UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
BETHESDA, MD 20814

Memorandum

Date: April 12, 2010

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SUBJECT : Overview of Phthalates Toxicity*

The attached report provides a brief overview of the toxicity of dialkyl *o*-phthalates (o-DAP's). It is not intended to be comprehensive. Rather, it is intended to provide an introduction to the vast body of scientific literature on the health risk of phthalates exposure. The salient properties of o-DAP's are discussed, including their physicochemical properties, commercial uses, toxicity, and human exposure. This summary report is accompanied by detailed staff toxicity reviews of six banned phthalates as well as a contractor report summarizing the toxicities of five phthalate substitutes (these documents were cleared separately).

The information in this report will be provided to the Chronic Hazard Advisory Panel on Phthalates. This panel will convene in 2010 to assess the potential health effects of cumulative exposure to phthalates from all sources, including children's toys, child care products, and cosmetics.

* These comments are those of the CPSC staff, have not been reviewed or approved by, and do not necessarily represent the views of, the Commission.

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OVERVIEW OF DIALKYL *ORTHO*-PHTHALATES

Introduction

Dialkyl *ortho*-phthalates (*o*-DAP's) are a class comprising about 30 commercial products, 18 of which are high production volume (HPV) chemicals in the U.S. (ExxonMobil 2001). *o*-DAP's are used primarily as plasticizers for polyvinyl chloride (PVC) and as solvents. The general structure is a diester of 1,2-dicarboxy-benzene (Figure 1). The two alkyl groups may be similar or dissimilar; they may be branched or linear; and they may contain aromatic substitutes, e.g., butyl benzyl phthalate (BBP) or other functional groups. The *o*-DAP's are of particular interest due to widespread human exposure and the observation that certain *o*-DAP's induce reproductive and developmental health effects in animals. In addition, certain developmental effects of *o*-DAP's are believed to be additive. Thus, the effects of exposure to multiple phthalates may be greater than the effects of the individual compounds.

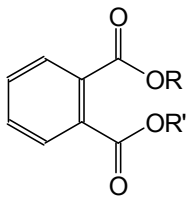

Figure 1. Dialkyl *o*-Phthalate

The health effects of certain *o*-DAP's have been reviewed by various groups, including the Agency for Toxic Substances and Disease Registry (ATSDR), the Australian Government (National Industrial Chemicals Notification and Assessment Scheme, NICNAS), the Center for the Evaluation of Research on Human Reproduction (CERHR), the European Chemicals Bureau (ECB), and the National Research Council (NRC 2009).

CPSIA

The Consumer Product Safety Improvement Act of 2008 (CPSIA)[2] 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) (Table 1). 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 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 (including DINP) or phthalate alternatives other than those permanently banned should be declared banned hazardous substances.

The CPSC staff has completed the following reports to support the work of the CHAP on Phthalates:

[2] Public Law 110-314.

- Toxicity reviews of the six phthalates specifically addressed in the CPSIA (three permanently banned and three banned on an interim basis). The six toxicity reviews have been peer reviewed by independent scientists.
- Toxicity reviews of five phthalate substitutes (contractor report).
- A review of published exposure studies on phthalates (contractor report).
- Laboratory studies of plasticizers in children's articles.

Table 1. Dialkyl *ortho*-phthalates (*o*-DAP's) banned by the Consumer Product Safety Improvement Act of 2008 (CPSIA)

Phthalate	CAS number [a]
Permanent ban	
Dibutyl phthalate (DBP)	84-74-2
Benzyl butyl phthalate (BBP)	85-68-7
Di(2-ethyhexyl 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)	26761-40-0, 68515-49-1

[a] CAS, Chemical Abstracts Service

In addition to the six regulated phthalates, there are also numerous other phthalates and phthalate mixtures in commerce. Other phthalates, including, but not limited to, di-*n*-propyl phthalate, diisobutyl phthalate, di-*n*-pentyl phthalate, dicyclohexyl phthalate, and di(2-propylheptyl) phthalate may also contribute to the cumulative health risks of phthalates.

The purpose of this report is to provide a brief overview of the toxicity of the o-DAP's. This report is not intended to be comprehensive. Rather, it is intended to introduce the reader to the vast body of scientific literature on the health risks of phthalates exposure. The salient properties of o-DAP's are discussed, including their physicochemical properties, commercial uses, toxicity, and human exposure. This review will focus on the six phthalates specifically mentioned in the CPSIA plus dimethyl phthalate (DMP) and diethyl phthalate (DEP). The information in this report will be provided to the CHAP on Phthalates. The toxicity data for five phthalate substitutes has been reviewed separately (Versar and SRC 2010), and will also be provided to the CHAP.

Chemistry and Use

The *o*-DAP's are hydrophobic compounds with low vapor pressures (Table 2). They are generally viscous liquids with high boiling points and low melting points. They have low water solubility. Some of the high molecular weight *o*-DAP's (DEHP, DINP, DIDP) are extremely hydrophobic with logK values from 7.5- to 8.8 (NICNAS 2008).

Table 2. Physico-chemical properties of selected dialkyl ortho-phthalates (NICNAS 2008a).

Phthalate	MW	Chain Length	VP (Torr)	Log K	Water solubility (mg/L)	MP (°C)	BP (°C)
Dimethyl phthalate (DMP)	194.2	1	$6.0x10^{-3}$	1.5—2.1	4.3	5.5	284
Diethyl phthalate (DEP)	222.2	2	$1.6 x10^{-3}$	2.5	1	--	298
Di-*n*-butyl phthalate (DBP)	278.3	4	$7.3 x10^{-5}$	4.6	$1x10^{-2}$	-69	340
Butyl benzyl phthalate (BBP)	298.3	4, 6	$6.0 x10^{-7}$	4.8	$2.8x10^{-3}$	<-35	--
Di(2-ethylhexyl) phthalate (DEHP)	390.6	6	$1.0 x10^{-7}$	7.5	$3.0x10^{-3}$	-47	384
Di-n-octyl phthalate (DnOP)	390.6	8	$1.0 x10^{-7}$	8.1	$5.0x10^{-4}$	-25	390
Diisononyl phthalate (DINP)	418.6	8—9	$4.5 x10^{-7}$	8.8	$6x10^{-5}$	-50	>400
Diisodecyl phthalate (DEHP)	447.0	9—10	$3.8 x10^{-7}$	8.8	$2x10^{-7}$	-45	>400

Approximately 30 *o*-DAP's are in commercial use (ExxonMobil 2001) (Table 3). While most are used to plasticize PVC, some are used as solvents and in other applications. The molecular weight, volatility, degree of branching on the alkyl group, and other physico-chemical properties determine their uses. The National Library of Medicine (NLM) lists 460 compounds with the substructure 1,2-benzenedicarboxylic acid (NLM 2009). Most of the 460 compounds are *o*-DAP's or monoesters, after excluding those with other substitutions on the phthalate ring.

The chemical industry classifies o-DAP's by the length of their carbon backbone or molecular weight. Lower molecular weight *o*-DAP's are defined as those with straight-chain backbones up to 3 carbon atoms in length. Dimethyl phthalate (DMP) and diethyl phthalate (DEP) are used as solvents, plasticizers for cellulosic plastics, and as carriers for fragrance materials. They may be found in cosmetics, personal care products, air fresheners, inks, cellulosic plastics, and light sticks. Lower weight o-DAP's are frequently used as "carriers" for fragrances.

Medium molecular weight, or transitional, *o*-DAP's (backbone length C4-to-C6) may be used as solvents or a plasticizers for PVC. Di(2-ethylhexyl) phthalate (DEHP) is used in certain medical devices, including blood storage bags, hemodialysis tubing, and extracorporeal membrane oxygenation tubing (ECMO).

Table 3. Commercial Dialkyl *Ortho*-Phthalates [a, b]

	CAS no.	Dialkyl *Ortho*-Phthalate (abbreviation)
1	84-66-2	1,2-Benzenedicarboxylic acid, diethyl ester (DEP)
2	84-69-5	1,2-Benzenedicarboxylic acid, diisobutyl ester (DIBP) [b]
3	84-74-2	1,2-Benzenedicarboxylic acid, dibutyl ester (DBP)
4	84-75-3	1,2-Benzenedicarboxylic acid, dihexyl ester
5	84-77-5	1,2-Benzenedicarboxylic acid, didecyl ester
6	85-68-7	1,2-Benzenedicarboxylic acid, butyl benzyl ester (BBP) [b]
7	117-81-7	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester (DEHP)
8	117-84-0	1,2-Benzenedicarboxylic acid, dioctyl ester (DnOP)
9	119-06-2	1,2-Benzenedicarboxylic acid, ditridecyl ester
10	131-11-3	1,2-Benzenedicarboxylic acid, dimethyl ester (DMP)
11	16883-83-3	1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl-3-(2-methyl-1-oxopropoxy) propyl phenylmethyl ester
12	27554-26-3	1,2-Benzenedicarboxylic acid, diisooctyl ester (DIOP)
13	28853-12-0	1,2-Benzenedicarboxylic acid, diisononyl ester (DINP-2) [b]
14	53306-54-0	1,2-Benzenedicarboxylic acid, di(2-propylheptyl) ester (DPHP) [b]
15	68515-40-2	1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters
16	68515-41-3	C7-C9 phthalate
17	68515-43-5	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters
18	68515-44-6	1,2-Benzenedicarboxylic acid, diheptyl ester, branched and linear
19	68515-45-7	1,2-Benzenedicarboxylic acid, dinonyl ester, branched and linear
20	68515-47-9	1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich
21	68515-48-0	1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich (DINP-1)
22	68515-49-1	1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich (DIDP)
23	68515-50-4	1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear
24	68648-93-1	1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters
25	85507-79-5	1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear
26	71888-89-6	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich
27	111381-89-6	1,2-Benzenedicarboxylic acid, heptyl nonyl ester, branched and linear
28	111381-90-9	1,2-Benzenedicarboxylic acid, heptyl undecyl ester, branched and linear
29	111381-91-0	1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear

[a] Source: ExxonMobil 2001 and other sources.

[b] Not listed in ExxonMobil 2001.

High molecular weight *o*-DAP's (≥C7 or a ring structure) are mainly used as plasticizers for PVC. They may also be used as plasticizers in other plastics such as polyvinyl acetate and flexible polyurethane foams, in elastomers, rubbers, in flexible coatings, adhesives, and sealants. High molecular weight *o*-DAP's like diisononyl phthalate (DINP) are favored in applications requiring low migration (teethers and toys) or low volatility (automobile interiors). High molecular weight *o*-DAP's may be found in automobile interiors, electrical insulation, vinyl flooring, home furnishings, toys, garden hose, carpet backing, footwear, rainwear, stationery, and other applications. However, rigid PVC materials such as pipe, windows, and siding are not plasticized.

Many of the commercial *o*-DAP's are technical mixtures. For example, commercial linear *o*-DAP's often contain branched chain impurities and vice versa. They may also contain mixtures of *o*-DAP's with different chain lengths, such as di(C9-C11) phthalate. Some *o*-DAP's such as diisooctyl (DIOP), diisononyl (DINP), and diisodecyl (DIDP) phthalates are complex substances, that is, they are mixtures of many isomers with different branching. For ≤6 carbons, the prefix "iso" means that two methyl groups are attached to the penultimate carbon atom of an otherwise straight chain. For >6 carbons, "iso" means a mixture of many isomers with different branching.

Toxicokinetics

The *o*-DAP's are generally rapidly absorbed and eliminated following oral exposure. They do not bioaccumulate. The diester is rapidly cleaved to the monoester in the digestive tract (Albro and Thomas 1973). The monoesters are generally considered to be the species responsible for toxic effects. The monoesters may be further cleaved to form *ortho*-phosphate (Figure 2). o-DAP's with longer side chains (C4 or longer) are subject to oxidative metabolism. Various metabolites may be excreted either free or conjugated with glucuronic acid. Lower molecular weight *o*-DAP's and their metabolites are excreted in the urine. Medium and high molecular weight *o*-DAP's such as DEHP and DINP are excreted in both urine and feces.

A number of *o*-DAP metabolites have been detected in human urine, bile, feces, blood, milk, and saliva. The monoesters are the most abundant metabolites of the lower molecular weight o-DAP's, he monoesters are the most abundant metabolites of the lower molecular weight o-DAP's, whereas the oxidative metabolites are the most abundant metabolites of the higher molecular weight o-DAP's. Therefore, the oxidative metabolites are the preferred biomarkers for DINP and DEHP. Early biomonitoring studies lacked sensitivity because they were performed before the oxidative metabolites were identified.

The rate of *in vivo* dermal absorption generally declines as the molecular weight increases (Elsisi et al. 1989; Figure 3).

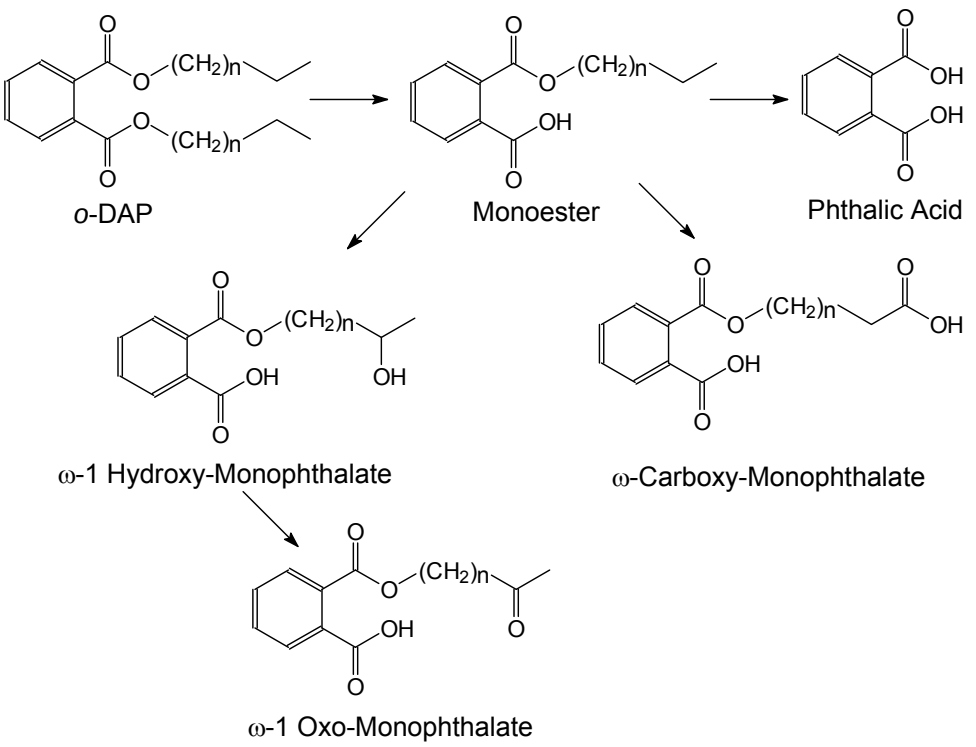

Figure 2. Metabolism of *ortho*-Dialkyl Phthalates (*o*-DAP's). Adapted from Frederiksen et al. 2007.

Toxicity

Most *o*-DAP's have very low acute oral toxicity, with diallyl phthalate being the most toxic (NICNAS 2008a). They are weak skin and eye irritants and generally are negative or weak skin sensitizers. They generally are not genotoxic in a range of standard genotoxicty assays. Most of the laboratory research on *o*-DAP toxicity in animals has focused on chronic effects, especially reproductive and developmental toxicity, carcinogenicity, and chronic organ toxicity. However, not all health effects are associated with all *o*-DAP's.

Chronic Toxicity

Several *o*-DAP's have been tested in repeat-dose feed studies in animals. Of the eight *o*-DAP's considered here, all have been tested in subchronic studies and five have been tested in 2-year bioassays (Table 3). The liver is the single target organ that the eight *o*-DAP's have in common (Table 4). Liver effects include increased liver weight, peroxisome proliferation, and histopathological effects. Not all of these effects were reported with all of the *o*-DAP's. Other frequent targets of *o*-DAP toxicity are the kidney (7/8), testes (4/8), and to a lesser degree the thyroid (2/8).

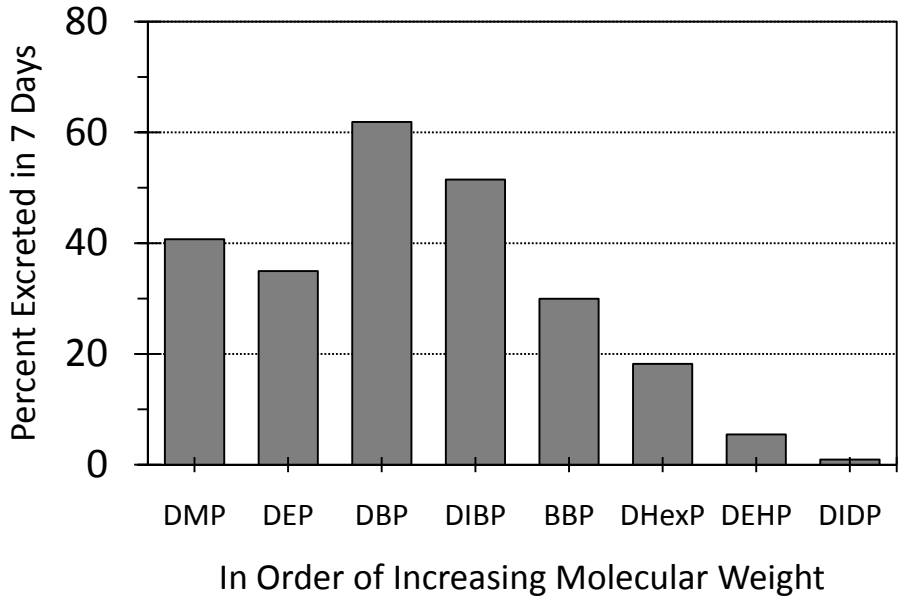

Figure 3. Percutaneous absorption of phthalate esters. Percentage of the applied dose excreted in urine and feces following 7 days of exposure in F344 rats (Elsisi et al. 1989). Phthalate esters are arranged by order of increasing molecular weight.

Role of PPARα

The activation of the alpha isoform of the peroxisome proliferator-activated receptor (PPARα) and induction of peroxisome proliferation in rats and mice are characteristic of many *o*-DAP's. PPARα is a nuclear receptor that induces pleiotropic responses in rodents, including increased lipid metabolism, increased hepatocellular proliferation, and decreased hepatocellular apoptosis. PPARα is believed to play a central role in the hepatocarcinogenesis of *o*-DAP's, as well as other toxicological effects. Peroxisome proliferation can be assayed microscopically by the increase in number and density of peroxisomes or biochemically by increases in peroxisomal β-oxidation, which is typically measured as palmitoyl CoA oxidase activity.

Many, but not all, of the toxicological effects of DINP in animals are probably mediated by the nuclear receptor PPARα. DINP also activates PPARγ, although the significance of PPARγ activation is largely unknown (Peraza et al. 2006). The roles of PPARα, β, and γ in toxicity are reviewed in Peraza et al. (2006).

There is a considerable amount of data suggesting that PPARα activation is required for the pleiotropic effects in rodent liver that include hepatomegaly, increased cell proliferation, peroxisome proliferation, and hepatocellular neoplasms (Ashby et al. 1994; CPSC 2001; Klaunig et al. 2003). The principle evidence for the role of PPARα is that these effects are not observed in PPARα-null mice (Hays et al. 2005; Lee et al. 1995; Peters et al. 1997a, b; Ward et al. 1998). Recently, however, a PPARα-independent carcinogenic mode of action has been proposed for DEHP (Ito et al. 2007).

Table 4. Available Animal Toxicity Studies with Selected Dialkyl *o*-Phthalates (*o*-DAP's) [a]

Dialkyl o-Phthalate		Acute	Subchronic	Chronic	Reproductive	Prenatal	Perinatal [b]	Neurotoxicity	Human	Genetox	Cancer	Reviewed in:
Dimethyl phthalate	DMP	X	X	--	--	X	X	--	+ / -	X	--	NICNAS 2008a,b
Diethyl phthalate	DEP	X	X	--	X	X	X	--	+ / -	X	--	NICNAS 2008a,c
Dibutyl phthalate	DBP	X	X	--	X	X	X	--	+ / -	X	--	Williams 2010a
Benzyl butyl phthalate	BBP	X	X	X	X	X	X	--	+ / -	X	X	Williams 2010b
Di-n-octyl phthalate	DnOP	X	X	--	X	+ / -	--	--	+ / -	X	--	Carlson 2010a
Di(2-ethylhexyl) phthalate	DEHP	X	X	X	X	X	X	--	+ / -	X	X	Carlson 2010b
Diisononyl phthalate	DINP	X	X	X	X	X	X	--	--	X	X	Babich & Osterhout 2010
Diisodecyl phthalate	DIDP	X	X	X	X	X	--	--	--	X	X	Osterhout 2010

[a] X, study available; --, study not available; + / -, limited data available.
[b] Includes exposure from gestational days 16 through 19.

Table 5. Toxicological Endpoints of Selected Dialkyl *o*-Phthalates (*o*-DAP's) [a, b]

Dialkyl o-Phthalate		Liver	Kidney	Testes	Thyroid	PP [b]	PPAR [c]	Reproduction	Male sexual [d] development	Other development	Genotoxicity	Liver tumor	Reviewed in:
Dimethyl phthalate	DMP	X	X	--	--	--	ND	ND	--	--	--	ND	NICNAS 2008a,b
Diethyl phthalate	DEP	X	X	--	--	--	--	X	--	+/-	--	ND	NICNAS 2008a,c
Dibutyl phthalate	DBP	X	X	X	--	X	X	X	X	X	--	ND	Williams 2010a
Benzyl butyl phthalate	BBP	X	X	X	--	X	X	X	X	X	--	--	Williams 2010b
Di-n-octyl phthalate	DnOP	X	--	--	X	ND	X	--	ND	+/-	--	ND	Carlson 2010a
Di(2-ethylhexyl) phthalate	DEHP	X	X	X	X	X	X	X	X	X	--	X	Carlson 2010b
Diisononyl phthalate	DINP	X	X	X	--	X	X	--	+/-	X	--	X	Babich & Osterhout 2010
Diisodecyl phthalate	DIDP	X	X	--	--	X	X	--	ND	X	--	--	Osterhout 2010

[a] X, positive effect; --, no effect; +/-, weak or questionable effect; ND, not determined.
[b] Peroxisome proliferation; see also Barber et al. 1987.
[c] Induction of PPARα *in vitro* by the corresponding monoester; Bility et al. 2004.
[d] Effects consistent with the "phthalates syndrome." See also Gray et al. 2001.

Other toxic effects were reduced in severity or delayed in appearance in PPARα-null mice, including effects in the kidney and testes (Ward et al. 1998).

Some liver effects, principally spongiosis hepatis, may be independent of PPARα. Spongiosis hepatis is a degenerative lesion found in rats and medaka fish. Increased incidence of spongiosis hepatis has been reported in rats chronically exposed to a number of compounds, including both genotoxic and non-genotoxic carcinogens, non-carcinogens, PPARα agonists, and non- PPARα agonists. Thus, the structure activity relationships suggest that spongiosis hepatis occurs independently of peroxisome proliferation.

In contrast, DEHP induced malformations in both PPARα-null and wild-type mice, following pre-natal exposure (Peters et al. 1997c). The role of PPARα in causing the malformations following perinatal exposure, which results in the "phthalate syndrome," has not been studied with the PPARα-null model. However, structure activity relationships suggest that these effects are also independent of PPARα.

Of the eight *o*-DAP's reviewed here, five were able to induce peroxisome proliferation in rats (Table 4). DMP and DEP were negative; DnOP induced minimal peroxisome proliferation in rats following high dose long duration exposures. However, only DEHP, DINP, and DIDP were able to induce peroxisome proliferation by 10-fold or more (Figure 4B). The other *o*-DAP's tested induced peroxisome proliferation by less than 5-fold. It is noteworthy that the linear *o*-DAP's DBP, 610P, 711P, and DUP were relatively weak inducers.

The ability to activate either mouse or human PPARα was assayed *in vitro* (Bility et al. 2004). It is interesting to note that monobutyl phthalate (the monoester of butyl benzyl phthalate) induced the mouse PPARα by more than 10-fold, whereas it was a weak inducer of peroxisome proliferation *in vivo* (Figure 4A). DnOP was also a strong inducer of mouse PPARα, but was only a peroxisome proliferator following high dose long-duration exposures (reviewed in Carlson 2010a).

Reproductive and Developmental Effects

Reproductive and developmental effects have been observed in experimental animals. *In utero* exposure to *o*-DAP's during organogenesis may result in a variety of variations and malformations, including the kidney and skeletal system. Effects on reproductive ability in males and females have also been reported.

The Center for the Evaluation of Risks to Human Reproduction (CERHR) has reviewed the reproductive and developmental effects of seven phthalates. The CERHR classifies chemicals into one of six "degrees of concern" ranging from "insufficient" through "serious" (Table 6). The CERHR classicification is based on: (a) the weight of the evidence for reproductive or developmental effects in humans and (b) published exposure estimates. The CERHR considered each phthalate independently; they did not address cumulative risk. Additional data have become available since the reviews were completed that could raise or lower the degree of concern.

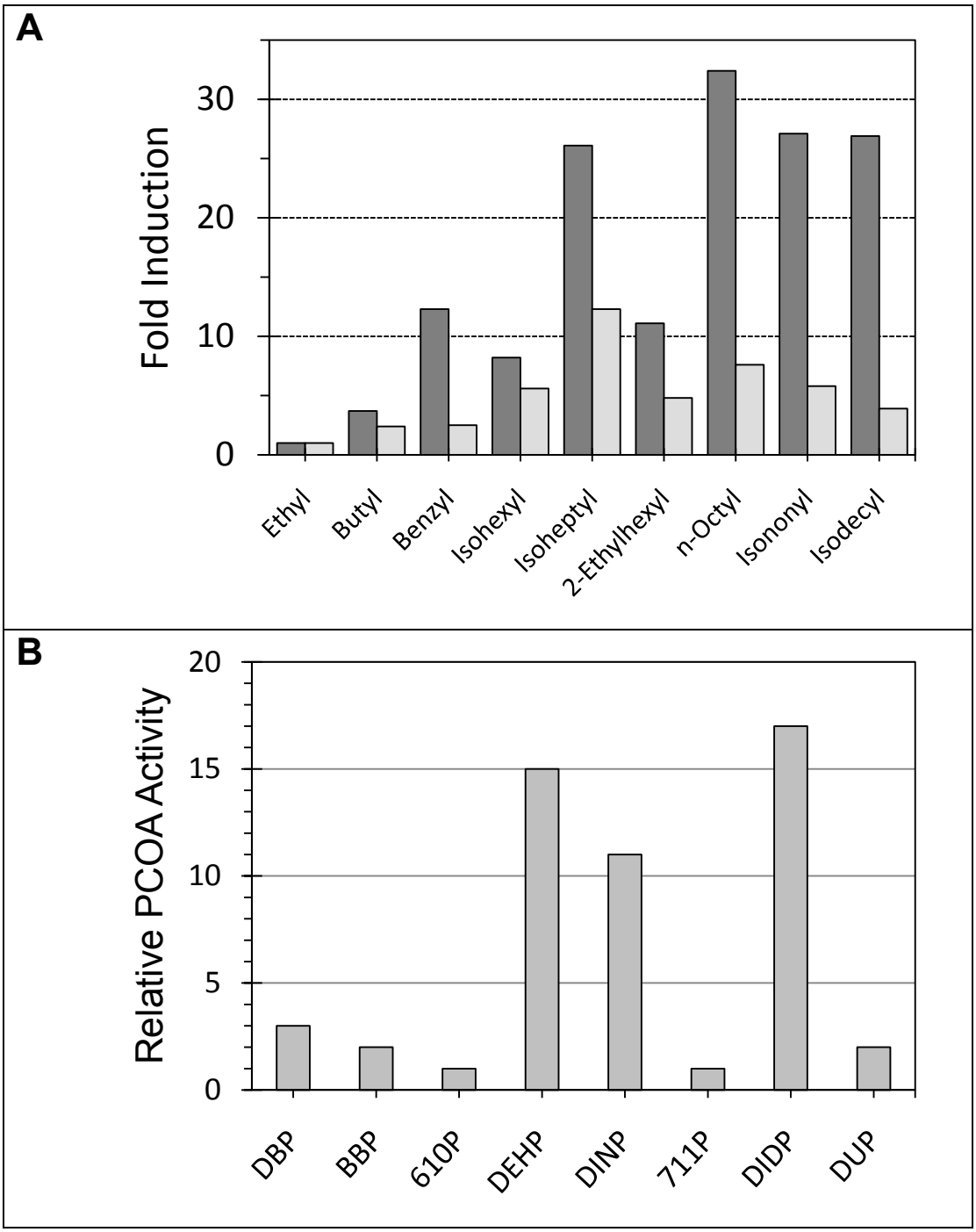

Figure 4. Induction of PPARα and peroxisome proliferation. A). *In vitro* activation of mouse (dark gray bars) or human (light gray bars) PPARα by the corresponding monoesters of the *o*-DAP's (Bility et al. 2004). B). *In vivo* induction of peroxisome proliferation, as palmitoyl CoA oxidase (PCOA) activity, by *o*-DAP's in rats (Barber et al. 1987). Note that the horizontal axes list different *o*-DAP's. 610P, mixture containing C6-C10 di-*n*-alkyl phthalates; 711P, mixture containing C7-C11 di-*n*-alkyl phthalates; DUP, di-*n*-undecyl phthalate.

The CERHR concluded that there was "serious concern" for critically ill male infants exposed to DEHP during invasive medical procedures (Table 6). They also concluded that there was "concern" for male infants from mouthing of toys containing DEHP. The CERHR concluded that there was "concern" of developmental effects for the male offspring of women undergoing certain medical treatments and "some concern" for reproductive effects in male and female adults exposed to DEHP. DEHP is no longer used in the manufacture of teethers, rattles, soft plastic toys, and many children's products.

The CERHR also concluded that there was "some concern" for the risk of developmental effects in the offspring of women of reproductive age who have high DBP exposures. DBP exposures in young women are greater than those of the general population. Exposure of these women to DBP has been attributed to the use of cosmetics (Blount et al. 2000)

However, the most severe effects are observed in males exposed during late gestation *in utero*. Certain *o*-DAP's suppress testosterone production, which in turn results in a disruption of normal sexual development. In addition to the males, behavioral effects in female offspring have also been reported.

Developmental Effects of *ortho*-Dialkyl Phthalates in Animals

Perinatal Exposure. The developmental effects of the *o*-DAP's have been well-studied in animals. A thorough review of the developmental effects of *o*-DAP's in general is beyond the scope of this report. Briefly, perinatal exposure to certain phthalates is associated with the "phthalate syndrome" in rats, which encompasses a range of effects on the development of the male genitourinary system including reduced anogenital distance (AGD), nipple retention, undescended testes, testicular atrophy, testicular histopathology, underdeveloped gubernacular cords, and hypospadias (reviewed in Foster et al. 2001; Foster 2006; Howdeshell et al. 2008). These effects persist into adulthood, even in the absence of further exposure (Barlow et al. 2004; compare McIntyre et al. 2001). Furthermore, the antiandrogenic effects of concurrent exposure to multiple phthalates are additive (Howdeshell et al. 2008), which has serious implications for human risk assessment.

The male developmental effects of *o*-DAP's are mainly due to the inhibition of testosterone synthesis (Mylchreest et al. 1998; Foster et al. 2001; Gray et al. 2000; Parks et al. 2000), along with reduced expression of insulin-like hormone 3 gene (insl3) (Wilson et al. 2004). The specific cellular and molecular targets of *o*-DAP's are unknown (Howdeshell et al. 2008). However, both the Sertoli cells and Leydig cells are affected (reviewed in Corton and Lapinskas 2005). *o*-DAP's alter the expression of numerous genes involved in testosterone and estrogen metabolism (Corton and Lapinskas 2005).

Table 6. Phthalates evaluated by the Center for the Evaluation of Risks to Human Reproduction

Phthalate	Year	Degree of Concern [a]					
		Insufficient	*Negligible*	*Minimal*	*Some*	*Concern*	*Serious*
Dibutyl phthalate (DBP)	2000		R adult [b]	D	D high [c]		
Butyl benzyl phthalate (BBP)	2003	D	R adult F	R adult M			
Di-n-hexyl phthalate	2003	D / R					
Di-n-octyl phthalate (DnOP)	2003	D	R				
Di(2-ethylhyexyl) phthalate (DEHP)	2006			R adult	M young [d]	M infant <1 y [e]	Critically ill M infant [f]
Diisononyl phthalate (DINP)	2003			D / R			
Diisodecyl phthalate (DIDP)	2003		R	D			

[a] The degrees of concern are defined by the CERHR.

[b] D, developmental; F, female; M, male; R, reproductive.

[c] Risk of developmental effects in the offspring of some highly exposed women of reproductive age.

[d] Males exposed during pregnancy and males >1 year of age.

[e] Male infants <1 year old (includes mouthing; 1 to 30 μg/kg-d) and male offspring of women undergoing certain medical treatments.

[f] Critically ill male infants undergoing certain medical treatments.

Testicular effects of *o*-DAP's have also been reported in guinea pigs (Gray et al. 1982), mice, (Gray et al. 1982; Ward et al. 1998), rabbits (Higuchi et al. 2003), and ferrets (Lake et al. 1976). Hamsters were resistant due to slow metabolism of the phthalate ester to the monoester, which is believed to be the active metabolite. Hamsters responded to the monoester, however (Gray et al. 1982). *o*-DAP's that are known to induce male reproductive effects include straight chain esters with 3 to 6 carbon atoms (Foster et al. 1980), and branched chain esters with 2-alkyl substitutions (for example, DEHP) (Foster et al. 1981; Gray et al. 2000; Ostby et al. 2000) (Table 7). DINP is a relatively weak testicular toxicant in comparison to other active phthalates, perhaps because only some DINP isomers have 2-alkyl substituents (Gray et al. 2000). Recently, it has been shown that the reproductive effects of simultaneous exposure to multiple *o*-DAP's are additive (Howdeshell et al. 2008). Furthermore, simultaneous exposure to *o*-DAP's and other antiandrogens—vinclozalin, procymidone, linuron, and prochlaz—is also reported to produce cumulative developmental effects (Christiansen et al. 2009; Rider et al. 2008). Cumulative effects may occur even though the modes of action of antiandrogens may differ. Some are androgen receptor antagonists, while others (i.e., the *o*-DAP's) interfere with testosterone synthesis.

Table 7. Ability of phthalate diesters to induce testicular effects in male rats

Active Compounds	Inactive Compounds
Linear Dialkyl Phthalates	
di-*n*-propyl *o*-phthalate (DPP) [a, b]	dimethyl *o*-phthalate (DMP) [a, c, d]
di-*n*-butyl *o*-phthalate (DBP) [a]	diethyl *o*-phthalate (DET) [a,c, d]
di-*n*-pentyl *o*-phthalate [a]	di-*n*-butyl isophthalate [b]
di-*n*-hexyl *o*-phthalate [a]	di-*n*-butyl terephthalate [b]
	di-*n*-heptyl *o*-phthalate [a]
	di-*n*-octyl *o*-phthalate (DnOP) [a]
Branched Dialkyl Phthalates	
di-*n*-butyl *o*-phthalate (DBP) [b]	di-tert-butyl *o*-phthalate [b]
di-isobutyl *o*-phthalate [b]	di(2-ethylhexyl) terephthalate (DOTP) [c, d]
di-sec-butyl *o*-phthalate [b]	
di(2-ethylhexyl) phthalate (DEHP) [c, d]	
diisononyl phthalate (DINP) [c, d]	
benzyl butyl phthalate (BBP) [c, d]	

[a] Foster et al. 1980. Based on testicular atrophy in juvenile male SD rats.
[b] Foster et al. 1981. Based on testicular atrophy in juvenile male SD rats.
[c] Gray et al. 2000. Based on developmental effects in males following prenatal exposure.
[d] Ostby et al. 2000. Based on developmental effects in males following prenatal exposure.

The optimal window for induction of male developmental effects is gestational day (GD) 16 through 19, when sexual differentiation occurs (Carruthers and Foster 2005; Gray et al. 1999). Therefore, older developmental screening assays that expose the dams on GD 6 through 15 are likely to miss the optimum window for male development (Foster 2006). Rodents are most sensitive to the antiandrogenic effects of *o*-DAP's *in utero*. However, *o*-DAP exposure at higher doses also induces testicular effects in adolescent and adult males, with adolescents being more sensitive than adults (Higuchi et al. 2003; Sjöberg et al. 1986).

Prenatal Exposure. In addition to effects on male reproductive development, *o*-DAP's induce various structural abnormalities when exposure takes place earlier in gestation, during organogenesis. The mechanism for induction of these malformations is unknown, but may involve zinc deficiency in the embryo (Peters et al. 1997c).

Role of PPARα. The PPARα receptor mediates many, but not all, of the toxic effects of the *o*-DAP's (reviewed in Peraza et al. 2006). Whether the toxic effects are mediated by PPARα is significant because humans may respond differently to PPARα agonists than rodents (reviewed in Klaunig et al. 2003). PPARα activation leads to peroxisome proliferation and hepatocarcinoma induction in rodent liver, but not in humans (see Carcinogenicity).

The ability of phthalates to cause malformations during organogenesis appears to be independent of the PPARα receptor (Peters et al. 1997c). Malformations were induced equally in PPARα (+/+) and (-/-) mice when the dams were exposed to DEHP on GD 8 and 9. Ward et al. (1998) exposed 6-week old PPARα (+/+) and (-/-) mice to dietary DEHP for up to 24 weeks. No effects were seen in the livers of PPARα (-/-) mice. The appearance of lesions in the testes and kidneys was delayed, but the lesions were similar to those in the PPARα (+/+) mice. The authors suggested that there may be both PPARα-dependent and PPARα-independent mechanisms for effects seen in the testis and kidney (Ward et al. 1998).

It is not known whether PPARα is required for the induction of the effects observed in males when exposure occurs during sexual development (Corton and Lapinskas 2005). However, DBP is a weak PPARα agonist and a potent developmental toxicant, whereas DINP is a relatively good PPARα agonist (compared to other *o*-DAP's), and a weak developmental toxicant. This suggests that the effects associated with the phthalate syndrome are not dependent on PPARα activation.

Studies in Humans

Recently, it has been suggested that *o*-DAP's may contribute to the occurrence of the "testicular dysgenesis syndrome" in humans, that is, testicular germ cell cancer, cryptorchidism, hypospadia, and low sperm count (Mahood et al. 2007). In other words, testicular dysgenesis might be the human equivalent of the phthalate syndrome in rats.

Several authors have studied the relationship between urinary phthalate metabolites and semen quality (Duty et al. 2003, 2004; Johnsson et al. 2005). These studies are generally limited in that the study population was subfertile and subjects are concurrently exposed to multiple phthalates .

Swan et al. reported that reduced AGD was associated with prenatal exposure to DBP, diisobutyl phthalate, diethyl phthalate, and BBP, as measured by urinary metabolite levels (Marsee et al. 2006; Swan et al. 2005). Reduced AGD is one of the effects seen in animal studies (see above). No association was found for DEHP. This study suggests that effects similar to those associated with the phthalates syndrome in rats may also occur in humans. However, AGD has been rarely studied in humans. Measurements of AGD were made, on average, at 12 months of age, rather than at birth. Exposures were also based on a single measurement during pregnancy and, therefore, may not reflect the average phthalate exposure during pregnancy. The observation of a positive effect with diethyl phthalate is surprising, because it is not active in rats. The lack of an effect with DEHP is equally surprising, because DEHP is one of the most potent *o*-DAP's in animals, and human exposure is widespread. Furthermore, human exposure to *o*-DAP's is generally in the µg/kg-d range, whereas the effects in animals are found at mg/kg-d levels.

Main et al. (2006) investigated the relationship between the levels of *o*-DAP metabolites in breast milk in 3-month old male infants with (n=62) or without (n=68) cryptorchidism. The study was conducted in Finland and Denmark. No association was found between *o*-DAP exposure and cryptorchidism. Overall, MBP levels in breast milk were the most strongly associated with perturbations in sex-related hormones. Strong associations were also found for MMP and MEP, which is unexpected because DMP and DEP do not cause antiandrogenic effects in animals. Some of the observed associations (MEHP negatively associated with FSH: inhibin B; positive association of MBP with LH:T) are in the opposite sense expected for antiandrogenic effects. However, the positive results with MMP and MEP and weak results with MEHP are consistent with other studies in male infants (Swan et al. 2005).

Zhang et al. (2009) reported an association between low birth weight and DBP levels in maternal blood samples, as well as umbilical cord blood. In the same study, DEHP and MEHP levels were associated with reduced birth length.

Overall, the human studies assessing *o*-DAP reproductive or developmental toxicity are confounded by concurrent exposures to multiple phthalates. In addition, exposures to individual phthalates tend to correlate with one another, which makes it difficult to determine which phthalate, or phthalates, are contributing to the observed effects. The findings of positive perturbations in sex-related hormones with DMP and DEP is puzzling, since these phthalates do not cause antiandrogenic effects in animals.

Carcinogenicity

The *o*-DAP's are generally negative in standard genotoxicity tests (Table 5). Any tumors induced by *o*-DAP's are likely due to non-genotoxic mechanisms.

Liver Tumors

Few *o*-DAP's have been tested in two-year bioassays, including only four of the eight *o*-DAP's reviewed here. Both DEHP (David et al. 1999, 2000a,b; Kluwe 1982; Moore 1996, 1997; NTP 1982) and DINP (Lington et al. 1998; Moore 1998a,b) induced hepatocellular tumors in rats and mice. BBP failed to significantly increase the incidence of hepatocellular tumors in rats and mice (NTP 1007). DIDP did not induce liver tumors in F344 rats; DIDP was not tested in mice (Cho et al. 2008).

There is a general correlation between peroxisome proliferation (including non-phthalate PPARα agonists) and hepatocellular carcinogenicity in rats and mice. The hepatocellular tumors induced by DEHP and DINP are believed to arise through a PPARα-dependent mode of action (CPSC 2001; Klaunig et al. 2003). This conclusion is supported by a plethora of data, especially studies in PPARα-null mice (Hays et al. 2005; Peters et al. 1997b). However, activation of human PPARα does not lead to hepatocellular proliferation or tumorigenesis (Morimura et al. 2006). The 2001 CHAP on DINP concluded, "The PPARα-mediated mechanism of hepatocarcinogenesis is pronounced in rodents, but believed not readily induced in humans, especially at the doses resulting from current use of consumer products. The human risk was therefore seen as negligible or non-existent (CPSC 2001)." A consensus group convened by the International Life Sciences Insitute (ILSI) by the United States Environmental Protection Agency (EPA) and Health Canada concluded that peroxisome proliferation is unlikely to lead to cancer in humans (Klaunig et al. 2003).

Recently, the possibility of a PPARα-independent mode of action for the induction of liver tumors has been proposed for DEHP (Ito et al. 2007). However, it appears that the PPARα-independent MOA does not occur in wild-type (i.e., PPARα-expressing) mice. Additional investigation is needed to determine the significance of this result with DEHP. Considering all of the evidence, the CPSC staff concludes that DEHP and DINP induce hepatocellular tumors in mice and rats by a mode of action that is not likely to occur in humans.

Other Tumor Sites

Strong peroxisome proliferators have been associated with testicular interstitial cell tumors and pancreatic tumors, in addition to hepatocellular tumors, comprising the so-called "tumor triad" (Biegel et al. 2001). Limited evidence of testicular and pancreatic tumors was found for *o*-DAP's. The incidences of pancreatic adenoma and adenoma or carcinoma (combined) were elevated in F344 rats exposed to BBP (NTP 1997). Benign Leydig cell tumors (not interstitial cell tumors) were found in F344 rats exposed to DEHP (reviewed in Carlson 2010a). Interstitial cell tumors of the testes were observed in both controls and in F344 rats exposed to DINP (Lington et al. 1997; Moore 1998a). No conclusions could be made, due to the high background incidence.

The incidence of testicular interstitial cell hyperplasia was significantly elevated at the high dose (1.0%) in Sprague-Dawley rats treated with DINP-A, a form of DINP that was never produced commercially (Bio/dynamics 1986). Interstitial cell tumors were non-significantly elevated at the high dose. There were also non-significant increases in hyperplasia and tumor incidence in the pancreas and endometrium in this study.

Significantly elevated levels of mononuclear cell leukemia (MNCL) were observed in two-year studies of F344 rats exposed to BBP, DEHP, or DINP. However, MNCL has a high background level in F344 rats, and increases in MNCL incidence are common findings in two-year studies with this rat strain. Furthermore, no other hematopoietic neoplasms were induced by the phthalates in any other animals strain tested. Therefore, the relevance of the MNCL to humans is uncertain at best.

There was a small increase in the incidence of renal tubular cell carcinomas in male F344 rats exposed to DINP (Moore 1998a). Experimental evidence demonstrates that these tumors arose by a mechanism involving the accumulation of α2u-globulin, which is a protein that is specific to the male rat (Caldwell et al. 1999). The CPSC staff does not consider renal tubular cell tumors induced by this mechanism to be relevant to human risk assessment (Schaeffer 1991).

Acceptable Daily Intake

The CPSC staff reviewed all of the available toxicity data on the six phthalates that are the subject of section 108 of the CPSIA: dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), di-(2-ethylhexyl) phthalate (DEHP), di-*n*-octyl phthalate (DnOP), diisononyl phthalate (DINP), and diisodecyl phthalate (DIDP). The staff also derived acceptable daily intake (ADI) levels for multiple endpoints for each of the six phthalates (Table 8).

Overall, chronic liver toxicity was the most sensitive endpoint for BBP, DnOP, and DINP. With BBP, however, chronic liver effects were only slightly more sensitive than effects on the kidney, testes, and development. For DIDP, kidney toxicity was slightly more sensitive than the liver. Reproductive or developmental effects were the most sensitive endpoints for DBP. For DEHP, chronic effects on the testes were slightly more sensitive than developmental effects.

Exposure

In reviewing data on human exposure to phthalates, the reader should keep in mind that the uses of phthalates may change over time and may differ between countries. For example, much of the data relating to children's articles predates the recent regulations issued in the United States and Europe. Manufacturers may already be reformulating their products to reduce phthalate exposure. There is a general trend to replace DEHP with DINP or DIDP. The exposure data on phthalates has been reviewed in detail (Versar 2010b).

Table 8. Derivation of Non-Cancer Acceptable Daily Intake (ADI's) Levels for Selected Dialkyl *o*-Phthalates (*o*-DAP's) [a]

***o*-DAP [b]**	**Endpoint**	**Effect**	**Species/ strain**	**Study design**	**NOAEL** (mg/kg-d)	**LOAEL** (mg/kg-d)	**UF**	**ADI** (mg/kg-d)	**Reference**
DBP	Liver	Increased weight (M/F)	F344 rat	13 weeks	176	356	100	1.8	NTP 1995
	Kidney	Increased weight (M/F)	F344 rat	13-weeks	176	356	100	1.8	NTP 1995
	Reproductive	Reduced fertility (M)	Wistar rat	GD 13-20	20	100	100	0.2	Mahood 2007
	Developmental	Reduced birth weight; decreased AGD (M)	SD rat	GD 1-21	50	ND [d]	100	0.5	Zhang 2004
BBP	Liver	Increased weights (M/F)	Crj:CD SD IGS rat	2 gen	100	200	100	1.0	Aso 2005
	Kidney	Increased weights (M) Nephropathy (F)	F344 rat	2 years	ND	120-300	100	1.2	NTP 1997
	Testes	Decreased spermatozoa	F344 rat	13 weeks	200	ND [d]	100	2.0	NTP 1997
	Developmental	Decreased AGD Undescended testes	Wistar rat	Prenatal	167	250	100	1.7	Ema 2003
DnOP	Liver	Histopathology; Biochemical changes (M)	SD rat	13 weeks	36.8	350.1	100	0.37	Poon et al. 1997
DEHP	Liver	Increased absolute and relative liver weight (M)	F344 rat	2 years	5.8	28.9	100	0.058	David et al. 2000a; Moore 1996; ECB 2008
	Testes	Aspermatogenesis	F344 rat	2 years	ND	5.8	1,000	0.0058	David et al. 2000a
	Developmental	Reproductive tract malformations (F)	SD rat	GD 8-17	ND	11	1,000	0.011	Gray et al. 2009

Table 8. Derivation of Non-Cancer Acceptable Daily Intake (ADI's) Levels for Selected Dialkyl *o*-Phthalates (continued) [a]

o-DAP [b]	Endpoint	Effect	Species/ strain	Study design	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	UF	ADI (mg/kg-d)	Reference
DINP	Liver	Histopathology (M>F)	F344 rat	2 years	15	152	100	0.12 [c]	Lington et al. 1997
	Kidney	Mineralization	F344 rat	2 years	88	359	100	0.88	Moore 1998a
	Reproductive	Reduced fertility (M/F)	SD rat	2-gen	665	ND [d]	100	6.6	Waterman et al. 2002
	Developmental	Reduced pup weight (M)	SD rat	GD 15 - PND 10	30-66	307-657	100	1.0 [e]	Masutomi et al. 2003
DIDP	Liver	Histopathology	Dog	13 weeks	15	75	100	0.15	Hazelton Laboratories 1968
	Kidney	Increased kidney weight	F344 rat	2 years	ND	13-17	100	0.13-0.17	Cho et al. 2008
	Reproductive	Reduced ovary weight; increased testes weight; delayed vaginal opening	SD rat	2-gen	233—645	ND [d]	100	2.3	Hushka et al. 2001
	Developmental	Skeletal variations	Wistar rat	GD 6-15	40	200	100	0.4	Hellwig et al. 1997

[a] Abstracted from the CPSC staff toxicity reviews.

[b] Abbreviations: ADI, acceptable daily intake; BBP, benzyl butyl phthalate; *o*-DAP; *ortho*-dialkyl phthalate; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DIDP, diisodecyl phthalate; DINP, diisononyl phthalate; DnOP, di-n-octyl phthalate; F, females; GD, gestational day; LOAEL, lowest observed adverse effects level; M, males; ND, not determined; NOAEL, no observed adverse effect level; PND, postnatal day; UF, overall uncertainty factor.

[c] Derived from the maximum likelihood estimate of the BMD_{05} of 0.12 mg/kg-d.

[d] The NOAEL was the highest dose tested.

[e] Derived from the maximum likelihood estimate of the dose at which the pup weight decreased by one standard deviation, 100 mg/kg-d.

Biomonitoring

Biomonitoring generally provides the most reliable estimates of total exposure to pollutants. However, biomonitoring generally cannot be used to identify sources or routes of exposure. The measurement of urinary metabolites has become the preferred method for biomonitoring studies of *o*-DAP exposure. Measuring metabolites, rather than the parent compound reduces errors due to sample contamination, because *o*-DAP's are ubiquitous compounds that may be found in laboratory equipment and laboratory flooring, for example. Urine is relatively easy to collect and store. Sampling programs, such as the National Health and Nutrition Examination Survey (NHANES) and National Children's Study collect urine samples from defined populations.

Early biomonitoring studies (e.g., Blount et al. 2000) measured only the monoesters, which are the initial metabolites of the *o*-DAP's. However, the monoesters of the longer-chain *o*-DAP's such as DINP and DEHP undergo further oxidative metabolism. Thus, while the monoesters are the major metabolites for lower molecular weight o-DAP's, they are minor metabolites of the higher molecular weight *o*-DAP's. As a result, the early studies are limited by low sensitivity.

Biomonitoring studies of *o*-DAP's have been reviewed recently (Fromme et al. 2007; Wittassek and Angerer 2007; Versar 2010; Wittassek et al. 2007). These studies show that virtually all humans are exposed to a variety of *o*-DAP's. At least 21 metabolites of 10 *o*-DAP's have been measured in biomonitoring studies (Table 9). However, individual studies generally do not measure the entire suite of metabolites.

Typical biomonitoring results for the general population in the United States (Kohn et al. 2000) and German university students (Wittasek et al. 2007a) are shown in Tables 10 and 11, respectively. Overall, there is reasonably good agreement between the two studies, keeping in mind that the United States study did not include oxidative metabolites of DEHP and DINP, which limits their sensitivity. It is also interesting to note that, in the German study, DBP and DEHP exposures declined slightly (by roughly 2-fold) between 1998 and 2003 (Wittasek et al. 2007a), whereas DINP exposures increased slightly (by about 2-fold) during the same time period (data not shown).

The lowest ADI levels derived by the CPSC staff are included in Tables 10 and 11 for comparison. While it is encouraging that the median and 95th percentiles of phthalate exposures estimated in the United States do not exceed the ADI's for individual phthalates, additional work needs to be done. Cumulative risks will be addressed by the CHAP on phthalates. The data in the tables are for the general population. They do not include infants and expectant mothers. Additional biomonitoring data have recently become available, and additional data from ongoing programs such as NHANES and the National Children's Study are expected.

Additional biomonitoring data are reviewed in the CPSC contractor's report on phthalate exposure (Versar 2010). Overall, there is a considerable data base of urinary metabolites in the general population from NHANES and other sources. Limited data are available for special subpopulations, such as children under age 6 and expectant mothers. The National Children's Study plans to measure urinary phthalate metabolites of mothers and their children.

Table 9. Urinary metabolites of dialkyl *ortho*-phthalates (*o*-DAP's) [a]

Phthalate / Abbreviation [b]		Metabolite / Abbreviation	
Dimethyl phthalate	DMP	Monomethyl phthalate	MMP
Diethyl phthalate	DEP	Monoethyl phthalate	MEP
Di-*n*-butyl phthalate	DBP	Mono-*n*-butyl phthalate	MBP
Diisobutyl phthalate	DIBP	Monoisobutyl phthalate	MIBP
Butylbenzyl phthalate	BBP	Monobenzyl phthalate	MBzP
		Monobutyl phthalate [c]	MBP
Dicyclohexyl phthalate	DCHP	Monocyclohexyl phthalate	MCHP
Di(2-ethylhexyl) phthalate	DEHP	Mono(2-ethylhexyl) phthalate	MEHP
		Mono(2-ethyl-5-oxohexyl) phthalate	MEOHP
		Mono(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
		Mono(2-carboxymethylhexyl) phthalate	MCMHP
		Mono(2-ethyl-5-carboxypentyl) phthalate	MECPP
Di-*n*-octyl phthalate	DnOP	Mono-*n*-octyl phthalate	MNOP
		Mono(3-carboxypropyl) phthalate	MCPP
Diisononyl phthalate	DINP	Monoisononyl phthalate	MINP
		Mono(carboxyisooctyl) phthalate	CO_2-MINP
		Mono(hydroxyisononyl) phthalate	OH-MINP
		Mono(oxoisononyl) phthalate	Oxo-MINP
Diisodecyl phthalate	DIDP	Monoisodecyl phthalate	MIDP
		Mono(carboxyisononyl) phthalate	CO_2-MINP
		Mono(hydroxyisodecyl) phthalate	Oxo-MINP
		Mono(oxoisodecyl) phthalate	OH-MINP

[a] Adapted from Versar 2010.

[b] The abbreviations for the phthalates and their metabolites are not standardized. Some authors may use different abbreviations.

[c] BBP is preferentially hydrolyzed to monobenzyl phthalate.

Sources of Phthalate Exposure

While biomonitoring studies provide robust estimates of total exposure, identifying and quantifying the sources of human exposure has been more difficult (Wormuth et al. 2006). Food has generally been considered the greatest source of phthalate exposure (ATSDR 2002). Phthalate residues have been found in many foods, especially foods high in lipid content (reviewed in Versar 2010). It is not clear, however, whether the source of the phthalates is general environmental contamination, food processing, or packaging. However, phthalate manufacturers and the Food and Drug Administration have reported that phthalates are not frequently used for food packaging in the United States.

Table 10. Phthalate exposures in the U.S. general population estimated from urinary metabolite levels [a]

Phthalate	Exposure (μg/kg-d)			ADI [b]
	Median	*95th Percentile*	*Maximum*	(μg/kg-d)
Diethyl phthalate (DEP)	12	110	320	ND
Di-n-butyl phthalate (DBP	1.5	7.2	110	200
Butylbenzyl phthalate (BBP)	0.88	4.0	29	1,000
Dicyclohexyl phthalate (DCHP)	0.026	0.25	2.3	ND
Di(2-ethylhexyl) phthalate (DEHP)	0.71	3.6	46	5.8
Di-*n*-octyl phthalate (DnOP)	0.0096	0.96	13	370
Diisononyl phthalate (DINP)	<LOD [c]	1.7	22	120

[a] From Kohn et al. 2000. Intakes were estimated from the urinary metabolite data on 289 samples reported in Blount et al. 2000. Based on monoester levels only. Oxidative metabolites of DEHP and DINP were not measured.

[b] ADI, acceptable daily intake, as derived by the CPSC staff.

[c] LOD, limit of detection; ND, not determined.

Table 11. Phthalate exposures in German students estimated from urinary metabolite levels [a]

Phthalate	Exposure (μg/kg-d)			ADI [b]
	Median	**95th Percentile**	**Maximum**	**(μg/kg-d)**
Di-n-butyl phthalate (DBP)	4.1	19.1	116	200
Diisobutyl phthalate (DIBP)	1.4	5.7	29.0	ND
Butylbenzyl phthalate (BBP)	0.26	1.6	27.3	1,000
Di(2-ethylhexyl) phthalate (DEHP)	3.5	10.1	39.8	5.8
Diisononyl phthalate (DINP)	0.29	1.7	20.2	120

[a] From Wittasek et al. 2007a. Data are from 629 individuals obtained between 1988 and 2003. Oxidative metabolites were measured for DEHP and DINP.

[b] ADI, acceptable daily intake, as derived by the CPSC staff.

Personal care products, such as lotions, perfumes, and nail polish, may contain lower molecular weight phthalates. Many products with fragrances, such as scented candles and room fresheners, also contain lower molecular weight phthalates. Phthalates may also be found in adhesives, caulks and sealants, and paints and coatings.

Many consumer products, such as vinyl flooring, home furnishings, rain coats, and some footwear, are made from PVC. PVC is used in toys and other children's products, although the use of PVC and phthalates in children's products is declining due to recent regulations (Dreyfus 2010). Household dust may be an important source of residential exposure to phthalates, especially for children. The sources of the phthalates in household dust and the processes by which phthalates accumulate in dust have not been elucidated, but they are presumably from home furnishings and other household products. Building materials such as windows, siding, and plumbing are frequently made from PVC, although manufacturers report that these products do not contain plasticizers. PVC is also commonly used in automobile interiors.

Medical devices constitute a special, but significant source of exposure to DEHP. DEHP is used in blood storage bags, tubing, and other devices. High exposures can occur to individuals receiving blood transfusions, undergoing major surgery, or undergoing kidney dialysis. It has also been reported that phthalates are used in some enteric coated or time-release medications.

In addition, phthalates are found in the environment, including ambient air, indoor air, and water.

Discussion

Dialkyl *o*-phthalates (*o*-DAP's) are a family of high production volume chemicals that are used as plasticizers and solvents in a variety consumer products, cosmetics, and medical devices. Virtually all humans are exposed to multiple *o*-DAP's. Although *o*-DAP's are not acutely toxic, chronic exposure results in a number of adverse effects in animal studies. Chronic organ toxicity, including histopathological effects in the liver and kidney, is the most common effect of *o*-DAP's. Several *o*-DAP's activate the nuclear receptor PPARα, which leads to peroxisome proliferation, mitogenesis, and tumor formation in the livers of rats and mice. However, the tumorigenic effects of PPARα induction are not believed to occur in humans. *o*-DAP's are not genotoxic.

Several *o*-DAP's adversely affect reproduction and development in experimental animals. Most notable, are adverse effects of certain *o*-DAP's on sexual development in male offspring when the pups are exposed *in utero*. These effects are due primarily to the inhibition of testosterone production by the testes. Of particular concern is the finding that the effects of concurrent exposures to multiple *o*-DAP's are additive. Moreover, the effects of other antiandrogenic compounds are also additive in combination with *o*-DAP's.

The Consumer Product Safety Improvement Act of 2008 (CPSIA) requires the U.S. Consumer Product Safety Commission (CPSC) to convene a Chronic Hazard Advisory Panel (CHAP) to assess the cumulative risks from total exposure to phthalates. The CHAP will advise the Commission on whether any additional regulations on phthalates or phthalate substitutes are needed. The CPSC staff has completed several reports to assist the CHAP in their work, including:

- Toxicity reviews of the six phthalates specifically addressed in the CPSIA (Babich and Osterhout 2010; Carlson 2010a,b; Osterhout 2010; Williams 2010a,b). These have been peer reviewed by independent scientists.
- Toxicity reviews of five phthalate substitutes (Versar and SRC 2010).
- A review of published exposure studies on phthalates (Versar 2010).
- Laboratory studies of plasticizers in children's articles (Dreyfus 2010).

Several activities on phthalates are also underway at the EPA. The Integrated Risk Information System (IRIS) program is developing risk assessments for eight phthalates (Table 12). The IRIS risk assessments will include hazard identification, derivation of reference doses, and a cumulative risk assessment. The Office of Pollution Prevention and Toxics (OPPT) is considering whether to issue regulations for a slightly different set of eight phthalates.

Table 12 U.S. Environmental Protection Agency (EPA) Phthalates Activities

Name		CAS no.	OPPT	IRIS
Diethyl phthalate	DEP	84-66-2		X
Di-n-butyl phthalate	DBP	84-74-2	X	X
Diisobutyl phthalate	DIBP	84-69-5	X	X
Di-n-pentyl phthalate	--	131-18-0	X	X
Butylbenzyl phthalate	BBP	85-68-7	X	X
Di-n-octyl phthalate	DnOP	117-84-0	X	
Di(2-ethylhexyl) phthalate	DEHP	117-81-7	X	X
Diisononyl phthalate	DINP	68515-48-0	X	X
Diisodecyl phthalate	DIDP	68515-49-1	X	
Di(2-ethylhexyl) adipate	DEHA	103-23-1		X

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