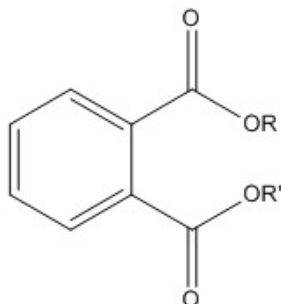


Potential Designated Chemicals:
***ortho*-Phthalates**
(1,2-Benzenedicarboxylic acid esters)



July 16, 2015 Meeting of the Scientific Guidance Panel
Biomonitoring California¹

Introduction

o-Phthalates are esters of 1,2-benzenedicarboxylic acid, with the general structure as shown above. R and R' are commonly alkyl groups, as in di-2-ethylhexyl phthalate (DEHP), for example. *o*-Phthalates are widely used as plasticizers to increase flexibility. They are also used in personal care products and cosmetics as solvents.

The *o*-phthalates currently on the list of designated chemicals for Biomonitoring California are shown below. These were designated based on their inclusion in the National Reports on Human Exposure to Environmental Chemicals program of the Centers for Disease Control and Prevention (CDC). The Scientific Guidance Panel recommended these *o*-phthalates as priority chemicals in March 2009.

o-Phthalates currently on the lists of designated and priority chemicals:

Benzylbutyl phthalate (BzBP)	Di-2-ethylhexyl phthalate (DEHP)
Di- <i>n</i> -butyl phthalate (DnBP)	Diisodecyl phthalate (DIDP)
Diisobutyl phthalate (DIBP)	Diisononyl phthalate (DINP)
Dicyclohexyl phthalate (DCHP)	Dimethyl phthalate (DMP)
Diethyl phthalate (DEP)	Di- <i>n</i> -octyl phthalate (DnOP)

¹ California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 *et seq.*

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Six *o*-phthalates are listed under Proposition 65 as known to the State of California to cause cancer and/or reproductive toxicity (OEHHA, 2015). Of these, di-*n*-hexyl phthalate (DnHxP) is not on the list of designated chemicals.

Proposition 65 listed <i>o</i>-phthalate	Type of toxicity
Benzylbutyl phthalate (BzBP)	developmental
Di- <i>n</i> -butyl phthalate (DnBP)	developmental, male, female
Di-2-ethylhexyl phthalate (DEHP)	cancer, developmental, male
Di- <i>n</i> -hexyl phthalate (DnHxP)	female, male
Di-isodecyl phthalate (DIDP)	developmental
Di-isononyl phthalate (DINP)	cancer

Restrictions on the use of a number of phthalates in the US, Canada, Europe, and Japan are leading to changing use patterns. In California, DEHP, DnBP, BzBP, DINP, DIDP, and DnOP were banned for use in children's toys and childcare articles at concentrations above 0.1%, effective January 2009 (California Health and Safety Code §108935-108939). The California legislation directed manufacturers to use the least toxic alternative in replacing phthalates and prohibited use of phthalates that are carcinogens or reproductive toxicants. Existing federal regulations on phthalates in children's toys are similar (Consumer Product Safety Improvement Act, 2008). The US Consumer Product Safety Commission (CPSC, 2014a) recently proposed a permanent federal ban on the use of DINP, DIBP, DCHP, di-*n*-pentyl phthalate (DPenP), and DnHxP in children's products at concentrations greater than 0.1%.

DEHP is being replaced in some applications with DINP and/or DIDP (Zota et al., 2014; Yen et al., 2011). Based on an analysis of NHANES² urinary metabolite data from 2001 to 2010, Zota et al. (2014) found decreasing exposures to DEHP, DnBP, and BzBP, and increasing exposures to DINP, DIBP, and DIDP.

There is an extensive body of literature on *o*-phthalates. This summary provides a brief overview of information relevant to the criteria for designated chemicals. We highlight available findings for *o*-phthalates not currently included on Biomonitoring California's list of designated chemicals.

If the Panel were to recommend adding the class of *o*-phthalates to the list of designated chemicals, the Program could include any member of this class in future biomonitoring studies. Listing the class would give the Program the flexibility to track changing exposures to *o*-phthalates as market shifts occur.

² National Health and Nutrition Examination Survey

Chemical identity and production/import volume

The following table (on page 4) lists selected o-phthalates and available US production/import volumes. An asterisk (*) denotes the o-phthalates not currently on the list of designated chemicals. Though alternatives are beginning to emerge, o-phthalates are still the most widely used plasticizers globally. Tullo (2015) estimated that worldwide consumption of plasticizers was 8 million metric tons (18 billion pounds), of which 70% was o-phthalates.

Selected phthalates³: US production/import volume for reporting years 2006 and 2012

Chemical (in approximate order of alkyl chain length)	CASRN	Production/import volume (lbs) ⁴
Diethyl phthalate (DEP)	84-66-2	2006: 10M – < 50M 2012: 5.6M
Diallyl phthalate (DAP)*	131-17-9	2006: 1M – < 10M 2012: withheld ⁵
Di- <i>n</i> -butyl phthalate (DnBP)	84-74-2	2006: 10M – < 50M 2012: 7M
Diisobutyl phthalate (DIBP)	84-69-5	2006: 500K – < 1M 2012: 454K
Benzylbutyl phthalate (BzBP)	85-68-7	2006: 50M – < 100M 2012: 50M – < 100M
Di- <i>n</i> -hexyl phthalate (DnHxP)*	84-75-3	2006: 500K – < 1M 2012: 48K
Diisoheptyl phthalate (DIHpP)*	71888-89-6	2006: 50M – < 100M 2012: withheld
Di-2-ethylhexyl phthalate (DEHP)	117-81-7	2006: 100M – < 500M 2012: 153M
Di- <i>n</i> -octyl phthalate (DnOP)	117-84-0	2006: 10M – < 50M 2012: withheld
Diisononyl phthalate (DINP)	68515-48-0	2006: 100M – < 500M 2012: 100M – 250M
	28553-12-0	2006: 100M – < 500M 2012: 108M
Diisodecyl phthalate (DIDP)	26761-40-0	2006: 1M – < 10M 2012: 500K – < 1M
	68515-49-1	2006: 100M – < 500M 2012: 163M
Di-2-propylheptyl phthalate (DPHP) ⁶	53306-54-0	2006: 1M – < 10M 2012: 50M – < 100M
Diundecyl phthalate (DUP)*	3648-20-2	2006: 10M – < 50M 2012: 10M – < 50M
Diisoundecyl phthalate (DIUP)*	85507-79-5	2006: 1M – < 10M 2012: 8M
Diisotridecyl phthalate (DTDP)*	68515-47-9	2006: 10M – < 50M 2012: 10M – < 50M

*Not currently on the list of designated chemicals for Biomonitoring California.

³ Refer to the glossary on page 13 for a complete list of o-phthalates mentioned in this document.

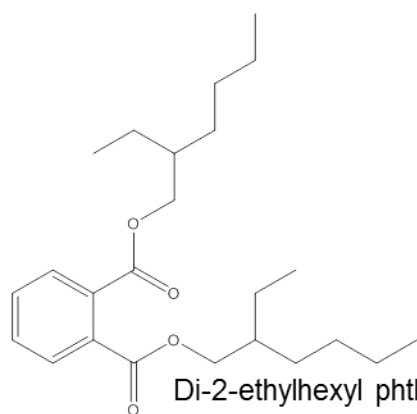
⁴ From US EPA (2006; 2012a).

⁵ This information was withheld by the manufacturer (US EPA, 2012a).

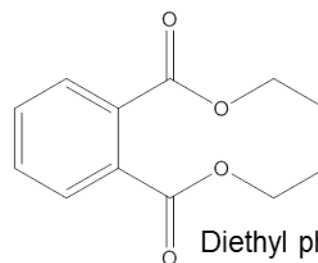
⁶ DPHP is a specific isomer of DIDP. DIDP is on the list of designated chemicals.

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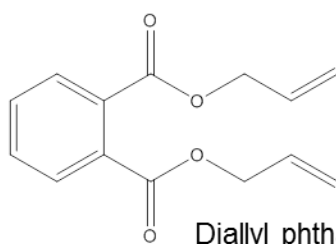
Below are some example structures of *o*-phthalates.



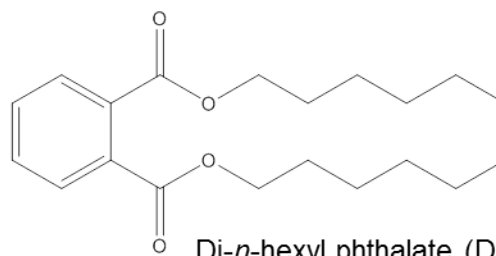
Di-2-ethylhexyl phthalate (DEHP)



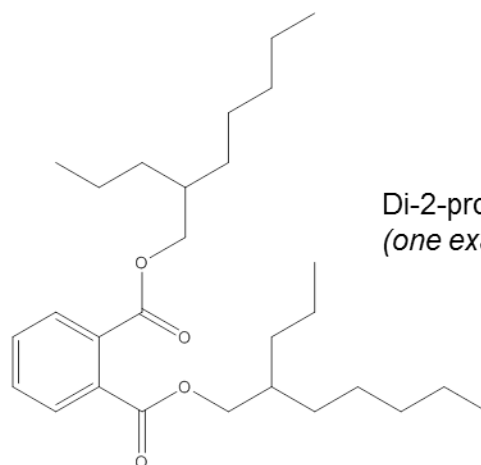
Diethyl phthalate (DEP)



Diallyl phthalate (DAP)



Di-*n*-hexyl phthalate (DnHxP)



Di-2-propylheptyl phthalate (DPHP)
(one example *DIDP* isomer)

Exposure or potential exposure to the public or specific subgroups

o-Phthalates are extensively used in a wide variety of applications. Example plastic products containing *o*-phthalates include shower curtains, children's toys, processing equipment for food, packaging materials, automotive plastics, and plastic medical supplies, such as tubing and bags for intravenous fluids or blood. *o*-Phthalates are used in a variety of building materials such as vinyl flooring, wires and cables,

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wallpaper, and carpet backing (Just et al., 2015; CPSC, 2010; ATSDR, 2002). They are found in paints, adhesives, and coatings for medications (CPSC, 2010; Just et al., 2015; Kelley et al., 2013). *o*-Phthalates are used in personal care products and cosmetics for many purposes including: fragrance carriers; to prevent brittleness and cracking in nail polish; as skin moisturizing, softening, and penetrating agents; and as antifoaming agents (Koo and Lee, 2004). Scented products like air fresheners can also contain *o*-phthalates.

The following sections summarize data on detections of selected *o*-phthalates in food, personal care products, consumer products, dust, and indoor air.

Diet:

Diet is considered to be a major route of exposure to high molecular weight *o*-phthalates, such as DEHP, DINP, and DIDP (Koch et al., 2013). *o*-Phthalates can migrate into food from food processing and handling equipment (like tubing, conveyor belts, and gloves), as well as food packaging materials (Kappenstein et al., 2012; Gallart-Ayala et al., 2013). *o*-Phthalates may also be in food due to widespread presence in the environment (Kappenstein et al., 2012). A number of *o*-phthalates⁷ are approved for use in food contact surfaces and materials and as indirect food additives (US FDA, 2014a; 2014b; 2014c).

Bi et al. (2013) found diallyl phthalate (DAP) and DPenP each in over half of the vegetable oil samples purchased in Delaware supermarkets (n=21) at levels ranging from below the detection limit to 306 µg/kg (DAP) or 876 µg/kg (DPenP). Neither of these *o*-phthalates is currently on the list of designated chemicals. In comparison, DEHP was found in all samples, with levels ranging from 50.3 to 6,166 µg/kg. Three other *o*-phthalates not currently included on the list of designated chemicals, di-*n*-propyl phthalate (DnPP), DnHxP, and di-*n*-heptyl phthalate (DnHpP) were each detected in less than 15% of vegetable oil samples.

Schechter et al. (2013) found DnHxP in 15% of food samples (n=72) collected from Albany, New York in 2011. For example, DnHxP was found in two samples of ice cream (maximum=8.82 µg/kg wet weight [wt]), one sample of ground beef (4.83 µg/kg wet wt), and in one of two butter samples tested (1.58 µg/kg wet wt). For comparison, DEHP was detected in 74% of the samples at levels ranging from 3.71 to 1158 µg/kg wet wt.

⁷ *o*-Phthalates approved by US FDA for use in food contact materials and/or as indirect food additives include: DMP, DAP, DEP, DnBP, DIBP, BzBP, DCHP, DEHP, DIDP, and DUP.

Personal care products:

o-Phthalates are directly added to many personal care products, but can also migrate into the products from packaging (Guo and Kannan, 2013). Routine use of personal care products may contribute to high levels of exposure to certain o-phthalates, such as DEP (Philippat et al., 2015a; Just et al., 2010; Guo and Kannan, 2013). DEP is commonly used in personal care products that contain fragrances (Philippat et al., 2015a; US FDA, 2014d).

Dodson et al. (2012) conducted a broad survey of o-phthalates and other chemicals in a variety of consumer products, which they categorized as “conventional” versus “alternative” based on specific criteria. They used a compositing approach, combining as many as seven conventional products of a particular type to create a single sample for analysis. Except for sunscreen, the alternative products were analyzed individually. DEP was one of the most frequently detected compounds in composite samples of conventional personal care products, such as soap, lotion, and shaving cream. It was also found in samples of alternative body lotion, conditioner, and sunscreen. DEHP was found in both conventional and alternative personal care products. DnHxP, not currently on the list of designated chemicals, was detected in the composite conventional lipstick sample. A single sample of an alternative shaving cream contained four phthalates (DEHP, DnBP, BzBP, and DINP), as well as the phthalate alternative di(2-ethylhexyl) adipate, illustrating the potential for multiple exposures. Dicyclohexyl phthalate (DCHP) and DINP were detected only in alternative personal care products, which the authors highlighted as possible evidence of substitution.

Guo and Kannan (2013) reported that DEHP was the most frequently detected phthalate in a survey of personal care products collected in Albany, New York in 2012. The detection frequency in “leave-on” and “rinse-off” products was 66% and 76%, respectively. The authors proposed that the DEHP in the products was coming from the plastic packaging. DEP, DIBP, and DnBP⁸ were also found in leave-on products (DFs were 53%, 23%, and 39%, respectively) and rinse-off products (DFs were 24%, 27%, and 17%, respectively). With regard to concentrations, DEP was found at the highest levels, ranging up to a maximum of nearly 8000 µg/g wet wt in perfume. DMP and BzBP were found in about 10% of the leave-on and rinse-off products evaluated. DnHxP, not currently on the list of designated chemicals, was detected in 3% of leave-on products and 7% of rinse-off products. The highest concentrations of DnHxP were found in deodorant (mean, 2.69 µg/g wet wt; max, 37.7 µg/g wet wt).

⁸Guo and Kannan (2013) used the abbreviation “DBP” (dibutyl phthalate), which is assumed to be DnBP.

Bao et al. (2015) conducted a survey of personal care products in China, with samples collected in 2013. The authors indicated that DEP was the most frequently detected o-phthalate (DF=29.8%), and that most concentrations were above 20 µg/g. The authors also reported detections in less than 5% of products of some o-phthalates not currently on the list of designated chemicals: di(methoxyethyl) phthalate (DMEP), diphenyl phthalate (DPhP), and bis(4-methyl-2-pentyl)phthalate (one isomer of diisohexyl phthalate [DIHxP]).

In a small study of personal care products (n=26) from Spain, Llompart et al. (2013) reported that DEP levels were higher in “leave-on” products (DF=53%; range from below the limit of detection [$<$ LOD] to 357 µg/g) compared to levels in “rinse-off” products (DF=29%; two detections at 2.5 and 0.72 µg/g). Several o-phthalates not currently on the list of designated chemicals were detected in leave-on products (n=19): DMEP (two detections, deodorant and hair product); DPhP (two detections, hand/skin lotion); DPenP (one detection, hair product), and diisopentyl phthalate (DIPenP) (one detection, hair product).

Children’s toys and childcare products:

In a study of 72 PVC toys and other childcare products purchased from 17 countries, Stringer et al. (2000) reported that DINP was the most frequently found o-phthalate (DF= 64%), followed by DEHP (DF= 48%). Five of the six children’s toys and products bought in the US were made in China; the sixth was made in the US. DINP concentrations in these toys and products ranged from $<$ LOD to 37.2% by weight. DEHP was found in only one teether purchased in the US (made in China), at 0.06%. In the teether that was bought and also made in the US, neither DEHP nor DINP were detected.

In a German study, DPHP was identified in children’s toys at concentrations ranging from approximately 10-48% by weight (Federal Institute for Risk Assessment, 2011).

CPSC (2014b) analyzed 1,125 children’s toys and childcare articles for o-phthalates, as part of enforcement of Section 108 of the Consumer Product Safety Improvement Act of 2008. Seven hundred and twenty-five (725) samples were found to have at least one of six regulated phthalates (DEHP, DnBP, BzBP, DINP, DIDP, and DnOP) at levels above 0.1%. Most of the 725 samples contained DEHP (DF=96%). DINP and DnBP were detected much less frequently (DF=13% and 12%, respectively). In the remaining 400 children’s toys and childcare articles that did not contain one of the regulated phthalates, CPSC reported results for unregulated o-phthalates. DIBP was found in 132 of the 400 samples, and DPHP was found in 16 of the 400 samples

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Other consumer products:

Recent data on emerging *o*-phthalates in other consumer products were limited. The Dodson et al. (2012) survey discussed above included consumer products like vinyl products, household cleaners, laundry detergent, and car care products. DEHP was found at high concentrations in a vinyl pillow protector and a composite sample of two vinyl shower curtains. DEP was found in conventional laundry, cleaning and car care products, and was also detected in an alternative stain remover. DnPP, not currently on the list of designated chemicals, was not detected in any of the conventional products but was found in a sample of alternative laundry bleach, as well as samples of baking soda and borax.

Dust:

Dodson et al. (2015) studied phthalates in house dust samples collected in Richmond and Bolinas homes in 2006. Three phthalates not currently on the list of designated chemicals were detected: DnHxP (DF=96%), DPenP (DF=12%), and DnPP (DF=2%). The median level of DnHxP was 0.66 µg/g, with a maximum value of 110 µg/g. Median values for DPenP and DnPP in dust were <LOD. For comparison, DEHP was detected in 100% of samples, at a median level of 140 µg/g and a maximum of 800 µg/g.

DnHxP was measured in two other US studies of phthalates in dust. Guo and Kannan (2011) detected DnHxP in all indoor dust samples from Albany, New York at a median level of 0.6 µg/g. Rudel et al. (2003) found DnHxP in 76% of house dust samples collected from homes in Cape Cod, Massachusetts at a median level of 1.1 µg/g. For comparison, DEHP was detected in 100% of dust samples from these two studies (median levels of 304 and 77 µg/g, respectively).

Kubwabo et al. (2013) measured phthalate levels in Canadian house dust samples collected from 2007 to 2010. Some *o*-phthalates not currently on the list of designated chemicals were detected: DnHxP (DF=89%; median=0.47 µg/g), diisooheptyl phthalate (DIHpP) (DF = 98%, median=18.9 µg/g), diundecyl phthalate (DUP) (DF = 99%, median=3.9 µg/g), and a C7-C9 alkyl benzyl phthalate (DF= 95%; median=1.24 µg/g). For comparison, DEHP, DINP, and DIDP were found in 100% of samples at median levels of 462, 112, and 111 µg/g, respectively.

Air:

Rudel et al. (2010) studied phthalates in paired indoor and outdoor air samples collected in 2006 in Richmond (n=40) and Bolinas (n=10). DEP, DnBP, and DIBP were detected in 100% of indoor air samples from Richmond (median levels were 330, 140, and 140 ng/m³, respectively) and in Bolinas (320, 140, and 81 ng/m³, respectively). The detection frequency of DEHP was 90% in indoor air samples from Richmond

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(median=69 ng/m³) and 50% in indoor air samples from Bolinas (median=47 ng/m³). Three *o*-phthalates not on the list of designated chemicals were each found in 2% of Richmond indoor air samples: DnHxP (maximum=52 ng/m³), DPenP (maximum=4.0 ng/m³), and DnPP (maximum= 2.3 ng/m³). DnHxP was found in 6% of Richmond outdoor air samples (maximum=15 ng/m³).

Known or suspected health effects

There is an extensive body of toxicological literature on some *o*-phthalates, including DEHP. A number of *o*-phthalates are identified as male reproductive toxicants (DEHP, DnBP, DnHxP), female reproductive toxicants (DnBP, DnHxP), and/or developmental toxicants (DEHP, DIDP, DnBP) (OEHHA, 2015). DEHP and DINP are carcinogens. For many other *o*-phthalates, only limited data are available.

In male rats, *in utero* exposure to anti-androgenic phthalates has been shown to result in abnormalities in reproductive tract development, the entire spectrum of which is termed the “phthalate syndrome” (Mylchreest et al., 1998, 2000; Gray et al., 2000; Foster, 2005; 2006). Some characteristics of phthalate syndrome include various malformations of male reproductive organs, including hypospadias, cryptorchidism (undescended testes), and reduced anogenital distance (AGD). Phthalate exposure in humans is linked with some of these conditions as well. Several studies have found that decreased AGD in baby boys was associated with higher maternal urinary phthalate levels (Swan et al., 2005; Suzuki et al., 2012; Bustamante-Montes et al., 2013; Bornehag et al., 2015; Swan et al., 2015).

The Chronic Health Advisory Panel (CHAP, 2014) on Phthalates and Phthalate Alternatives convened by CPSC reviewed limited studies on reproductive and developmental toxicity for many phthalates not yet on the list of designated chemicals, including DPenP, DnHxP, DIHpP, and DnHpP (see CPSC, 2011a; 2011b; 2011c; 2011d; 2010). CHAP identified the following *o*-phthalates as anti-androgenic phthalates capable of producing rat phthalate syndrome, in order of activity: DPenP > BzBP ~ DnBP ~ DIBP ~ DnHxP ~ DEHP ~ DCHP > DINP (see also Gray et al., 2000; National Research Council, 2008). DPenP and DnHxP are not currently on the list of designated chemicals.

In a recent review of the literature on effects of *o*-phthalates on the ovary, Hannon and Flaws (2015) reported that DEHP disrupts ovarian folliculogenesis at numerous points during development. DnBP and BzBP disrupted follicle development and DINP was found to decrease the number of corpora lutea in adult rats after perinatal exposure. Hannon and Flaws also summarized findings that *o*-phthalates can alter ovarian steroidogenesis at a number of steps in the estradiol synthesis pathway.

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Phthalates have also been shown to affect neurodevelopment, and epidemiological studies have found associations between phthalate levels and differences in cognition and behavior (Miovodnik et al., 2014). In experimental studies, possible mechanisms for observed neurodevelopmental effects include changes in brain aromatase activity (DEHP), interference with calcium signaling (DEHP, BzBP, DnBP), effects on brain lipids (DEHP), effects on brain dopamine pathways (DEHP, DnBP, DCHP), changes in levels of certain neurotransmitters (DEHP, DCHP), and alterations in thyroid homeostasis (DEHP, BzBP, DnBP, DnOP, DINP) (Miovodnik et al., 2014).

Boas et al. (2012) also reviewed o-phthalate mediated disruption of thyroid homeostasis in experimental studies. BzBP, DnBP, and DnOP were found to interfere with the sodium/iodide symporter. Boas et al. (2012) summarized findings that DnBP and BzBP inhibited thyroid hormone uptake into cells. BzBP inhibited T3 binding to the thyroid hormone binding protein transthyretin. In epidemiological studies, urinary levels of DEHP and DnBP were negatively associated with serum thyroid hormone levels (Boas et al., 2012).

o-Phthalates have been implicated in the development of allergies and asthma in some studies (North et al., 2014). However, there have been mixed reports on the association of phthalates and allergic disease (North et al., 2014; Bornehag and Nanberg, 2010; Bekö et al., 2015). In a study in female BALB/cJ mice, Larsen and Nielsen (2008) concluded that sensitization depended on both the lipophilicity and stereochemistry of the phthalate. In a recent epidemiological study, Bekö et al. (2015) reported significant associations between non-dietary exposure (i.e., inhalation or dermal) to phthalates and allergic sensitization among children with asthma, rhinoconjunctivitis, or atopic dermatitis.

In utero exposure to low doses of MEHP was reported to induce obesity in male mice (Hao et al., 2012), and several other phthalates have been found to affect adipogenesis, possibly through activation of peroxisome proliferator activated receptors (PPARs) (Pereira-Fernandes et al., 2013; Hurst and Waxman, 2003). Disruption of thyroid homeostasis has also been discussed as another possible mechanism for o-phthalate induced obesity (Kim and Park, 2014). Goodman et al. (2014) conducted a systematic review of epidemiological studies that looked at potential associations between phthalate exposure and health endpoints related to obesity, type 2 diabetes, and cardiovascular disease, and found no consistent patterns.

Twenty o-phthalates⁹ were evaluated in US EPA's high-throughput chemical Toxicity Forecaster (ToxCastTM) program (Dix et al., 2007; Kavlock et al., 2012). ToxCast

⁹ The o-phthalates and some metabolites evaluated in US EPA's ToxCast program were: DAP, DMP, monomethyl phthalate, DnBP, DIBP, monobutyl phthalate, BzBP, monobenzyl phthalate, DEP, DnHxP,

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includes several hundred *in vitro* assays, including assays related to androgen, estrogen, and thyroid receptor pathways, gene expression and activity of PPARs, and cell proliferation. Most of the *o*-phthalates tested in ToxCast were active in assays targeting the estrogen receptor pathway and the PPAR subtypes, but few were active in assays targeting the androgen receptor pathway. *o*-Phthalates with four to six carbons in their alkyl side chain backbones were the phthalates active in the most ToxCast assays overall (US EPA, 2015).

Potential to biomonitor

Physical chemical properties:

o-Phthalates are not persistent or bioaccumulative. Log K_{ow} increases and vapor pressure declines with increasing alkyl chain length (National Industrial Chemicals Notification and Assessment Scheme [NICNAS], 2008).

Metabolism:

Phthalates are rapidly metabolized to their monoesters (Koch and Calafat, 2009). Oxidation of the monoester results in formation of the hydroxyl, oxo, and carboxyl secondary metabolites. For high molecular weight phthalates, the monoester is readily converted to these oxidized metabolites. The oxidized secondary metabolites are the main metabolites for long-chain phthalates (DEHP, DINP, and DPHP) and the monoesters are the main metabolites for short chain phthalates (Wittassek and Angerer, 2008). Both the monoester and the oxidized secondary metabolites are conjugated with glucuronic acid and excreted in the urine (Koch and Calafat, 2009).

Past biomonitoring studies:

Widespread exposure to many *o*-phthalates, including DEHP, DnBP, and DEP, has been demonstrated in biomonitoring studies worldwide (Philippat et al., 2015a; Zota et al., 2014; Calafat et al., 2011; Göen et al., 2011; Wittassek et al., 2007; Cutanda et al., 2015; Guo et al., 2011). Limited biomonitoring data for *o*-phthalates that are not currently on the list of designated chemicals were located, and are briefly discussed below.

Schütze et al. (2015) investigated time trends of DPHP metabolites in urine samples collected between 1999-2012 and stored in the German Environmental Specimen Bank. Mono-oxo-propylheptyl phthalate (oxo-MPHP) was detected in samples from 2009 (n=60, 3.3% > LOQ) and 2012 (n=60, 21.7% > LOQ) but was not detected in any samples from 1999, 2003, or 2006. oxo-MPHP concentrations ranged from less than the limit of quantitation (LOQ=0.25 µg/L) to 0.96 µg/L. Mono(propyl-6-hydroxyheptyl)

DnOP, DEHP, DINP, MEHP, DIUP, diisopropyl phthalate, DIPenP, DCHP, octyl decyl phthalate, and DIDP.

phthalate was also only detected in samples from 2009 (3.3% >LOQ; range <LOQ [0.3 µg/L] to 0.64 µg/L) and 2012 (3.3% >LOQ; range from <LOQ [0.3 µg/L] to 0.36 µg/L). Mono(propyl-6-carboxyhexyl) phthalate was not detected in any samples.

Silva et al. (2011) measured DPenP metabolites in 45 urine samples collected in 2009 from US adult residents. Mono(4-hydroxypentyl) phthalate (MHPP) was detected in 29% of adult urine samples (range from <LOD [0.7 µg/L] to 8 µg/L). Mono-*n*-pentyl phthalate (MPenP) was not detected (LOD=0.6 µg/L).

Hartmann et al. (2015) found the DPenP metabolite MPenP in urine samples from Austrian children and adults collected between 2010 and 2012 (range of DFs across all age groups was 4.1 to 6.5%; n=595). The levels ranged from <LOQ (0.55 µg/L) to 4.5 µg/L.

Kasper-Sonnenberg et al. (2011) detected MPenP above the LOQ in 2% of urine samples from German mothers (n=103) and children (n=104) collected from late 2007 to early 2009. The urinary levels for children (6 to 8 years old) were not quantifiable; in mothers' samples the values ranged from <LOQ (0.20 µg/L) to 1.3 µg/L (Kasper-Sonnenberg et al., 2011). Kasper-Sonnenberg et al. (2014) detected MPenP above the LOQ in 7.4% of urinary samples from school-aged children (8 to 10 years old; n=465). The unadjusted 95th percentile was below the LOQ (0.2 µg/L). When adjusted for creatinine, the median MPenP urinary level was 0.09 µg/g creatinine and the 95th percentile was 0.26 µg/g creatinine.

Zimmermann et al. (2012) detected DAP in breast milk samples (n=30) collected from German women (27% of values were >LOQ; median=2.0 ng/g). For comparison, DIBP was detected above the LOQ in 77% of samples (median=1.0 ng/g). DEHP and DnBP were detected above the LOQs in 43% of samples (median levels were 2.3 and 0.6 ng/g, respectively).

Analytical considerations

The Environmental Health Laboratory's (EHL's)¹⁰ urinary phthalate metabolite method uses on-line solid phase extraction high performance liquid chromatography tandem mass spectrometry (SPE-HPLC-MS/MS). The current method can measure ten urinary phthalate metabolites with detection limits ranging from 0.1 to 0.9 µg/L. The on-line SPE-HPLC-MS/MS system allows rapid and simultaneous sample preparation and analysis of multiple phthalates in urine. EHL's method avoids the issues associated with a manual off-line approach, such as lack of repeatability and potential

¹⁰ EHL is in the California Department of Public Health and is one of Biomonitoring California's laboratories.

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contamination. Additional phthalate metabolites can easily be added to the method without loss of sensitivity, though further optimization and validation of the method might be required.

Incremental costs to expand the method will include the purchase of additional native and labeled standards, reagents, and other laboratory supplies.

Need to assess efficacy of public health action

Adding the entire class of *o*-phthalates as designated chemicals would allow Biomonitoring California to study whether emerging *o*-phthalates are found in California residents and at what levels. Listing these chemicals as a class would be a resource-efficient approach. For example, it would facilitate the use of non-targeted laboratory screening methods, allowing the state to determine which phthalates pose the highest exposure concerns in California. Using this approach, the most important phthalates could be tracked over time to monitor levels in urine.

Glossary of o-phthalates (alphabetical by acronym)

BzBP:	Benzylbutyl phthalate
DAP:	Diallyl phthalate
DCHP:	Dicyclohexyl phthalate
DEP:	Diethyl phthalate
DEHP:	Di-2-ethylhexyl phthalate
DIBP:	Diisobutyl phthalate
DIDP:	Diisodecyl phthalate
DIHpP:	Diisoheptyl phthalate
DIHxP:	Diisohexyl phthalate
DINP:	Diisononyl phthalate
DIPenP:	Diisopentyl phthalate
DIUP:	Diisoundecyl phthalate
DMEP:	Dimethoxyethyl phthalate
DnBP:	Di- <i>n</i> -butyl phthalate
DnHpP:	Di- <i>n</i> -heptyl phthalate
DnHxP:	Di- <i>n</i> -hexyl phthalate
DnOP:	Di- <i>n</i> -octyl phthalate
DnPP:	Di- <i>n</i> -propyl phthalate
DPenP:	Di- <i>n</i> -pentyl phthalate
DPHP:	Di-2-propylheptyl phthalate
DPhP:	Diphenyl phthalate
DTDP:	Diisotridecyl phthalate
DUP:	Diundecyl phthalate

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