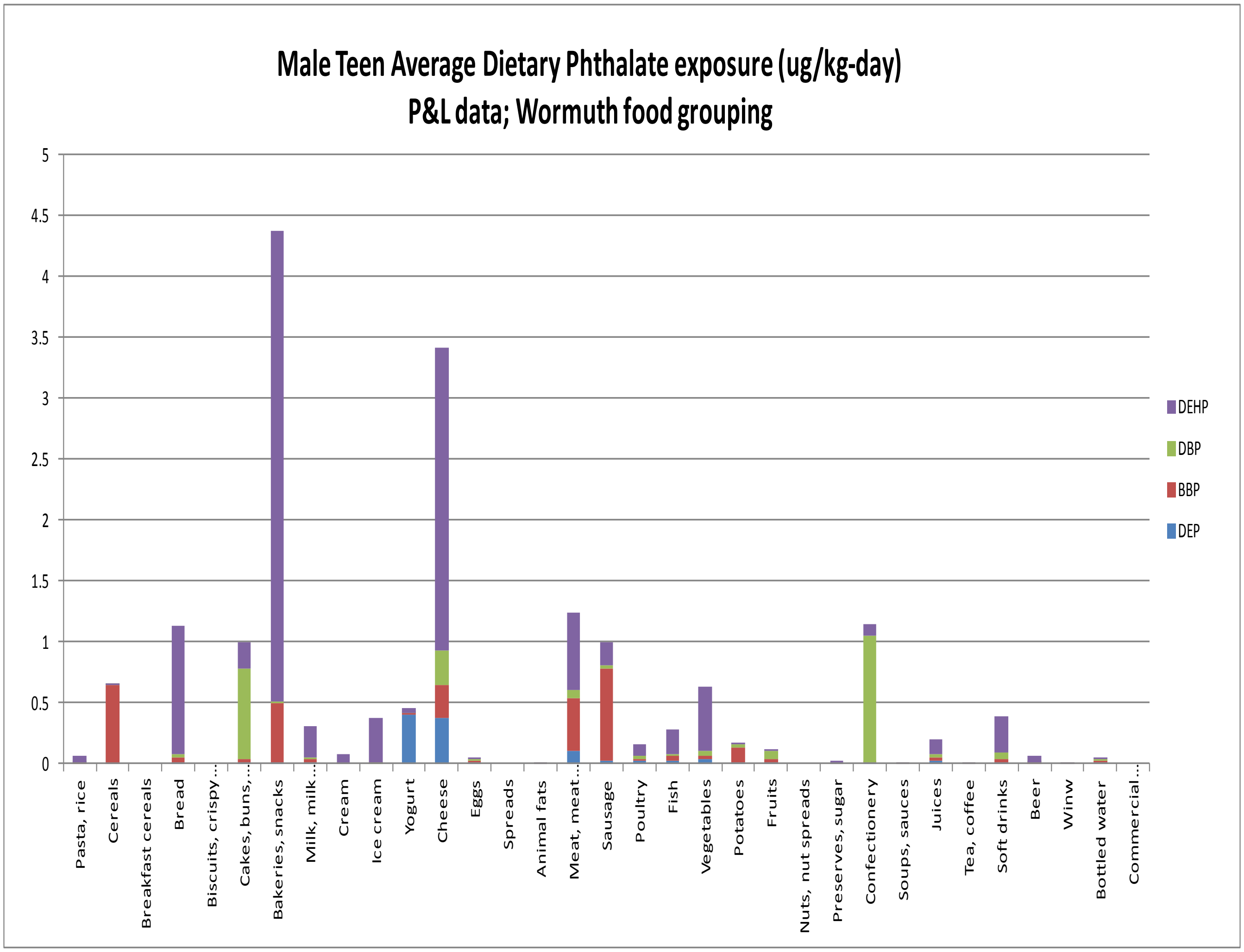


Figure E3-71 Male teen average dietary phthalate exposure (ug/kg-day); UK data; Wormuth food grouping.



1168 Figure E3-72 Male teen average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth
1169 food grouping.



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4.5.6 Female Adult Average Dietary Exposures and the Relative Contribution of Various Phthalates

Figure E3-73 Female adult average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.

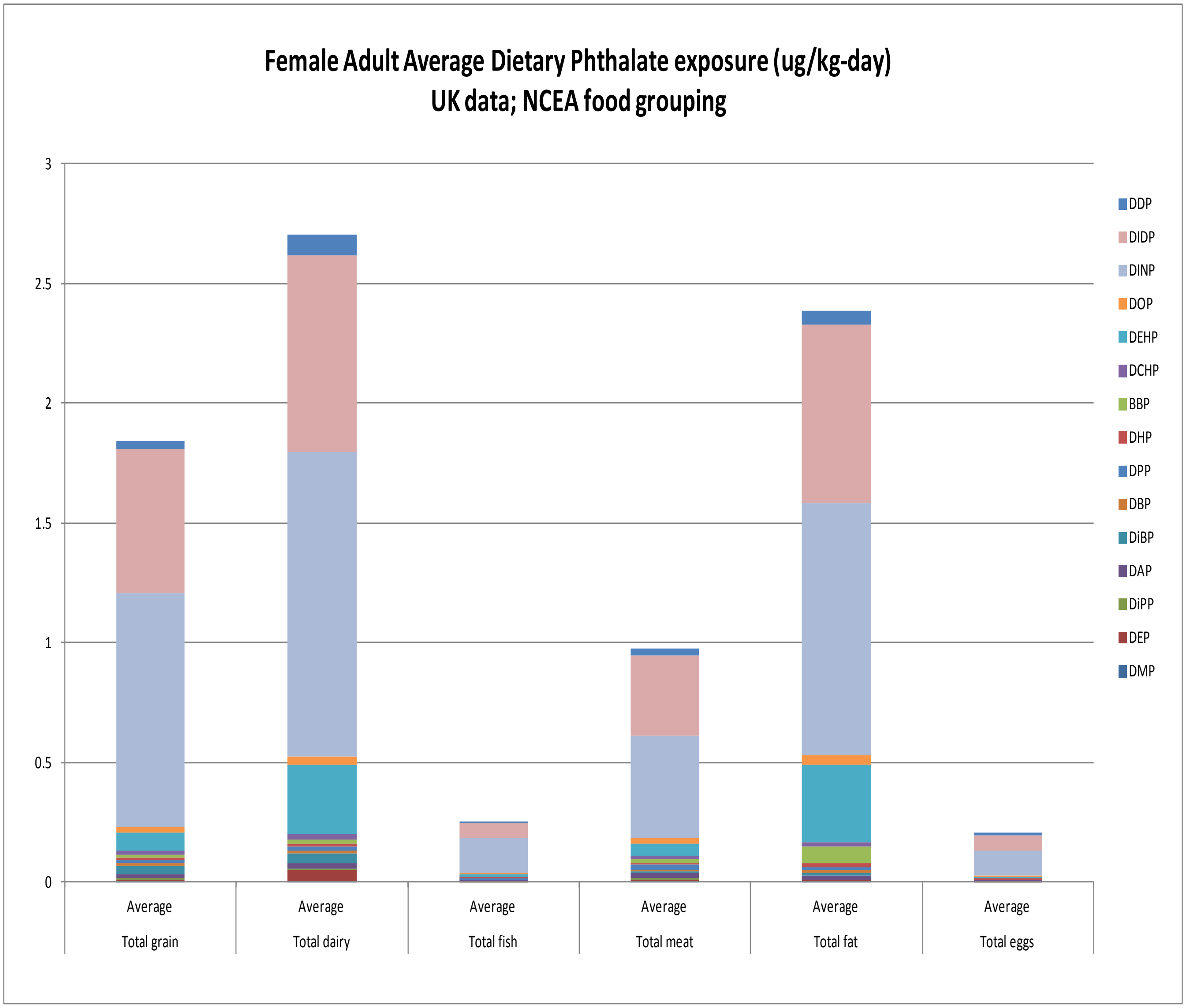
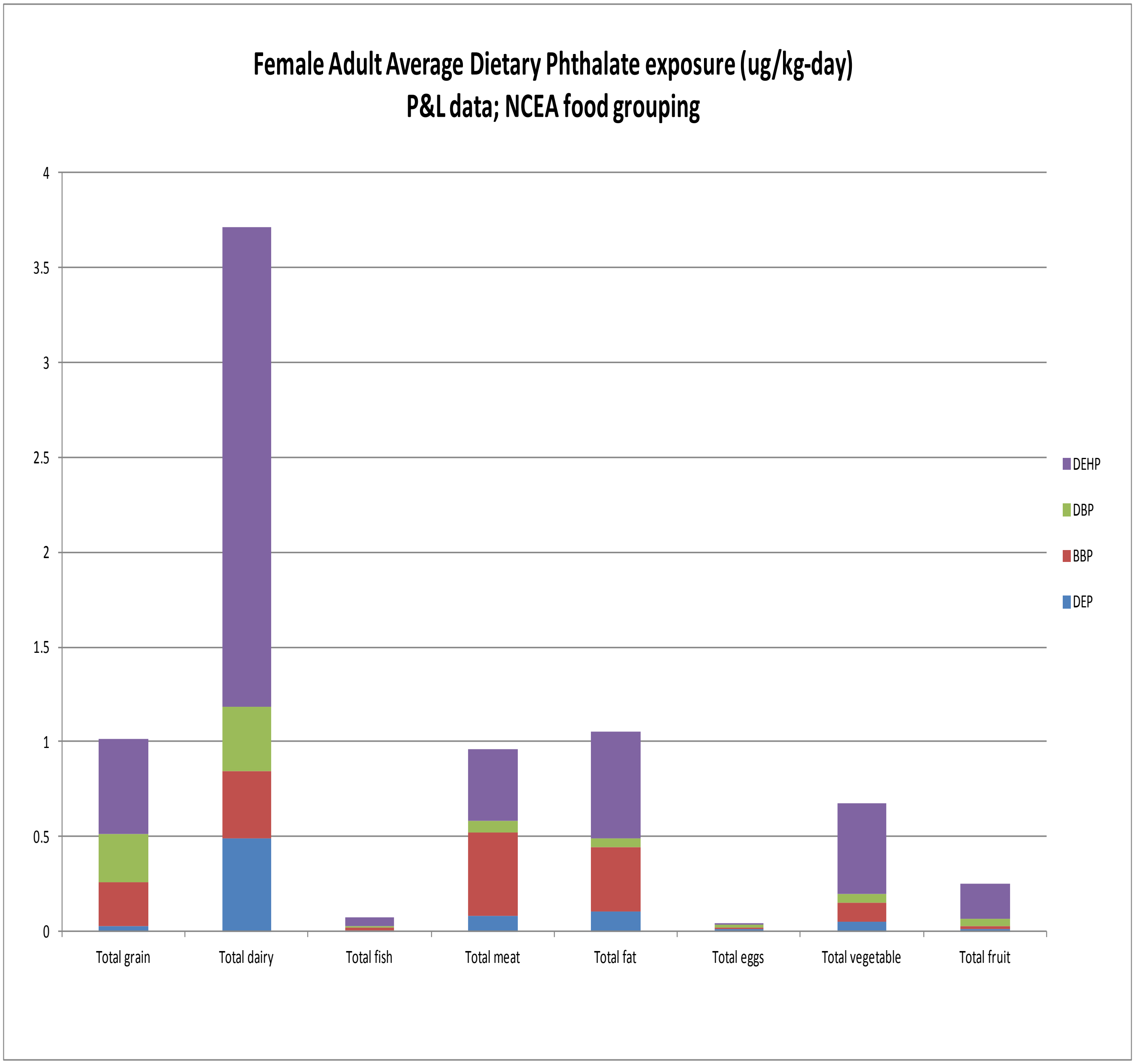
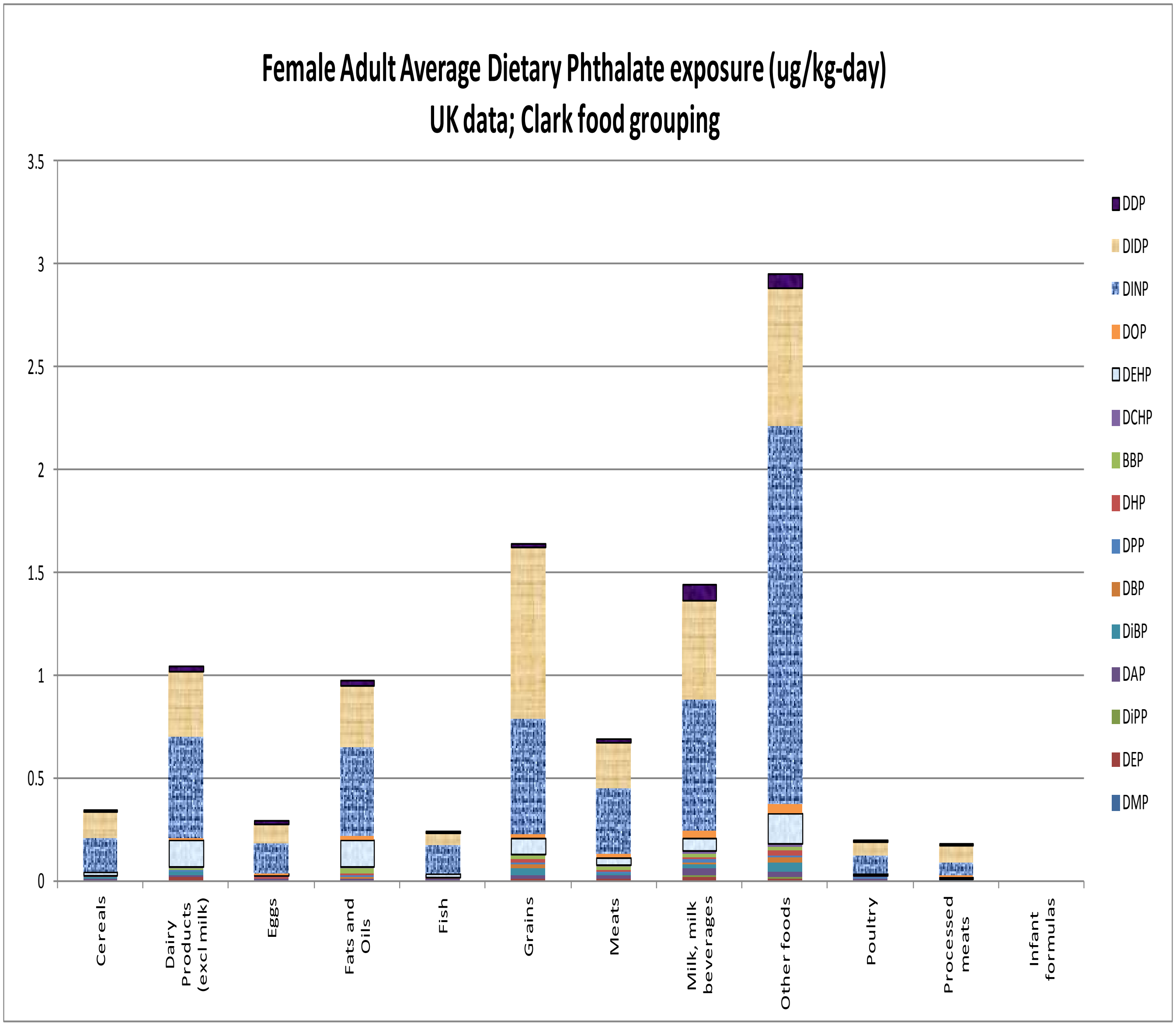


Figure E3-74 Female adult average dietary phthalate exposure (ug/kg-day); P&L data; NCEA food grouping.



1182 Figure E3-75 Female adult average dietary phthalate exposure (ug/kg-day); UK data; Clark food
1183 grouping.



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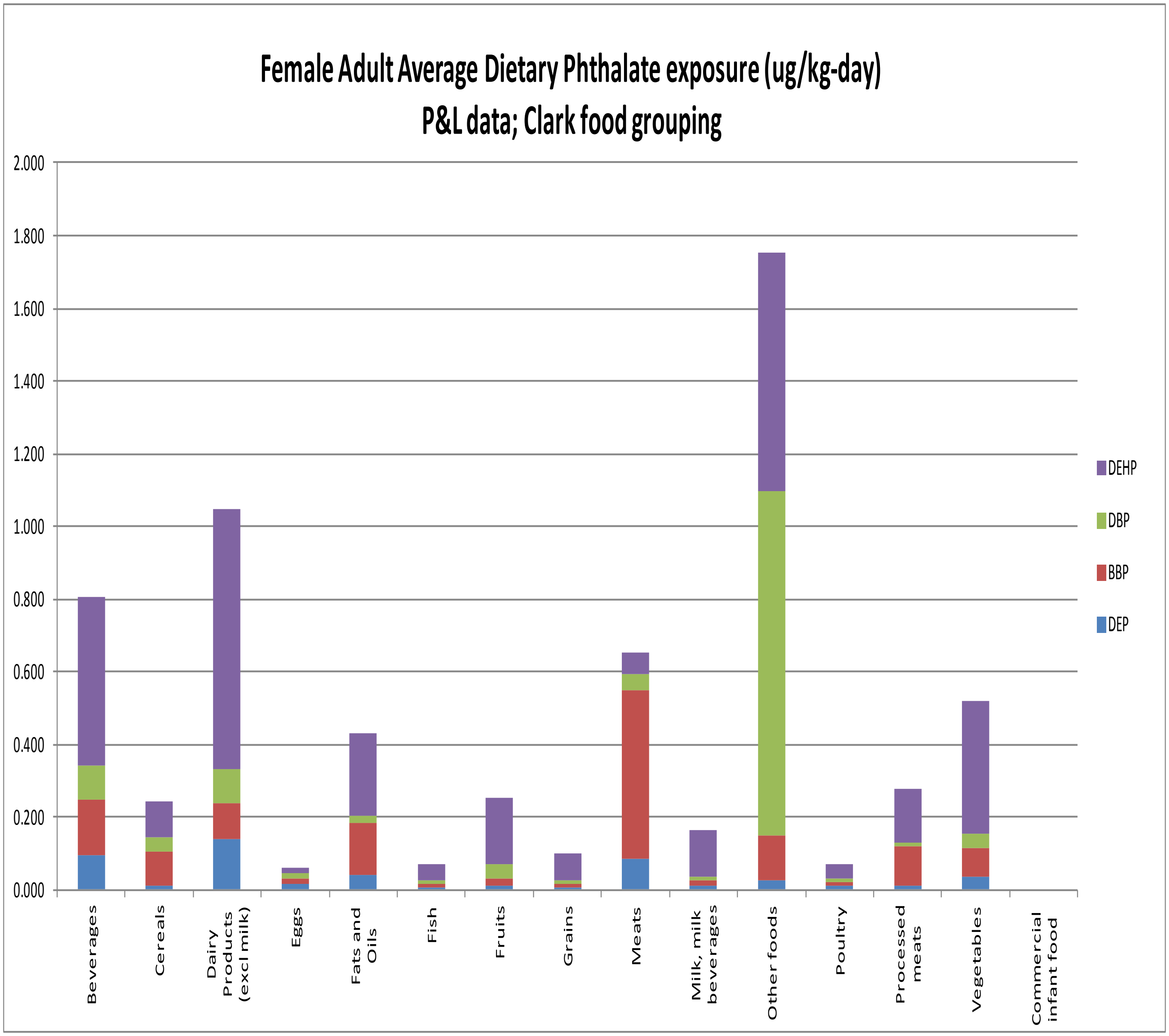
1186 Figure E3-76 Female adult average dietary phthalate exposure (ug/kg-day); P&L data; Clark
1187 food grouping.



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1190 Figure E3-77 Female adult average dietary phthalate exposure (ug/kg-day); UK data; Wormuth
1191 food grouping.

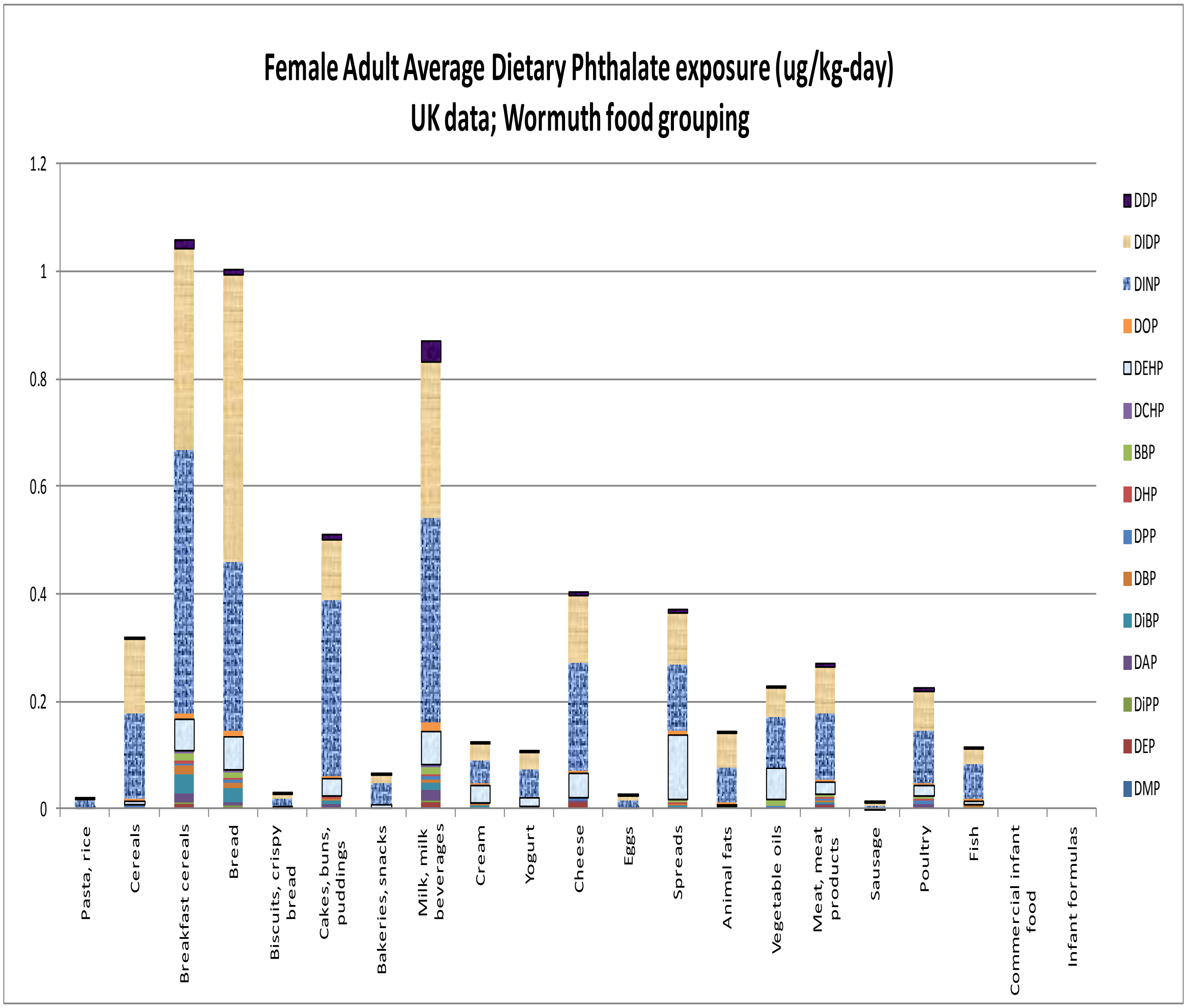

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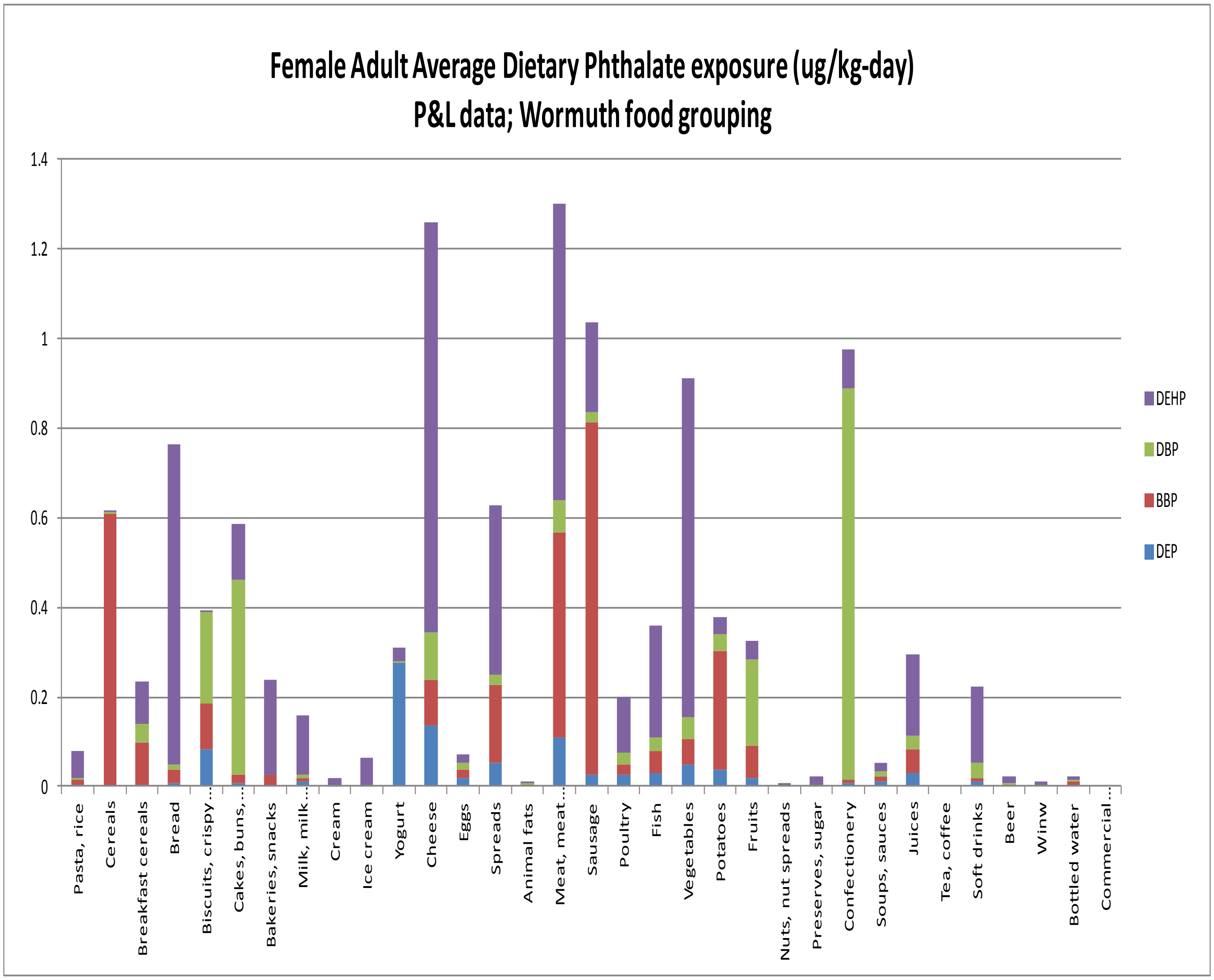
Figure E3-78 Female adult average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth food grouping.



4.5.7 Male Adult Average Dietary Exposures and the Relative Contribution of Various Phthalates

Figure E3-79 Male adult average dietary phthalate exposure (ug/kg-day); UK data; NCEA food grouping.

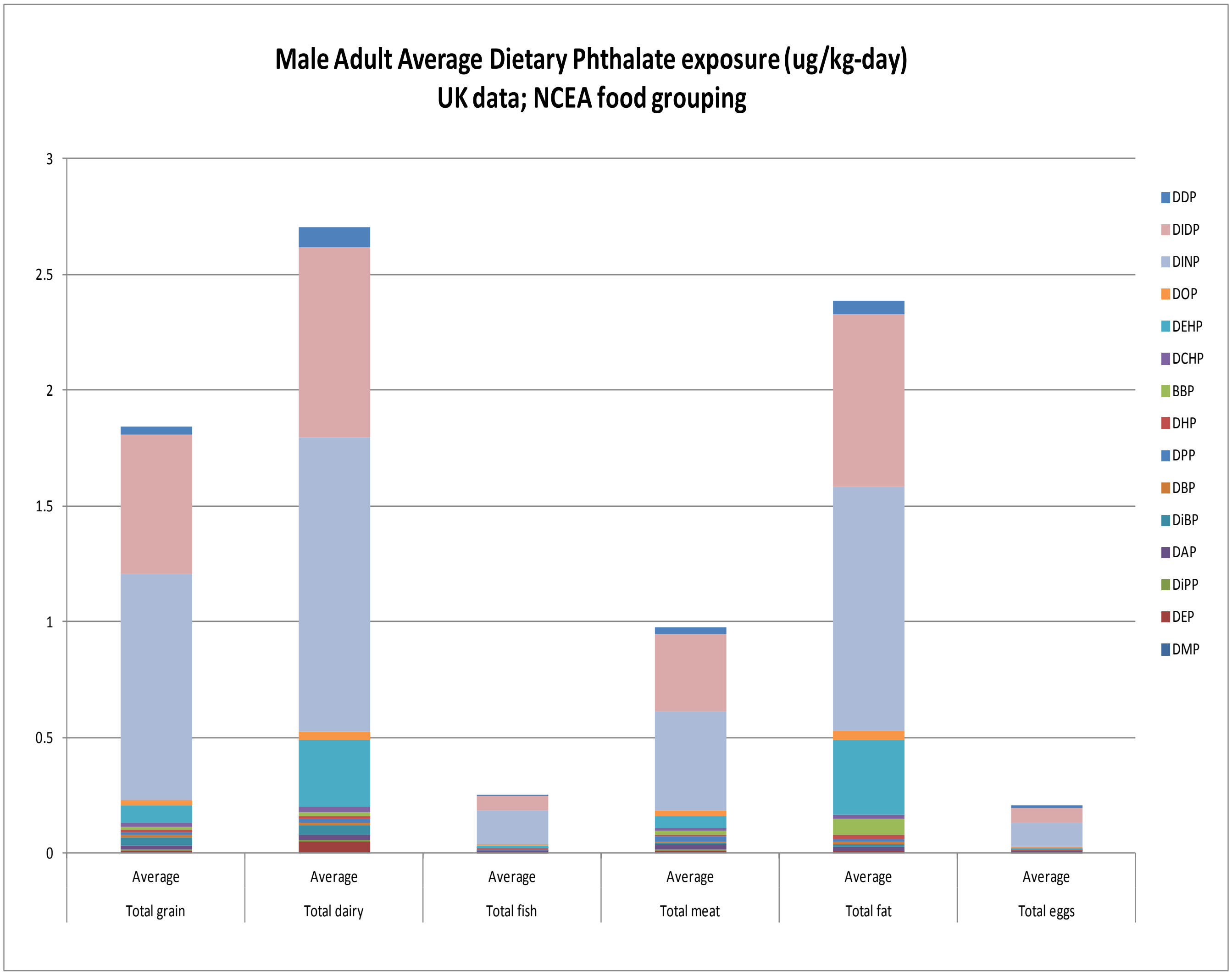


Figure E3-80 Male adult average dietary phthalate exposure (ug/kg-day); P&L data; NCEA food grouping.

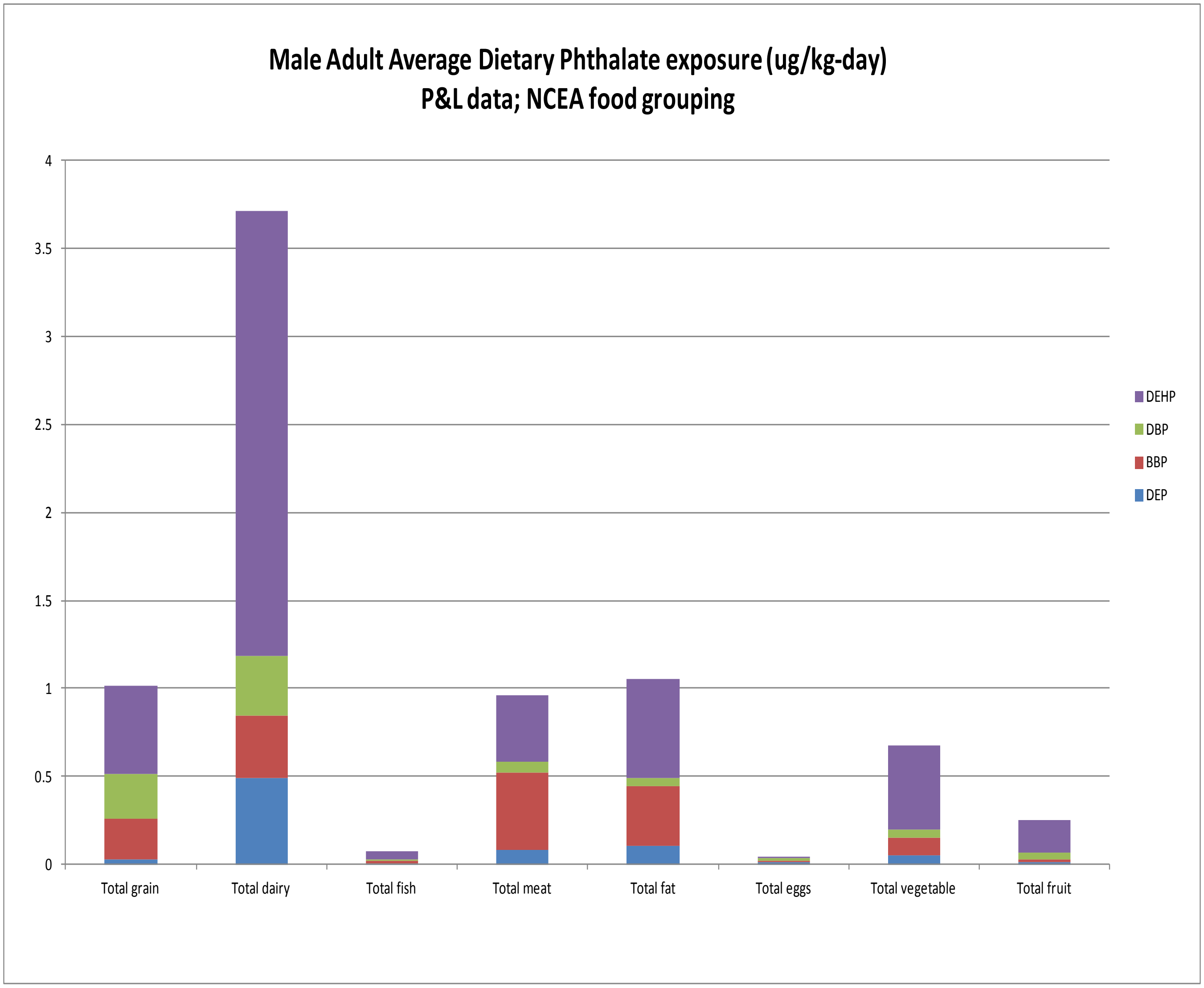
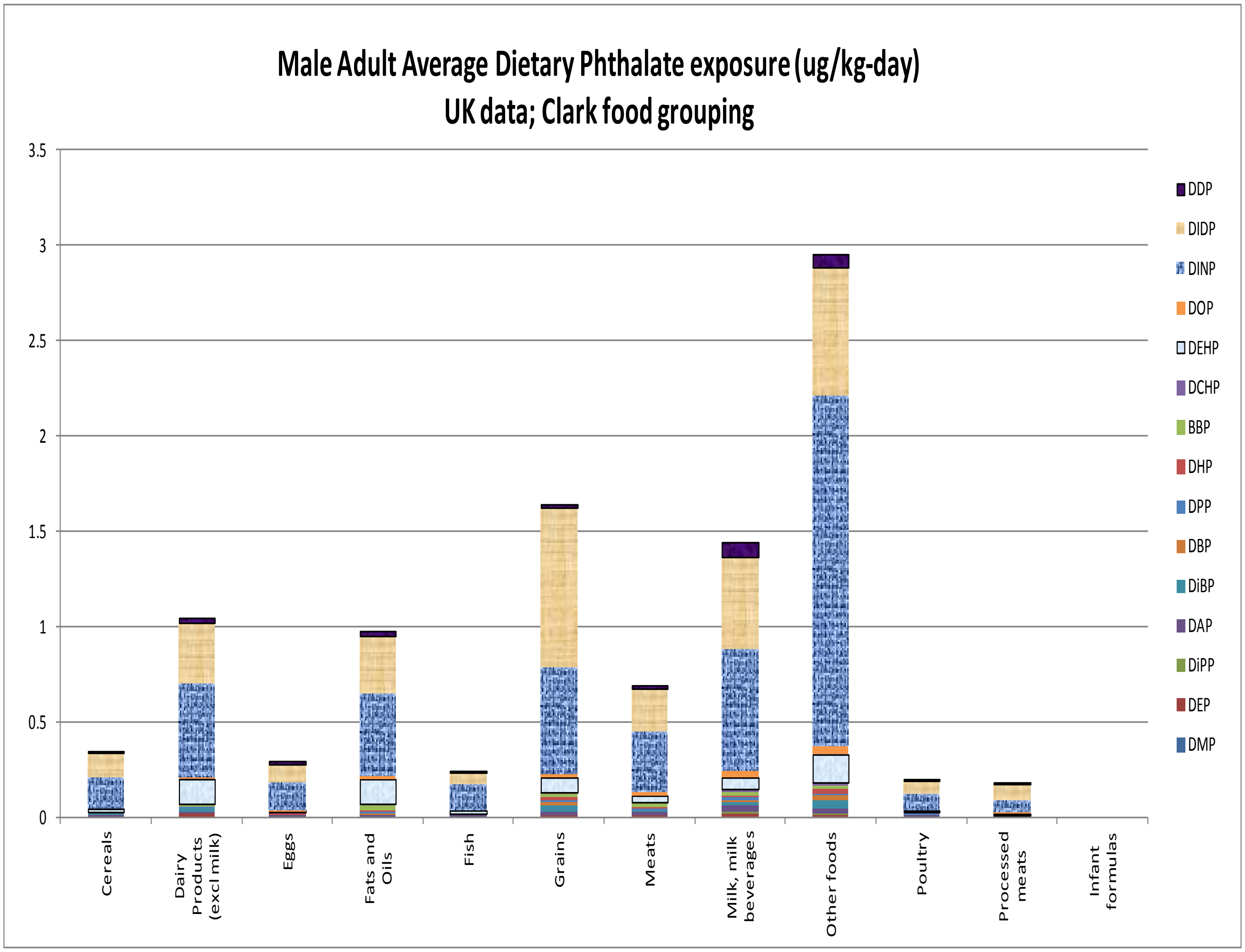


Figure E3-81 Male adult average dietary phthalate exposure (ug/kg-day); UK data; Clark food grouping.



1212 Figure E3-82 Male adult average dietary phthalate exposure (ug/kg-day); P&L data; Clark food
1213 grouping.

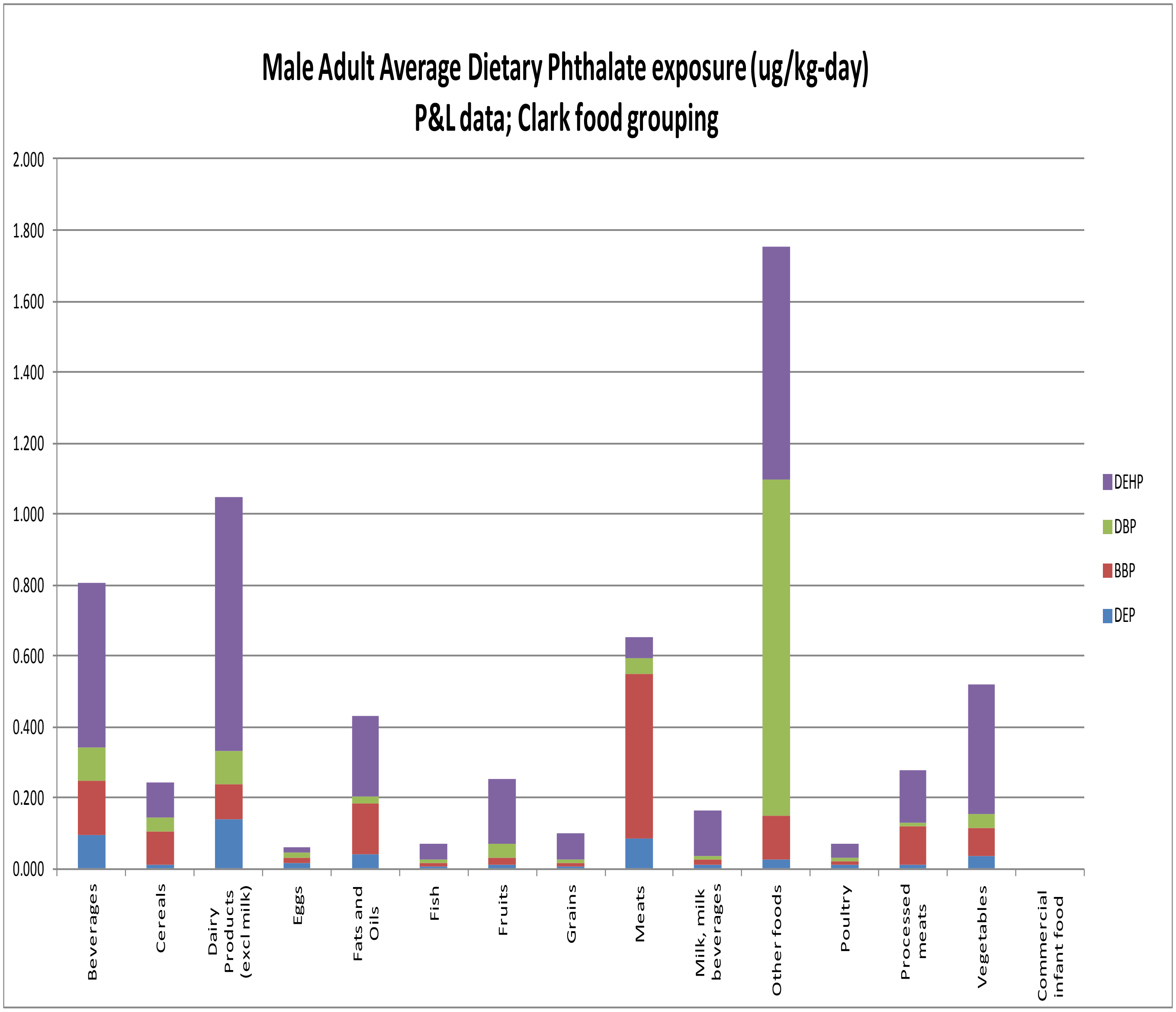
1214 

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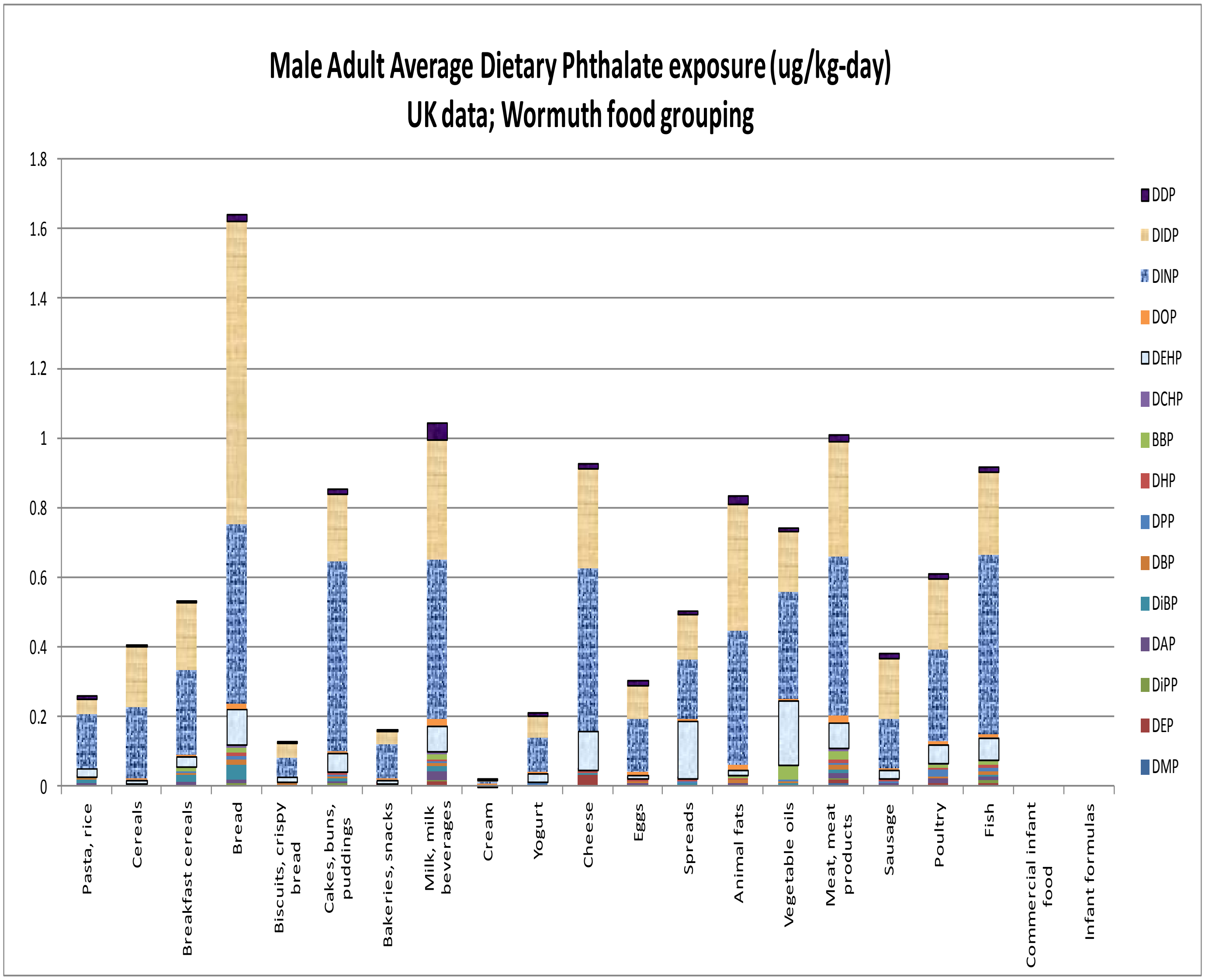
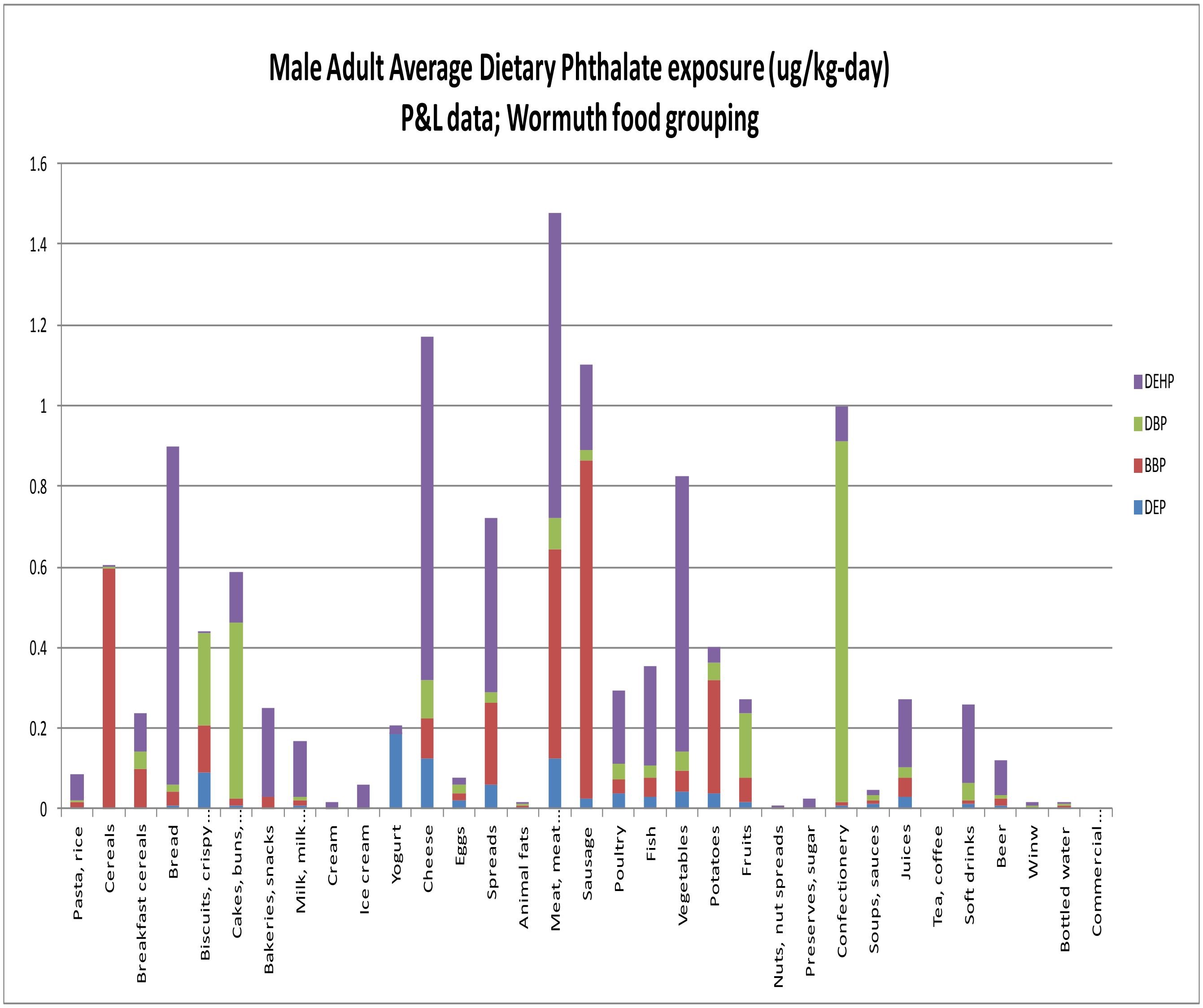
Figure E3-83 Male Adult Average Dietary Phthalate exposure (ug/kg-day); UK data; Wormuth food grouping.



1220 Figure E3-84 Male adult average dietary phthalate exposure (ug/kg-day); P&L data; Wormuth
1221 food grouping.



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