



## Human exposure, hazard and risk of alternative plasticizers to phthalate esters



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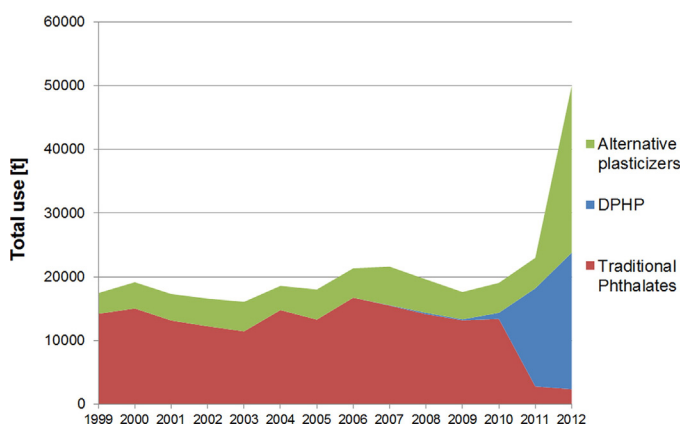
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### HIGHLIGHTS

- Alternative plasticizers are generally low-volatile, hydrophobic substances
- High production volumes with increasing trend in use
- More refined human exposure assessments necessary
- Data gaps exist regarding non-standard toxicological endpoints
- Human risks are low although exposure to DINCH and DEHT are increasing

### GRAPHICAL ABSTRACT



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### ABSTRACT

Alternative plasticizers to phthalate esters have been used for over a decade, but data regarding emissions, human exposure and health effects are limited. Here we review 20 alternative plasticizers in current use and their human exposure, hazard and risk. Physicochemical properties are collated for these diverse alternatives and log  $K_{OW}$  values range over 15 orders of magnitude and log  $K_{AW}$  and log  $K_{OA}$  values over about 9 orders of magnitude. Most substances are hydrophobic with low volatility and are produced in high volumes for use in multiple applications. There is an increasing trend in the total use of alternative plasticizers in Sweden compared to common phthalate esters in the last 10 years, especially for DINCH. Evaluative indoor fate modeling reveals that most alternatives are distributed to vertical surfaces (e.g. walls or ceilings). Only TXIB and GTA are predicted to be predominantly distributed to indoor air. Human exposure data are lacking and clear evidence for human exposure only exists for DEHT and DINCH, which show increasing trends in body burdens. Human intake rates are collected and compared with limit values with resulting risk ratios below 1 except for infant's exposure to ESBO. PBT properties of the alternatives indicate mostly no reasons for concern, except that TEHPA is estimated to be persistent and TCP toxic. A caveat is that non-standard toxicological endpoint results are not available and,

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similar to phthalate esters, the alternatives are likely “pseudo-persistent”. Key data gaps for more comprehensive risk assessment are identified and include: analytical methods to measure metabolites in biological fluids and tissues, toxicological information regarding non-standard endpoints such as endocrine disruption and a further refined exposure assessment in order to consider high risk groups such as infants, toddlers and children.

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## 1. Introduction

Plasticizers are chemical additives that provide durability, elasticity and flexibility of polymeric products (Wilkes et al., 2005). Phthalate esters (PEs) are the dominant substance class of plasticizers, and in particular bis-2-ethylhexyl phthalate (DEHP) has been the most widely used substance (Murphy, 2001; Sampson and de Korte, 2011). PEs exhibit a large variety of physicochemical properties and toxicities, and their wide environmental occurrence (indoors and outdoors) is a result of various applications in products ranging from polyvinyl chloride (PVC) flooring, cosmetics and home furnishing to vinyl toys (CIR, 2003; Peters, 2003; Pors, 2001). Commercial phthalate plasticizers can be released from polymers by volatilization to air, abrasion of the polymer, leaching in liquids and direct diffusion from the polymer to dust on the polymer surface, and contaminate the environment where they may pose a risk to humans (Afshari et al., 2004; Fromme et al., 2004; Fujii et al., 2003; Rudel et al., 2003). Several phthalate esters have been shown to cause negative health effects to animals (Foster et al., 2001; Higuchi et al., 2003; Li et al., 1998). Regarding humans, several studies have shown indications for effects. For example, anti-androgenic effects have been linked to internal PE concentrations (Bustamante-Montes et al., 2013; Huang et al., 2009). Because of this and their high volume and widespread use, certain PEs are regulated in the European Union (Amberg-Muller et al., 2010; EC, 1999, 2007a; Ventrice et al., 2013). For example, DEHP is listed among category 1B substances within the globally harmonized system of classification and labeling of chemicals (GHS). This system defines two categories of carcinogens: Category 1 for known or presumed to have carcinogenic potential and category 2 for suspected carcinogens. Category 1 has further subcategories: Largely based on human evidence (1A) and largely based on animal evidence (1B) (UNECE, 2011). DEHP has thus been banned in toys, childcare articles, cosmetics and medical devices (EC, 2007b, 2008, 2009; Kim et al., 2007a). Furthermore, the use of PEs is restricted in Canada and the United States (Canada-Gazette, 2010; Snijder et al., 2012) with regulatory limits set on the concentration of

DEHP, diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP) in childcare articles (USCPSC, 2007).

There is a need for alternative plasticizers that migrate to a lesser extent out of polymers and also have low toxicity (Atek et al., 2010; Beach et al., 2013). The toxic potential of current PEs is largely due to metabolic transformation to more toxic metabolites. Phthalates entering the human body are rapidly metabolized by phase I reactions (hydrolysis and subsequent oxidation reactions) followed by phase II metabolism and excretion through urine e.g. as monoesters or glucuronide conjugates (Wittassek et al., 2011). Relatively polar and low molecular weight phthalates are mostly metabolized to their stable hydrolytic monoesters whereas high molecular weight phthalates with  $\geq 8$  carbons in the alkyl chain are metabolized to their hydrolytic monoesters, which are in turn extensively transformed by  $\omega$ -,  $(\omega - 1)$ - and  $\beta$ -oxidation to oxidative products (alcohols, ketones and carboxylic acids) (Hauser and Calafat, 2005). Phthalate mono-ester and secondary oxidation metabolites are believed to have biological activity (Koch and Calafat, 2009; Koch et al., 2003; Silva et al., 2007b). Alternative plasticizers, however, should ideally produce metabolites with less severe consequences for human health.

Extensive research has been performed to identify alternatives for PEs. Currently, many different alternative plasticizers exist including adipates, benzoates, citrates, cyclohexane dicarboxylic acids, epoxidized vegetable oils, glycerol acetylated esters, phosphate esters, sebacates, terephthalates and trimellitates. Some substances have been used for more than several decades whereas others have more recently entered the market. For most alternative plasticizers, information on properties and toxicological studies are available but not well summarized. Additionally, some substances are not exclusively being used as plasticizers. For example, phosphate esters have also been widely used as flame retardants (Marklund et al., 2003; Wei et al., 2015). In this work, we consider the term “alternative plasticizer” as a synonym for non-phthalate plasticizers. We are aware of the fact that not all “alternative plasticizers” mentioned here are substances that have recently entered the market or are produced exclusively to replace PEs. Hence, all non-

phthalate chemicals that can be used as a plasticizer, thus presenting an “alternative”, are considered alternative plasticizers. Not only do we lack human exposure data for many of these substances, it is often debatable whether these alternatives are of concern to human health or not and the lack of toxicity data can make risk assessment difficult (ECDGE, 2000; SCENIHR, 2007; Stuer-Lauridsen et al., 2001). No comprehensive review of alternative plasticizers in the scientific literature is available and most reports on these substances are not available to the public, thus toxicological and exposure profiles might not be sufficiently assessed.

The aim of this review is to evaluate current substance classes of alternative plasticizers, and in particular:

1. Provide and discuss information on physicochemical properties, production volume, use, emissions, indoor fate, human exposure and health concerns of alternative plasticizers.
2. Address their human risk potential and their persistent/bioaccumulative/toxic (PBT) properties.
3. Specify data gaps that need to be filled to improve these assessments.

## 2. Physicochemical properties

The selection of substances was done according to their presence in the scientific literature and publicly accessible reports and databases. We present 20 substances in total that are used as alternative plasticizers (Fig. 1). Structurally, similarities exist between them and common PEs, for instance the presence of carbon-chains that vary in length or number (usually 2–3 side chains) connected to a chemical group (benzene, cyclohexane, phosphate etc.) via esterification. The physicochemical properties are presented in Table 1 together with those of four PEs for comparison.

The logarithm of the octanol-water partition coefficients ( $\log K_{OW}$ ) shows a wide range, for example 0.25 for the rather hydrophilic GTA and 14.84 for the very hydrophobic epoxidized soybean oil (ESBO). In order to compare partitioning behaviors, air–water partition coefficients ( $K_{AW}$ ) were calculated using the vapor pressure and solubility in water and plotted against  $\log K_{OW}$ . The results indicated a fairly high distribution over the chemical space map (Fig. 2) because of the large variability in  $\log K_{OW}$  and  $\log K_{AW}$  values (from 0 to 15 and –8 to 1 respectively). The selected PEs (DEHP, DINP, DIDP and bis(2-propylheptyl) phthalate (DPHP)) were among the more hydrophobic substances together with alternatives like bis(2-ethylhexyl) adipate (DEHA), diisodecyl adipate (DIDA) and diisononyl cyclohexane-1,2 dicarboxylate (DINCH). Other alternatives like glycerides, castor oil-mono, hydrogenated, acetates (COMGHA), tris-2-ethylhexyl trimellitate (TOTM) or ESBO are of similar lipophilicity but have lower  $\log K_{AW}$  values. As many of these substances have a long carbon-chain of 8 to 10 carbons and/or have hydrophobic benzene groups, these results are expected. The result for ESBO is considered to be highly uncertain due to the discrepancy between modeled and measured  $\log K_{OW}$  (14.8 and 6.2, respectively). A similar case was observed for tris-2-ethylhexyl phosphate (TEHPA), for which experiments indicated  $\log K_{OW}$  values of 4.1 and 4.2. Glycerin triacetate (GTA), bis(2-ethylhexyl) phosphate (DEHPA), di(propylene glycol) dibenzoate (DPGDB) and di(ethylene glycol) dibenzoate (DEGDB) belong to another group of alternatives which have fairly low  $\log K_{OW}$ . Most of these chemicals have shorter carbon-chains and as a consequence, are more hydrophilic (e.g. DEGDB, DPGDB and dibutyl adipate (DBA)). Despite the relatively long carbon-chain length (8 carbons) of the phosphate plasticizers, hydrophilic phosphate groups might substantially lower the hydrophobicity of DEHPA and TEHPA. Additionally, DEHPA mostly exists in ionic form under environmental conditions and has an estimated  $pK_a$  of 1.47 at 25 °C (ECHA, 2014b). Thus, the  $\log K_{OW}$  value for this compound was estimated for the dissociated form. In terms of  $\log$  octanol-air partition coefficient ( $K_{OA}$ ) values, GTA and trimethyl pentanyl diisobutyrate (TXIB) have relatively low values (6.6 and 6.9 respectively) while other alternatives have  $\log K_{OA}$  values of

around 8 to 10, similar to the selected phthalates. The extreme value of 22 for ESBO has to be regarded with caution as mentioned above. Overall, physicochemical properties of alternative plasticizers vary considerably depending on the substance group or the individual chemical. Many of them will likely partition to organic carbon rich matrices (soil, biota, dust etc.) because of high  $\log K_{OW}$  and  $\log K_{OA}$  values. Similarities between common PEs and alternatives exist for some cases. For example, TEHPA, alkylsulfonic phenyl ester (ASE), bis-2-ethylhexyl terephthalate (DEHT), DINCH, bis-2-ethylhexyl sebacate (DOS) and DIDA are close in the chemical space map (within 2 log orders) to the common PEs (Fig. 2).

To conclude, physicochemical properties are available for alternative plasticizers, although two major problems were encountered in this work. First, properties were measured at different temperatures even in recent reports (ECHA, 2014b). Hence, comparing values was not possible unless a correction for temperature was applied. However, the necessary information for temperature correction, such as enthalpies of phase changes, was not available. Therefore, model estimations were used, which potentially introduces error. The second problem encountered was the discrepancy between several experimental studies or between these studies and estimated values. As mentioned above, differences ranged from very small to several orders of magnitude. Definitely, more, and preferably experimental studies, should be conducted to reliably estimate the physicochemical properties of acetyl tributyl citrate (ATBC) (solubility in water), DEHA (solubility in water), ASE (solubility in water) and TEHPA ( $K_{OW}$  and solubility in water). Furthermore, only one or two measurements exist for some substances. Although seemingly reliable, additional measurements from different sources would verify these results and further improve the reliability of the measured values.

## 3. Production and use

An overview of use and applications of alternative plasticizers is given in Table 2. Polyvinyl chloride (PVC) applications with adipate plasticizers provide good technical performance at low temperatures because of their lower viscosities compared to PEs (Maag et al., 2010). Therefore, they are normally blended in with other low cost plasticizers to reduce cost and retain low temperature properties (Bee et al., 2014). The benzoates DEGDB and DPGDB are used mainly as additives in PVC flooring (Krauskopf and Goodwin, 2005). The citrate ATBC is used as a food contact substance (FDA, 2002) and is a common additive in cosmetics and medical products. Additionally, ATBC is an alternative to phthalates used in children's articles (ChemSystems, 2008; Johnson, 2002; Stuer-Lauridsen et al., 2001; USEPA, 2003). DINCH is used as an alternative plasticizer in high volumes and replaces phthalates such as DEHP and DINP in medical devices, toys and food packaging materials (Schutze et al., 2012). Phosphate esters such as DEHPA, TEHPA and tricresyl phosphate (TCP) are another group of alternative plasticizers mainly used as additives in concrete, floor and wall coverings, cables and adhesives due to their high resistance to ignition and burning (ECPI, 2007; Stuer-Lauridsen et al., 2001). The commercial form of TCP consists of a mixture of *ortho*-, *meta*-, and *para*-isomers. Phosphate esters are also used as flame retardant substances.

Sebacates are commonly used for flexible PVC applications requiring lower plasticizer volatility. Terephthalates are very similar substances to PEs with two adjacent ring substitutions occupying *para*-positions instead of *ortho*-positions, among which DEHT is the most common substance. DEHT is a structural isomer of DEHP and is used as a commercial alternative in a wide range of applications such as in plastic toys and childcare articles, films, pavement, stripping compounds, walk-off mats, vinyl products and beverage closures (Eastman, 2011; SCENIHR, 2007; USNLoM). The trimellitate TOTM is used in high temperature applications such as PVC cables with significantly improved extraction and migration resistance relative to other DEHP alternatives (Rahman and Brazel, 2006).

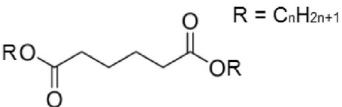
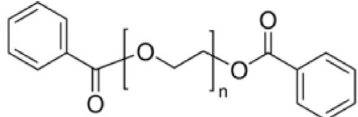
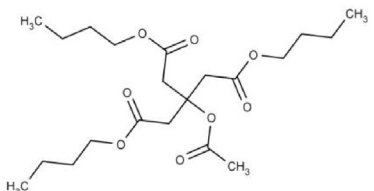
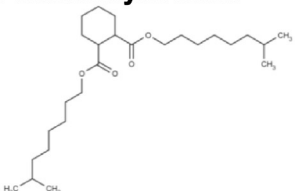
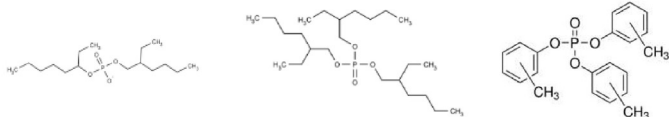
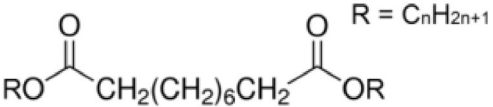
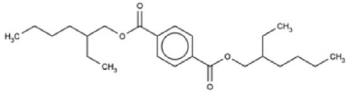
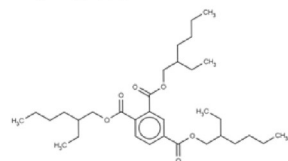
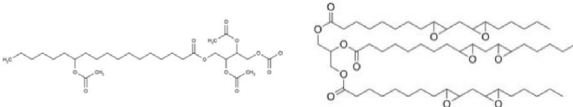
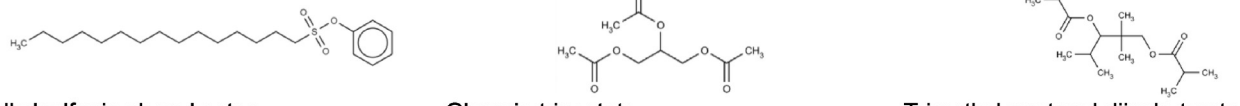
<b>Adipates</b>  Dibutyl adipate ( <b>DBA</b> ) CAS: 105-99-7 (n=4) Bis(2-ethylhexyl) adipate ( <b>DEHA</b> ) CAS:103-23-1 (n=8) Diisononyl adipate ( <b>DINA</b> ) CAS:33703-08-1 (n=9) Diisodecyl adipate ( <b>DIDA</b> ) CAS:27178-16-1 (n=10)		<b>Benzoates</b>  Di(ethylene glycol) dibenzoate ( <b>DEGDB</b> ) CAS:120-55-8 (n=1) Di(propylene glycol) dibenzoate ( <b>DPGDB</b> ) CAS: 27138-31-4 (n=2)
<b>Citrates</b>  Acetyl tributyl citrate ( <b>ATBC</b> ) CAS: 77-90-7	<b>Cyclohexane dicarboxylic acids</b>  Diisononyl cyclohexane-1, 2-dicarboxylate ( <b>DINCH</b> ) CAS: 166412-78-8	
<b>Phosphate esters</b>  Bis(2-ethylhexyl) phosphate ( <b>DEHPA</b> ) CAS: 298-07-7 Tris(2-ethylhexyl) phosphate ( <b>TEHPA</b> ) CAS:78-42-2 Tricresyl phosphate ( <b>TCP</b> ) CAS: 1330-78-5	<b>Sebacates</b>  Dibutyl sebacates <b>DBS</b> CAS:109-43-3 (n=4) Bis(2-ethylhexyl)sebacates ( <b>DOS</b> ) CAS: 122-62-3(n=8)	
<b>Terephthalates</b>  Bis(2-ethylhexyl) terephthalate ( <b>DEHT</b> ) CAS: 6422-86-2	<b>Trimellitates</b>  Tris-2-ethylhexyl trimellitate ( <b>TOTM</b> ) CAS: 3319-31-1	<b>Vegetable oil derivatives</b>  Glycerides, castor oil-mono, hydrogenated, acetates ( <b>COMGHA</b> ) CAS: 736150-63-3 Epoxidized soybean oil ( <b>ESBO</b> ) CAS: 8013-07-8
<b>Others</b>  Alkylsulfonic phenyl ester ( <b>ASE</b> ) CAS:91082-17-6 Glycerin triacetate ( <b>GTA</b> ) CAS: 102-76-1 Trimethyl pentanyl diisobutyrate ( <b>TXIB</b> ) CAS: 6846-50-0		

Fig. 1. Chemical structures, names, abbreviations and CAS numbers of 20 alternative plasticizers.

Other alternative plasticizers are ESBO and COMGHA, which are *vegetable oil derivatives* derived from soybean and castor oil, respectively. The structures of these plasticizers in Fig. 1 represent the main component of the product composition (>85%). The ability of ESBO to prevent autocatalytic breakdown of the polymer at high temperature makes it an important additive in PVC products. It is therefore a common additive in PVC gaskets, which are used to improve sealants in food products (Pedersen et al., 2008). GRINDSTED® SOFT-N-SAFE (trade name for COMGHA) has replaced DEHP and DINP, but is also a substitute for di-n-butyl phthalate (DnBP) and benzylbutyl phthalate (BBzP) in

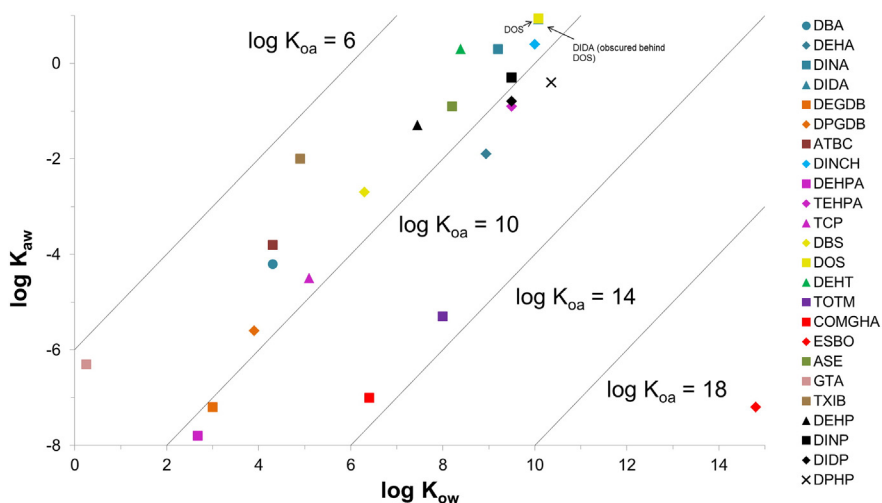
PVC, films, adhesives, printing inks, sealants and cosmetics (Danisco, 2009).

Other alternative plasticizers include Mesamoll® II (trade name for ASE) is used in PVC, polyurethanes and rubbers (Lanxess, 2008) and is beneficial for articles which come into contact with water and alkalis because of its high saponification resistance relative to DEHP (Maag et al., 2010; Zoller and Marcilla, 2011). Another plasticizer, Triacetin (trade name for GTA), imparts plasticizing effects in cellulose-based products and is compatible with natural and synthetic rubber. It can be used as a substitute for DnBP and BBzP in adhesives, inks and coatings

**Table 1**

Physicochemical properties of common phthalate plasticizers and alternative plasticizers, taken from the ECHA database, unless otherwise noted.

Substance	Molar weight [g/mol]	Density [g/cm <sup>3</sup> ] at 20 °C	Vapor pressure [Pa] at 25 °C	Solubility in water [mg/l] at 25 °C	log K <sub>OW</sub> at 25 °C	Melting point [°C]
<i>Phthalate plasticizers</i>						
DEHP	390.56	0.98	$7.59 \times 10^{-4c}$	$2.49 \times 10^{-3}$	7.45	−50
DPHP	446.66	0.96	$4.91 \times 10^{-6a}$	$2.2 \times 10^{-6a}$	10.36 <sup>a</sup>	−48
DINP	418.61	0.97	$5.17 \times 10^{-a}$	$1.74 \times 10^{-5a}$	9.52 <sup>a</sup>	−54
DIDP	446.74	0.97	$1.84 \times 10^{-6a}$	$2.24 \times 10^{-6a}$	9.46 <sup>a</sup>	−45
<i>Alternative plasticizers</i>						
<i>Adipates</i>						
DBA	258.35	0.96	0.02	35	4.33 <sup>a</sup>	−32.4
DEHA	370.57	0.92	$4.27 \times 10^{-4a}$	$5.45 \times 10^{-3a}$	8.94	−67.8
DINA	398.62	0.92	$4.41 \times 10^{-4a}$	$3.98 \times 10^{-5a}$	9.24 <sup>a</sup>	−65
DIDA	426.67	0.92 (15 °C)	$2.5 \times 10^{-4a}$	$5.15 \times 10^{-6a}$	10.08 <sup>a</sup>	<−20
<i>Benzoates</i>						
DEGDB	314.33	1.20	$1.8 \times 10^{-5}$	34.3	3.04 <sup>a</sup>	24
DPGDB	342.39	1.12	$1.6 \times 10^{-4}$	8.43	4.3	−20
<i>Citrates</i>						
ATBC	402.48	1.05	$6.07 \times 10^{-4a}$	0.65	4.29 <sup>a</sup>	−57
<i>Cyclohexane dicarboxylic acids</i>						
DINCH	424.65	0.95	$1.28 \times 10^{-4a}$	$8.8 \times 10^{-6a}$	10	−54
<i>Phosphate esters</i>						
DEHPA	322.42	0.98	$2.4 \times 10^{-5a}$	182	2.67	−50
TEHPA	434.63	0.99	$1.1 \times 10^{-5}$	$1.46 \times 10^{-5a}$	9.49 <sup>a</sup>	−74
TCP	368.37	1.17	$8 \times 10^{-5d}$	0.36 <sup>b</sup>	5.11 <sup>b</sup>	−20
<i>Sebacates</i>						
DBS	314.46	0.93 <sup>a</sup>	$6.3 \times 10^{-4}$	0.04 <sup>a</sup>	6.3 <sup>a</sup>	−10
DOS	426.67	0.91	$2.62 \times 10^{-4a}$	$5.15 \times 10^{-6a}$	10.08 <sup>a</sup>	−80
<i>Terephthalates</i>						
DEHT	390.56	0.98	$2.86 \times 10^{-3a}$	$2.39 \times 10^{-4a}$	8.39 <sup>a</sup>	<−67.2
<i>Trimellitates</i>						
TOTM	546.78	0.99	$6.80 \times 10^{-8}$	$3.1 \times 10^{-3}$	8	−43
<i>Vegetable oil derivatives</i>						
COMGHA	500.50	1.00	$4.8 \times 10^{-8}$	<0.1	6.4	−21.5
ESBO	1000.00	1.01 <sup>a</sup>	$1.6 \times 10^{-20a}$	$1.6 \times 10^{-20a}$	14.84 <sup>a</sup>	−2
<i>Others</i>						
ASE	368.57	1.06	$4.89 \times 10^{-4}$	$5.23 \times 10^{-4a}$	3.88 <sup>a</sup>	−
GTA	218.20	1.16	0.33	58,000	0.25	−78
TXIB	268.41	0.94	1.13 <sup>a</sup>	11.46 <sup>a</sup>	4.91 <sup>a</sup>	−70

<sup>a</sup> Estimated with EPI Suite (USEPA, 2012) or SPARC.<sup>b</sup> (Saeger et al., 1979).<sup>c</sup> Average between various sources in the ECHA database and Schwarzenbach (2005).<sup>d</sup> (Boethling and Cooper, 1985).**Fig. 2.** Chemical space map showing log K<sub>OW</sub> and log K<sub>AW</sub> values of 4 selected phthalates and 20 alternative plasticizers. Colors represent a substance group whereas symbols show a specific compound within the group. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 2**  
Production and use of alternative plasticizers.

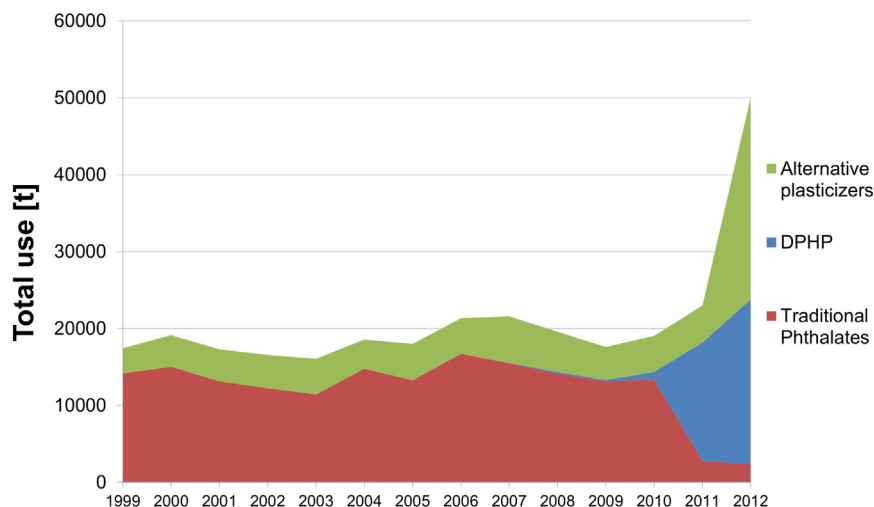
Category	Chemical	Production	Use	References
Adipates	DEHA	High production volume (OECD and HPVIS), 10 000–100 000 t/year in the EU	Toys, vinyl flooring, wire and cable, stationery, wood veneers, coated fabrics, gloves, tubing, artificial leather, shoes, sealants, carpet backing	ECHA (2014b), HPVIS 2014, OECD (2009), SCENIHR (2007), Stuer-Lauridsen et al. (2001)
	DBA	High production volume (OECD and HPVIS), 100–1000 t/year in the EU	Resins and floor wax	ECHA (2014b), HPVIS (2014), IPCS (1996), OECD (2009)
	DINA	High production volume (OECD and HPVIS), 1000+ t/year in the EU	Other than plasticizer: Skin conditioning agent, emollient, solvents	CIR 2010; ECHA (2014b), HPVIS (2014), OECD (2009)
	DIDA	High production volume (OECD and HPVIS), 1000–10 000 t/year in the EU	Similar use as DINA	CIR (2010), ECHA (2014b), HPVIS (2014), OECD (2009)
Benzoates	DEGDB	High production volume (OECD and HPVIS), 1000–10 000 t/year in the EU	Solvent for PVC, vinyl flooring, plasticizer in elastomers	ECHA (2014b), HPVIS (2014), Krauskopf and Goodwin (2005), OECD (2009), VELSCOL (2001a)
	DPGDB	High production volume (OECD and HPVIS), 10 000–100 000 t/year in the EU	Similar use as DEGDB	ECHA (2014b), HPVIS (2014), Krauskopf and Goodwin (2005), OECD (2009), VELSCOL (2001b)
Citrates	ATBC	High production volume (OECD and HPVIS), 10 000–100 000 t/year in the EU	Cosmetic products, toys, vinyl, adhesives, medical devices, pharmaceutical tablet coatings, food packaging	ChemSystems (2008), ECHA (2014b), HPVIS 2014, Johnson (2002), OECD (2009), Stuer-Lauridsen et al. (2001), USEPA (2003)
Cyclohexane dicarboxylic acids	DINCH	200 000 t/year in 2013, 10 000+ t/year in the EU	Medical devices, toys, food packaging, cosmetic products, shoes, exercise mats and cushions, textile coatings and printing inks	BASF (2011); ChemSystems (2008), ECHA (2014b), EFSA (2006), Nagorka et al. (2011a)
Phosphate esters	DEHPA	High production volume (OECD and HPVIS), 100–1000 t/year in the EU	PVC products in the hospital sector, packaging, cables, floor and wall covering	ECHA (2014b), HPVIS (2014), OECD (2009), Stuer-Lauridsen et al. (2001)
	TEHPA	High production volume (OECD and HPVIS), 1000–10 000 t/year in the EU	Similar applications as DEHPA	ECHA (2014b); HPVIS (2014); OECD (2009); Stuer-Lauridsen et al. (2001)
	TCP	High production volume (OECD and HPVIS), 1000–10 000 t/year in the EU	Plasticizer in PVC, mainly car interiors and furniture upholstery	Brommer et al. (2012), ECHA, 2014b, HPVIS (2014)x, OECD (2009), van der Veen and de Boer (2012)
Sebacates	DOS	High production volume (OECD and HPVIS), 1000–10 000 t/year in the EU	PVC products and elastomers	ECHA (2014b), HPVIS (2014), OECD (2009), Stuer-Lauridsen et al. (2001), USNLoM (2014b)
	DBS	High production volume (OECD), 100–1000 t/year in the EU	Plasticizer, flavoring agent, cosmetic and perfume additive	ECHA (2014b), OECD (2009), USNLoM (2014a)
Terephthalates	DEHT	High production volume (OECD and HPVIS), 10 000–100 000 t/year in the EU	PVC toys, coatings for cloth, electric connectors, flexible film, pavement, stripping compounds, walk-off mats, sheet vinyl flooring, childcare articles and beverage closures	Eastman (2011), ECHA (2014b), HPVIS (2014), OECD (2009), SCENIHR (2007), USNLoM (2014c)
Trimellitates	TOTM	High production volume (OECD and HPVIS), 10 000–100 000 t/year in the EU	Heat-resistant PVC articles, PVC products in the hospital sector, packing, cables, profiles and floor/wall coverings	ECHA (2014b), HPVIS (2014), OECD (2009), Stuer-Lauridsen et al. (2001)
Vegetable oil derivatives	COMGHA	1000–10 000 t/year in the EU	Food contact materials, medical devices, vinyl flooring, wallpaper, shrink wrap film, textile dyes, ink applications, adhesives, sealants, PVC containing films, tubes, bottles	(Danisco; DEPA; ECHA, 2014b; SCENIHR, 2007)
	ESBO	High production volume (OECD), 10 000–100 000 t/year in the EU	Closure gaskets used to seal glass jars, PVC resins in baby food jars	ECHA (2014b), Fantoni and Simoneau (2003), OECD (2009); Stuer-Lauridsen et al. (2001)
Others	ASE	High production volume (OECD), 10 000–100 000 t/year	PVC, polyurethanes, natural rubber, various kinds of synthetic rubbers	ECHA (2014b), Lanxess, 2008, OECD (2009)
	GTA	High production volume (OECD), 10 000–100 000 t/year in the EU	Cosmetic and pharmaceutical plasticizer, cellulose acetate plasticizer in the manufacture of cigarette filters, plasticizer for cellulose nitrate	ECHA (2014b); OECD (2009), Pepe et al. (2002), Uchinema-Chemie, (1994), Uchinema-International (1996)
	TXIB	High production volume (OECD), 1000–10 000 t/year in the EU	PVC toys, flooring, products in the hospital sector	Cain et al. (2005), Eastman, ECHA (2014b), OECD (2009); Stuer-Lauridsen et al. (2001)

and has been approved as an ingredient for food packaging (Garcia et al., 2006). TXIB, which is frequently used not only as a plastic additive in toys and childcare articles but also to increase the flexibility of films due to its low viscosity and good compatibility with all common plasticizers (Eastman, 2006).

Almost all of the above mentioned alternatives are listed as High Production Volume (HPV) chemicals in the 2007 OECD HPV list or in the Chemicals in the HPV Challenge (HPVIS) list (Table 2). The OECD list includes chemicals which are produced or imported in amounts greater than 1000 tonnes per year in at least one member country or region whereas the HPVIS list includes those produced or imported into the United States in quantities of 1 million lbs (500 tonnes) or more per year. Furthermore, some alternatives are being produced in very large quantities in the European Union, for example DINCH (10 000+ t/year) or DEHT (10 000–100 000 t/year). Therefore, based on production volumes, some alternatives could be relevant from an exposure point of view.

A thorough understanding of chemical use patterns is a prerequisite to enable assessment of chemical release, exposure and risks to humans. Use patterns can also be used to predict likely future exposure trends or changes in exposure patterns. The Nordic countries have a long tradition of collecting statistics on the use of chemical products. Therefore, use volumes of alternative plasticizers from the Substance in Preparations in Nordic Countries (SPIN) database (SPIN, 2015) were used as an illustrative example of consumption volumes. The SPIN database contains the use of a particular chemical in chemical products in the Nordic countries (Sweden, Denmark, Norway, Finland), but does not include imports of finished articles that might contain these chemicals. Consumption data were sometimes not available for all countries, thus Sweden was used as an example for the Nordic region because in almost every case, total use information from 1999 to 2012 was available.

The total use of phthalate plasticizers and alternative plasticizers from 1999 to 2012 in Sweden is summarized in Fig. 3. In addition to the selected phthalates above, diethyl phthalate (DEP), DnBP,

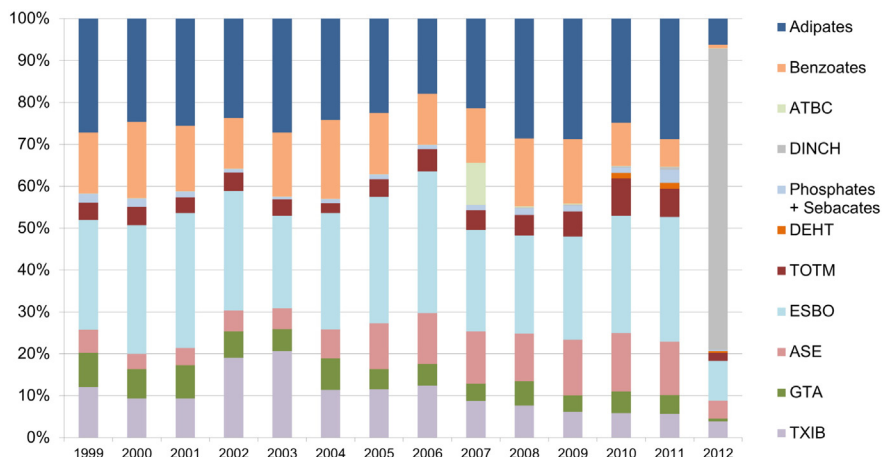


**Fig. 3.** Total use of “traditional phthalates” (sum of DEP, DnBP, DiBP, BBzP, DEHP, DINP and DIDP) and the more recently occurring DPHP compared to the use of alternative plasticizers (sum of substances listed in Table 2 excluding COMGHA) in chemical products in Sweden from 1999 to 2012.

di-isobutyl phthalate (DiBP) and BBzP were also included. In Fig. 3, these four, together with DEHP, DINP and DIDP are referred to as ‘traditional phthalates’. As use information for COMGHA was not available in the database, this substance is excluded from the following discussion. The total use of traditional phthalate plasticizers in Sweden remained fairly constant until a sudden decrease in 2010, when the use of DPHP rapidly increased, which illustrates the use of DPHP as a substitute for the traditional phthalates. Also, results from Schutze et al. showed that the general German population is increasingly exposed to DPHP (Schutze et al, 2015). The decrease of traditional PEs is largely attributable to the decline of DINP use, which in turn has been used as a substitute plasticizer for DEHP since the early 2000s (see Fig. A.1 in the Supplementary data). The total use of alternative plasticizers was about 3 times lower than PEs in 1999 and remained at the same level until a substantial increase from 2011 to 2012, surpassing the total use of PEs, which was mainly attributable to the increased use of DINCH (see Fig. 4). Hence, there has been a shift from using phthalate plasticizers to alternative plasticizers and the importance of alternatives will most likely continue to increase in the coming years, considering the environmental concerns and political focus on the phasing-out of

PEs in Sweden (Kemi, 2014). It is interesting to note that the observed shift coincided with a substantial increase in the use of plasticizers in general. There may be several possible reasons for this, such as rising market demands, lower plasticizing effect among alternative plasticizers leading to use of larger quantities, improved reporting frequency to the statistical database, or a combination of these.

The relative contribution of alternative plasticizers on the Swedish market is presented in Fig. 4. Between 1999 and 2011, adipates, ESBO, dibenzoates and TXIB accounted for the majority of the consumption volumes, whereas newly introduced plasticizers such as DEHT and DINCH appeared on the Swedish market around 2010, and the use of the latter saw a dramatic increase between 2011 and 2012, now making up 70% of the use of alternative plasticizers in Sweden. Other substances with relatively high usage are ESBO and DEHA, the latter of which makes up the majority of adipate plasticizers (supplementary Fig. A.2), whereas the relative use of substances like sebacates, phosphate esters and GTA is small. Interestingly, ATBC was used in higher quantities in one particular year (2007), a phenomenon observed also for Denmark, whereas usage in Norway remained constantly low. The reason for this temporary elevated use is unknown.



**Fig. 4.** Distribution of alternative plasticizers used in Sweden from 1999 to 2012.

#### 4. Emissions

Studies assessing emissions of alternative plasticizers are scarce. DEHA emission into air has been estimated by the United States Environmental Protection Agency to be 315,000 kg in the United States in 1994 (USEPA, 1996). DINCH emission from vinyl floors to indoor air was estimated by model prediction to be 3.6 kg for Sweden in 2012 (Holmgren et al., 2012). Based on physicochemical properties, potentially high emissions to air could be expected for TXIB, a substance with high vapor pressure. For this substance, specific emission rates (SER) were estimated in two different studies and range from 2 to 854  $\mu\text{g} / (\text{m}^2 \times \text{h})$  (Jarnstrom et al., 2008; Metiainen et al., 2002). For comparison, SER values for DEHP were calculated in two studies by Clausen et al. (2004; 2010) and ranged from 0.2 to 7.5  $\mu\text{g}/(\text{m}^2 \times \text{h})$ , indicating relatively low emissions compared to TXIB. In another study, Liang and Xu (2014) estimated emissions of DEHA and DINCH from crib mattress covers at different temperatures. Following this experimental work, the authors validated an emission model for predicting concentrations in indoor air. Results showed a concentration of 0.7  $\mu\text{g}/\text{m}^3$  in indoor air for DINCH and 1.05  $\mu\text{g}/\text{m}^3$  for DEHA. Unfortunately, no emission studies exist for other alternative plasticizers.

#### 5. Indoor fate

As shown above, plasticizers are mostly included in consumer products used in homes. Therefore, when assessing their sources, fate and exposure, the indoor environment is important and indoor fate is modeled here. Outdoor fate modeling was not included in this present study due to its comparatively small relevance for human exposure, although some outdoor fate properties like persistence and bioaccumulation will be discussed in the following section.

Indoor fate was assessed using the Stockholm Multimedia Urban Fate (SMURF) model (Cousins, 2012). It is a Level III Mackay-type fugacity-based chemical fate model, originally consisting of an indoor and an outdoor module. For this assessment, the outdoor module was removed and simulations performed using the indoor module only. The indoor environment consists of indoor air (gas and particle phases), vertical (walls and ceilings) and horizontal (floor) surfaces. The model assumes a thin layer of organic material covering the surfaces to

which chemicals can bind. Additionally, deposition of particles can occur onto the horizontal surface. Relevant input parameters were molecular weight, half-life in air,  $\log K_{OW}$  and  $\log K_{AW}$ . Molecular weight and half-life in air had a negligible effect on the indoor distribution. Thus, molecular weight was set constant to 500 and  $t_{1/2}$  to 52 h for better comparability and to determine the percentage of distribution in each compartment. We assume emission to air only, which was also kept constant at 1 kg/year. Results and conclusions are therefore restricted to this emission scenario only.

Steady state mass distribution of alternative plasticizers indoors showed only few substances which partition more than 60% to air (Fig. 5). These are TXIB and GTA, substances with relatively low molecular weights and fairly high vapor pressures. Other alternatives are more likely to distribute to vertical or horizontal surfaces. This also includes the common phthalate plasticizers DEHP, DINP, DIDP and DPHP, which favor vertical surfaces (60–80% mass distribution). The selected alternative plasticizers can roughly be divided into three groups: 1) Substances which favor vertical surfaces in the indoor environment, 2) Substances which favor horizontal surfaces and 3) those that preferably partition to indoor air. The first group consists of either chemicals with relatively high  $\log K_{OW}$  and  $K_{AW}$  such as DOS, DIDA, DINCH etc. or chemicals with lower  $\log K_{OW}$  and  $K_{AW}$  (DEGDB, DPGDB, DEHPA), as long as their  $\log K_{OA}$  is around 10. These preferably partition to organic material and can directly diffuse into organic material on walls and ceilings or interact with airborne particles followed by attachment to vertical surfaces. The second group, consisting of COMGHA and ESBO, favor horizontal surfaces and exhibit strong sorption to particles followed by deposition to the floor as dust. These substances have relatively high  $\log K_{OW}$  and low  $\log K_{AW}$  values, resulting in a high  $\log K_{OA} > 13$ . Therefore, they exhibit extremely high sorption capacity to organic particles as well as to the organic film on surfaces. However a lower distribution to vertical surfaces can be expected because in the model, deposition of organic particles mainly occurs in the vertical direction leading to a higher proportion on the horizontal surfaces. According to the model predictions, alternative plasticizers are more likely to be found on vertical and horizontal surfaces (e.g. in dust) than in indoor air, as are the selected PEs. Floor dust is commonly removed by vacuuming and mopping on a more regular basis than cleaning of walls and ceilings. Hence, chemicals

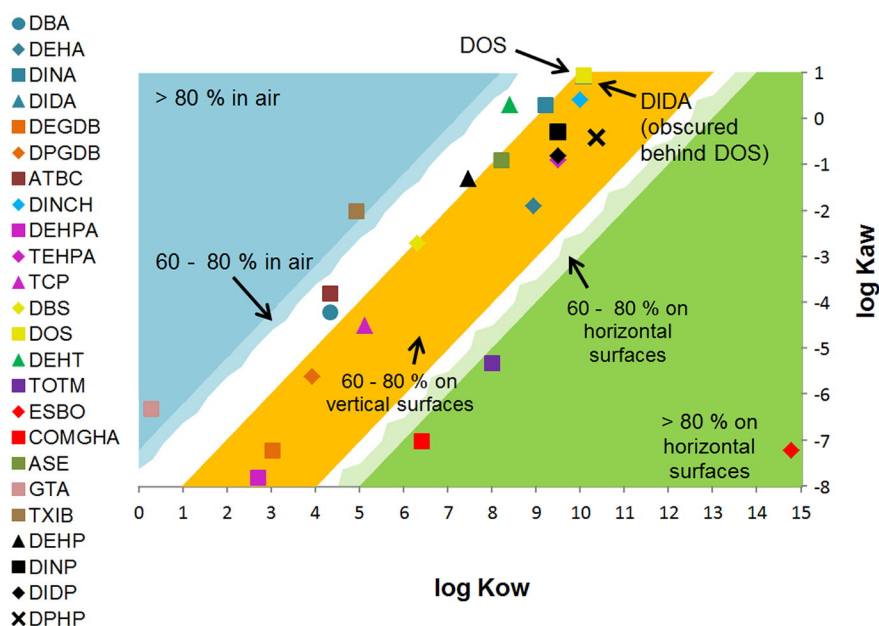


Fig. 5. Chemical space map of 4 selected phthalates and 20 alternative plasticizers showing distribution in the indoor environment. Symbol colors represent a substance group whereas symbols show a specific substance within the group (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).



attached to horizontal surfaces have the potential to be removed quicker and in higher amounts than those sorbed to vertical surfaces.

Based on these results, exposure to most PEs and their alternatives is more likely to occur via dermal uptake or dust ingestion as these substances will not partition strongly to indoor air. Exceptions are TXIB and GTA, which belong to the third group mentioned above and for which exposure via inhalation will be important. Dietary intake might be important for human exposure (although metabolism may limit food web bioaccumulation), but no conclusions could be drawn from the indoor fate modeling. Generally, alternative plasticizers can be expected in various exposure matrices in the indoor environment, although only very few exhibit strong partitioning to indoor air. Instead, it is likely that many alternatives will be detected in dust and/or food due to their low volatility and relatively high hydrophobicity.

## 6. Human exposure

Information relevant for human exposure to alternative plasticizers can be found in Table 3. In general, reported concentrations for alternative plasticizers are limited. Evidence for human exposure such as biomonitoring data are rare and exist only for DINCH and DEHT. In this section, we focus mainly on indoor exposure. However, dietary exposure was considered as well because plasticizers might partition into food or water from packaging or during food processing.

### 6.1. Concentrations in external and internal matrices

Among the adipates, DEHA is the most studied substance. In addition to its detection in food and breast milk (Cousins et al., 2007; Fromme

**Table 3**  
Measured concentrations of alternative plasticizers in exposure matrices.

Substance	Exposure data	Reference
<i>Adipates</i>		
DBA	No data	–
DEHA	8.2–470 µg/kg FW foodstuffs 2 µg/l breast milk 0.61 µg/g food 10–2800 µg/g fw duplicate diet (adults) 0.55 µg/g fw duplicate diet (15–20-month old children) Highest: 2.78 µg/g butter 4.8 mg/g crib mattress 5–15 ng/m <sup>3</sup> indoor air 2–10 µg/g dust	Palm-Cousins et al. (2007) Palm-Cousins et al. (2007) Kueseng et al. (2007) Fromme et al. (2007) Fromme et al. (2013) Tsumura et al. (2002) Boor et al. (2015) Rudel et al. (2003) Rudel et al. (2003)
DINA	Not detected	Tsumura et al. (2002)
DIDA	20 µg/l breast milk	Remberger et al. (2005)
<i>Benzoates</i>		
DEGDB	14.2% of total content in PE-free gloves for food contact	Kawamura et al. (2002)
DPGDB	9.5% of total content in PE-free gloves for food contact	Kawamura et al. (2002)
<i>Citrates</i>		
ATBC	Highest: 7.3 µg/g sake	Tsumura et al. (2002)
<i>Cyclohexane dicarboxylic acids</i>		
DINCH	Maximum :110 mg/kg dust 25 (2003) and 75 (2009) mg/kg dust 53.3 mg/g crib mattress	Nagorka et al. (2011a) Nagorka et al. (2011b) Boor et al. (2015)
<i>Phosphate esters</i>		
DEHPA	No data	–
TEHPA	Not detected in air Mean: 0.37 µg/g standard reference material (SRM 2585) Median: 0.2 mg/kg household dust Median: 0.8 mg/kg household dust	Bergh et al. (2011), Carlsson et al. (1997) Bergh et al. (2012) Kersten and Reich (2003) Nagorka and Ullrich (2003)
TCP	Up to 150 µg/g in car dust 2.2 mg/kg household dust	Brommer et al. (2012) Kersten and Reich (2003)
<i>Sebacates</i>		
DBS	Detected in polyvinylidene chloride (PVDC) wrapping films	Kawamura et al. (1999)
DOS	Not detected in Japanese food No data	Tsumura et al. (2002) –
<i>Terephthalates</i>		
DEHT	Maximum: 440 mg/kg dust (1997–2009)	Nagorka et al. (2011a)
<i>Trimellitates</i>		
TOTM	Mean: 20% w/w in PVC toys and childcare products	Biedermann-Brem et al. (2008)
<i>Vegetable oil derivatives</i>		
COMGHA	No data	–
ESBO	76–519 mg/kg food Average: 166 mg/kg product containing free oil	(Pedersen et al., 2008) Fankhauser-Noti et al. (2006), Fankhauser-Noti et al. (2005)
<i>Others</i>		
ASE	Up to 40.2% content (total weight) in PE-free PVC gloves Not found in the surveys of plasticizers in toys in the Netherlands and Switzerland	Kawamura et al. (2002) Maag et al. (2010)
GTA	Up to 550 ppm in Japanese gummy candy	Ogawa et al. (1992)
TXIB	10–73 µg/m <sup>3</sup> in painted bedrooms and living-rooms 1.64 µg/m <sup>3</sup> (indoors), 0.41 µg/m <sup>3</sup> (outdoors) in Swedish classrooms 20.8 µg/m <sup>3</sup> in a newly built Japanese houses	Wieslander et al. (1997) Kim et al. (2007b) Takeuchi et al. (2014)

et al., 2007, 2013; Kueseng et al., 2007; Tsumura et al., 2002), it was also found with a frequency of 8.5% in Japanese products that children often place in their mouth and/or have contact with through their skin (Kawakami et al., 2011). Exposure to DEHA via dermal uptake was expected to be very low as *in vitro* experiments showed low dermal absorption (Zhou et al., 2013). DEHA was present in new infant crib mattress covers (4.8 mg/g material, 11.1% detection frequency) and also detected with an average concentration of 8.4  $\mu\text{g}/\text{m}^3$  in infant's breathing zones while sleeping (Boor et al., 2015; Liang and Xu, 2014). Additionally, it was detected in dust (2–10  $\mu\text{g}/\text{g}$ ) and indoor air (5–15  $\text{ng}/\text{m}^3$ ) (Rudel et al., 2003). For other adipates, only a limited amount of information exists. DINA was not detected in one study (Tsumura et al., 2002) and DIDA was found in breast milk (Remberger et al., 2005). No exposure data were available for DBA.

Benzoate plasticizers were detected in PE-free gloves for food contact with 9.5% for DPGDB and 14.2% for DEGDB (Kawamura et al., 2002) based on weight content, but no other information was available, for example concentrations in exposure matrices such as dust, air, food or internal matrices such as blood or urine.

ATBC was detected in various types of food (Tsumura et al., 2002; Zygoura et al., 2011) and household products (Kawakami et al., 2011). In personal care products, it is being used mostly in fingernail products at concentrations up to 7% (Johnson, 2002), while in toys it was identified in 9% of samples on the Dutch market (FCPSA, 2008).

DINCH was detected mostly in dust up to 110 mg/kg (Nagorka et al., 2011a,b) and in new infant crib mattress covers with a mean of 53.2 mg/g and 44.4% detection frequency (Boor et al., 2015). Furthermore, metabolite concentrations were measured by Silva et al. (2013a) where urine samples were collected over six years in the period between 2000 and 2012. While DINCH metabolites were absent from urine samples in 2000 and 2001, the levels gradually increased in the later samples from 2007 and onwards. Another study investigated 22 random spot urine samples in 2010 (Schutze et al., 2012) and later analyzed 300 individual 24 h human urine samples from 1999 to 2012 (Schutze et al., 2014). Also, based on additional data obtained from Koch et al. (2013), it was shown that DINCH intake in the German population has increased since 2002, similar to the results of Silva et al. (2013a). It is therefore highly likely that body burdens will further increase with increasing production volumes and emissions as the time of peak exposure has likely not yet been reached (see representative use for Sweden above). More recently, a pharmacokinetic model has been developed to characterize DINCH exposure via ingestion (Schuetze et al., 2015). Unfortunately, the model was unable to reproduce long term concentrations as knowledge gaps still exist e.g. mainly regarding the relevance of certain uptake routes and their associated metabolic pathways.

For phosphates, a mean concentration of 0.37  $\mu\text{g}/\text{g}$  TEHPA was detected in a house dust standard reference material (SRM 2585, National Institute of Standards and Technology, USA) and raised the potential for human exposure through house dust (Bergh et al., 2012). It was also detected in household dust samples with median concentrations of 0.2 and 0.8 mg/kg (Kersten and Reich, 2003; Nagorka and Ullrich, 2003). No data was found for DEHPA. TCP was found in car dust with a concentration of 150  $\mu\text{g}/\text{g}$  (Brommer et al., 2012) and in household dust with a concentration of 2.2 mg/kg (Kersten and Reich, 2003).

Regarding sebacates, dibutyl sebacate (DBS) was reported to migrate from packaging materials into foods and was detected in polyvinylidene chloride (PVDC) wrapping films (Kawamura et al., 1999), but was not detected in Japanese food samples (Tsumura et al., 2002). Otherwise, no information on human exposure is available for DBS and DOS.

DEHT has been found to have very low migration from PVC to indoor air (Demir and Ulutan, 2013). It was detected in dust up to 440 mg/kg (Nagorka et al., 2011a). DEHT is listed in the US for use in closures with sealing gaskets for food containers. Levels must not exceed

750 mg/g DEHT in permitted vinyl chloride resins used in contact with food (USFDA, 2010b). It is also a subject of food contact notification no. 770 for use in plasticized vinyl chloride polymer formulations in repeated-use food contact applications (USFDA, 2010a). A recommendation for polymeric products containing plasticizers stated that migration of DEHT must not exceed 50 mg/kg foodstuff or food stimulant (BfR, 2007). More empirical exposure information, such as the relative importance of certain uptake pathways is definitely needed in the future (Ball et al., 2012).

Leaching of TOTM was reported to be lower compared to DEHP (Ito et al., 2008) and the substance was detected in 1% of samples including PVC toys and childcare products with a mean concentration of 20% w/w in the plastic (Biedermann-Brem et al., 2008). Also, Kambia et al. (2001) highlighted that TOTM is a superior alternative to DEHP for use in medical devices because of its lower potential migration to the human body.

For vegetable oil derivatives, a Danish case study found ESBO to be the principal plasticizer in 19 food samples with a concentration range of 76–519 mg/kg, which led to a withdrawal of affected products from the market (Pedersen et al., 2008). Similarly, the average concentration of ESBO in 86 products containing oil from the markets of various European countries was 166 mg/kg product, showing that ESBO was the predominant plasticizer in the composition of the gaskets in the container closures (Fankhauser-Noti et al., 2005, 2006). Bueno-Ferrer et al. (2010) has shown high ESBO migration into fat simulants. For COMGHA, no data concerning human exposure exist. However, the EU has not set any specific migration limits on food package materials regarding GOMGHA due to his high safety profile.

ASE made up 40.2% of the total weight content in PVC gloves containing non-phthalate plasticizers (Kawamura et al., 2002), but it was not found in the surveys of plasticizers in toys in the Netherlands and Switzerland (Maag et al., 2010). Information about GTA is very limited, although it was detected in Japanese gummy candy at levels up to 550 ppm (Ogawa et al., 1992). TXIB showed high volatilization from PVC structures (Jarnstrom et al., 2008), which could be expected due to its rather high vapor pressure and fate. TXIB is currently restricted in the EU with an established migration limit in food of 5 mg/kg. Furthermore, observed occurrences of its monoester in food were thought to be of no concern (Kempf et al., 2009). Studies involving measurement of TXIB in indoor environments exist, however, none of them assessing or estimating exposure routes. For example, TXIB was one of the most commonly found substances in indoor air in the study by Wieslander et al. (1997), where it was detected in 57% of the living rooms and 60% of the bedrooms with significantly increasing concentrations in newly painted dwellings. A study in 2005 investigated 300 Finnish dwellings and found TXIB to be one of the most abundant substances in indoor air (Saarinen et al., 2005). It was also detected in Swedish classrooms at a concentration of 1.64  $\mu\text{g}/\text{m}^3$  indoors, and 0.41  $\mu\text{g}/\text{m}^3$  outdoors (Kim et al., 2007b), while in Japan, TXIB had the highest air concentration of 20.8  $\mu\text{g}/\text{m}^3$  among the 34 substances found in a newly built house (Takeuchi et al., 2014).

## 6.2. Estimated human daily intake rates

Daily intake rates of the selected phthalates and alternative plasticizers have been estimated in a number of previous studies and are summarized in Table 4, together with the relevant references. For TXIB, DIDA, TCP and DEHT, no estimated intake rates were found in the literature and thus, were estimated as follows:

$$\text{Intake} \left( \frac{\mu\text{g}}{\text{kg bw} \times \text{d}} \right) = C_i \times \frac{a}{b} \quad (1)$$

where  $C_i$  is the concentration of the chemical in the target matrix ( $\mu\text{g}/\text{m}^3$  or  $\mu\text{g}/\text{ml}$ ),  $a$  is the assumed daily intake of the corresponding matrix (ml/day or  $\text{m}^3/\text{day}$ ) and  $b$  is the body weight (kg).

**Table 4**

Estimated human intake rates of phthalates and alternative plasticizers. Intake estimates from Stuer-Lauridsen et al. were calculated using the estimation and assessment of substances exposure (EASE) model. Values for DIDA, TCP and DEHT were calculated in this work using concentrations in Table 3.

Substance	Intake [ $\mu\text{g}/\text{kg bw}/\text{day}$ ]	Exposure route	Reference
<i>Phthalate plasticizers</i>			
DEHP	2.7	Total uptake based on urinary metabolite concentrations	Wittassek and Angerer (2008)
DINP	0.6	Total uptake based on urinary metabolite concentrations	Wittassek and Angerer (2008)
DIDP	<1	Total uptake based on urinary metabolite concentrations	Kransler et al. (2013)
DPHP	135, children	Oral and dermal uptake, based on worst case scenario for toys	BfR (2011)
<i>Alternative plasticizers</i>			
<i>Adipates</i>			
DBA	No data		
DEHA	0.46	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
	2.35, infants	Inhalation	Liang and Xu (2014)
	0.67, adults	Dietary uptake	Fromme et al. (2007)
	1.0, children (15–20 months old)	Dietary uptake	Fromme et al. (2013)
DINA	No data		
DIDA	2.92, infants	Dietary (breastmilk)	This study
<i>Benzoates</i>			
DEGDB	No data		
DPGDB	$4.36 \times 10^{-3}$	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
<i>Citrates</i>			
ATBC	$4.36 \times 10^{-3}$	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
	60, children	Inhalation and dermal uptake using teething rings	Stuer-Lauridsen et al. (2001)
	0.02	Dietary uptake as food additive	ECDGE (2000)
<i>Cyclohexane dicarboxylic acids</i>			
DINCH	8.10	Dietary uptake	NICNAS (2011)
<i>Phosphate esters</i>			
DEHPA	$4.36 \times 10^{-3}$	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
TEHPA	2.86	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
TCP	0.14	Inhalation	This study
<i>Sebacates</i>			
DBS	No data		
DOS	$4.36 \times 10^{-3}$	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
<i>Terephthalates</i>			
DEHT	0.29	Inhalation	This study
<i>Trimellitates</i>			
TOTM	$1.62 \times 10^{-13}$	Inhalation + oral + dermal uptake	Stuer-Lauridsen et al. (2001)
<i>Vegetable oil derivatives</i>			
COMGHA	No data		
ESBO	84.0, adults	Dietary uptake	EFSA (2004)
	2.30, children	Dietary uptake	Duffy and Gibney (2007)
	340–4650, infants	Dietary uptake	EFSA (2004)
<i>Others</i>			
ASE	No data		
GTA	111	Ingestion + dermal uptake	OECD (2002)
TXIB	8.5	Inhalation	This study

For DIDA, infant exposure via breast milk was addressed, using a body weight of 4.8 kg and an estimated intake of 0.7 l breast milk/day (USEPA, 2011), and a concentration in breast milk of 2  $\mu\text{g}/\text{l}$  (Table 3). For TXIB, exposure through inhalation was considered, using  $C_i$  of 73  $\mu\text{g}/\text{m}^3$  (Table 3) and an inhalation rate of 11.98  $\text{m}^3/\text{day}$  (USEPA, 2011). For TCP and DEHT, which have been detected in household dust, the intake through inhalation was calculated, assuming equal concentrations in dust particles as in inhalable aerosol particles as well as equilibrium conditions between the air and aerosol particles. Also, an indoor residence time of 983 min per day was considered (USEPA, 2011). The concentration in bulk air was thus estimated according to:

$$C_p \left( \frac{\mu\text{g}}{\text{m}^3 \text{ particles}} \right) = C_d \times \delta \quad (2)$$

$$C_a \left( \frac{\mu\text{g}}{\text{m}^3 \text{ air}} \right) = \frac{C_p}{K_p} \quad (3)$$

$$f_p \left( \frac{\text{m}^3 \text{ particles}}{\text{m}^3 \text{ air}} \right) = \text{TSP} \times \delta \quad (4)$$

$$C_i \left( \frac{\mu\text{g}}{\text{m}^3 \text{ bulk air}} \right) = C_a + C_p \times f_p \quad (5)$$

where  $C_d = 220 \mu\text{g}/\text{g}$  dust for TCP and  $440 \mu\text{g}/\text{g}$  dust for DEHT (see Table 3).  $\delta$  is the dust particle density of  $1700 \text{ kg}/\text{m}^3$  (Diamond et al., 2001) and TSP is the indoor air particle concentration of  $15 \mu\text{g}/\text{m}^3$  air (Ericsson et al., 2006). A simple regression of 0.13  $K_{OA}$  was used for  $K_p$  ( $\text{m}^3 \text{ air}/\text{m}^3 \text{ aerosols}$ ) (MacLeod et al., 2010), which is the gas-particle partitioning coefficient describing the amount of a chemical bound to airborne particles in relation to the amount partitioning to the gas phase at equilibrium.  $C_i$  is then calculated using the indoor air concentration  $C_a$ , indoor air-particle concentration  $C_p$  and the volume fraction of air-particles in bulk air  $f_p$ . Finally, a body weight of 70 kg was assumed for the intake estimations. Since dermal absorption and oral uptake were not considered for TCP and DEHT, results should be regarded with caution. For TXIB, however, inhalation can be considered the

major uptake pathway due to physicochemical data and indoor fate exposure results above.

No intake rate estimates were found in the literature for DBA, DINA, DEGDB, COMGHA, DBS and ASE and it was also not possible to estimate the rates due to lack of data on occurrence in exposure matrices. For DEHA, ATBC and ESBO, body-weight normalized intake rates for infants and children were also available in literature and showed mostly higher intake rates compared to adults (except for children's intake of ESBO based on the work of Duffy and Gibney). It should also be noted that the intake of TXIB has the unit of  $\mu\text{g}/\text{m}^3$  for better comparison with limit values in later chapters. Overall, intake rates have a high variability and range from  $1.62 \times 10^{-13}$  (TOTM) to  $4650 \mu\text{g}/\text{kg bw}/\text{day}$  (ESBO, infants) (Table 4). Substances showing relatively high intake include DEHA, DIDA, ATBC, ESBO, DINCH, GTA, TEHPA and DEHT, whereas for other substances, intake rates much smaller than  $1 \mu\text{g}/\text{kg bw}/\text{day}$  were calculated. Compared to phthalate plasticizers, they cover a similar range of intake. Regarding DPHP, the intake rate of children based on mouthing of toys was higher than other PE's.

As evident from Table 4, human intake rates have been derived for most alternative plasticizers, in previous studies and in the current review. However, all relevant exposure routes have not been covered. In contrast to the traditional phthalates (DEHP, DINP, DIDP), intakes of alternative plasticizers were not estimated based on urinary metabolite concentrations, hence, important uptake routes might have been neglected (for example from DEHT or TCP, where only inhalation was considered). The lack of studies measuring many alternatives in relevant exposure matrices like food, dust or air presents a major problem for characterizing exposure accurately. Ideally, biomonitoring studies should exist for each substance, which allow total exposure estimations from all possible sources. Unfortunately, this is only the case for a few substances such as DINCH.

### 6.3. Metabolism

Human internal exposure to PEs is usually assessed by analyzing biological specimens such as serum and urine for specific metabolites; a procedure not prone to contamination. Direct measurement of parent substances might introduce significant errors due to external contamination, which can occur throughout the analytical process (Latini, 2005). Many human biomonitoring studies have been performed to assess human exposure to DEHP, DINP and DIDP with the use of appropriate biomarkers (Koch and Angerer, 2007; Koch et al., 2005, 2007; Silva et al., 2007a). Lately, the increasing production volume of DPHP and its widespread use in consumer products made suitable analytical methods necessary for determination of three specific, secondary, oxidized metabolites, namely mono-2-(propyl-6-oxoheptyl)-phthalate (oxo-MPHP), hydroxy-mono-propylheptyl phthalate (OH-MPHP) and mono-2-(propyl-6-carboxy-hexyl)-phthalate (cx-MPHxP) in human urine (Gries et al., 2012; Leng et al., 2014).

However, only little information is available on the metabolic pathways of many alternative plasticizers. The investigation of metabolism and elimination kinetics of DINCH by Koch et al. (2013) pointed out cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl) octyl ester (OH-MINCH) as the predominant metabolite followed by cyclohexane-1,2-dicarboxylate-mono-(7-carboxylate-4-methyl)heptyl ester (cx-MINCH) and cyclohexane-1.

2-dicarboxylic mono oxisononyl ester (oxo-MINCH) as secondary metabolites, which are excellent biomarkers of the parent substance (Schutze et al., 2012). In contrast to DEHP, the metabolism of DEHA mainly results in the nonspecific metabolite adipic acid, while the oxidative metabolites (mono-2-ethylhexyl adipate (MEHA), mono-2-ethylhydroxyhexyl adipate (MEHHA) and mono-2-ethylohexyl adipate (MEOHA)) could be used as sensitive exposure biomarkers only at high exposure levels (Silva et al., 2013b). Also, the metabolic pathway of terephthalates is quite similar to adipates, since an extensive hydrolysis of both ester bonds on DEHT occurs, analogously to DEHA

(Barber et al., 1994). Benzoates, according to DEGB metabolism in rats, are hydrolyzed to benzoic acid, which is then conjugated with either glycine (major pathway) or glucuronic acid (minor pathway) prior to excretion (Maag et al., 2010). Finally, absorption and metabolism of ATBC is quite fast (<48 h for 99% excretion in urine and feces) with acetyl citrate, monobutyl citrate, acetyl monobutyl citrate, dibutyl citrate, and acetyl dibutyl citrate as resulting metabolites (Johnson, 2002). Lack of further information illustrates that analytical methods for alternative plasticizers in biological fluids and tissues should be developed. In order to ensure optimal human exposure assessment, it is very important to have the necessary tools and methods. Essential to human biomonitoring is the knowledge of the metabolic pathway of a particular chemical in order to identify appropriate biomarkers for analytical studies. For instance, the human metabolism of phthalates and DINCH is well known. Therefore, exposure to these substances can be well assessed by measuring relevant metabolites in human matrices like blood or urine. Unfortunately, this has not been done for all relevant alternative plasticizers. Following this, analytical methods should be developed and validated to have a robust method to measure either the parent substance or metabolites.

## 7. Toxicological information

For all selected alternative plasticizers, toxicological information is available to a certain extent. Since these substances are produced in high volumes, toxicological data are required in the EU and could be found in the ECHA database for registered substances (ECHA, 2014b). An overview of available information, results and data gaps can be found in Table A.1 in the Supplementary information. It was shown that acute and repeated dose toxicity, irritation/corrosion, sensitization, genotoxicity, reproductive toxicity and developmental toxicity are well covered endpoints. For almost all substances, acute toxicity and genotoxicity were found to be practically non-existent. A few alternatives caused eye irritation (ESBO, DEHPA, TEHPA). Carcinogenicity was investigated in many cases as well although for some substances, either no data existed or a lack of conclusive results was observed (e.g. DBA and DEHPA). Reproductive toxicity was only proven for TCP, which is one reason for its classification as a toxic substance (see above). Regarding endocrine disruption, more data gaps were identified. For instance, no information for DBA, DINA, DIDA, GTA, DEHPA, DOS, TXIB and ASE exist. In many cases, evidence of the endocrine disrupting potential was found, notably for ATBC, TEHPA and TCP. It should further be noted that three substances (ATBC, GTA and TCP) were found to be neurotoxic in animal experiments.

A comparative summary of the toxic potentials of alternative plasticizers is presented in Table 5. Here, derived no-effect levels (DNELs) were compiled from the ECHA database for registered chemicals (ECHA, 2014b). These values were derived from a no observed adverse effect concentration (NOAEC) or no observed adverse effect level (NOAEL), divided by an assessment factor. Most long-term DNELs of alternative plasticizers are relatively high compared to DEHP (one of the most toxic phthalate plasticizers). Also other phthalates (DINP, DIDP, DPHP) were less toxic than DEHP, having higher DNELs. For DBA, COMGHA, DOS and DBS no hazard was identified due to the extremely low toxicities measured. Almost all alternative non-phthalate plasticizers have a lower toxic potential than DEHP. However, compared to other phthalate plasticizers like DINP, DIDP and DPHP, the results were not so clear. For example, DIDA, TEHPA and TXIB were among the least toxic alternatives and have relatively high DNELs similar to DPHP and DINP. On the other hand, ATBC, DEGDB, ASE, ESBO, DEHPA and TCP had fairly low DNELs and could be considered more toxic. Because it was shown above that TCP is the only chemical in the list that fulfills the criteria of being toxic, low DNELs were expected for that substance.

DNELs also varied for a given substance depending on the uptake path. Here, comparisons could only be made between dermal and oral

**Table 5**

Long term inhalation/dermal/oral derived no-effect levels (DNEL) for the general population, taken from the ECHA database (ECHA, 2014b), ranked according to average DNEL (phthalates in bold).

Chemical	Long term inhalation DNEL for the general population [mg/m <sup>3</sup> ]	Long term dermal DNEL for the general population [mg/kg bw/day]	Long term oral DNEL for the general population [mg/kg bw/day]	Average DNEL
DEHP	<b>0.13</b>	<b>0.72</b>	<b>0.04</b>	<b>0.30</b>
DEHPA	0.87	0.25	0.25	0.46
TCP	0.08	1.25	0.05	0.46
DEGDB	1.4	0.8	0.8	1.00
ATBC	1.74	1	1	1.25
ESBO	2.8	0.8	0.8	1.47
ASE	6.5	0.47	0.47	2.48
TOTM	0.98	11.25	1.13	4.45
DPGDB	8.69	0.22	5	4.64
DEHT	6.86	3.95	3.95	4.92
DEHA	4.4	13	1.3	6.23
DIDP	<b>1.3</b>	<b>20.83</b>	<b>0.75</b>	<b>7.63</b>
DINA	6.6	17	1.7	8.43
GTA	35.28	2.5	2.5	13.43
DINCH	21	25	2	16.00
TXIB	32.6	18.8	18.8	23.40
DPHP	<b>8.52</b>	<b>61.25</b>	<b>4.9</b>	<b>24.89</b>
TEHPA	62.5	25	25	37.50
DIDA	18.2	196	19.6	77.93
DINP	<b>15.3</b>	<b>220</b>	<b>4.4</b>	<b>79.90</b>
DBA	No hazard identified	No hazard identified	No hazard identified	–
DOS	No hazard identified	No hazard identified	No hazard identified	–
DBS	No hazard identified	No hazard identified	No hazard identified	–
COMGHA	No hazard identified	No hazard identified	No hazard identified	–

uptake. Huge differences could be observed e.g. for DEHP (0.72 and 0.036 mg/kg/day for dermal and oral exposure, respectively) and also for TCP, TOTM, DPGDB, DEHA, DIDP, DINA, DINCH, DPHP, DIDA and DINP. For most substances, the oral DNEL was found to be lower than the dermal DNEL with the exception of DPGDB, which has a lower dermal DNEL of 0.22 mg/kg/day compared to its oral DNEL of 5 mg/kg/day. This was surprising as it can be usually assumed that oral uptake is the more efficient pathway due to the barrier properties of the skin.

## 8. Human risk

To assess human risk, human intake rates (Table 4) were compared to tolerable daily intakes (TDI) or derived no-effect levels (DNEL). The resulting risk ratios are presented in Table 6 and compared to common PEs. Since a common limit value exists for DINP and DIDP, the sum of both intake estimates was used for the calculation of a risk ratio. For TXIB, a concentration of 7.3 µg/m<sup>3</sup> was taken to derive a risk ratio as the long term inhalation DNEL is given in mg/m<sup>3</sup>. Unfortunately, it was not possible to calculate a risk ratio for all substances due to the lack of data to estimate intake rates. Substances with no intake estimation as well as no identified hazard include DBA, COMGHA and DBS. DOS was also practically nontoxic although a daily intake of 0.00436 µg/kg was estimated. For these chemicals, the risk can be seen as low. For DINA, DEGDB, and ASE, limit values exist (ECHA, 2014b). However, data gaps still exist as not enough information (e.g. measured concentrations in exposure media) were available in order to estimate intake rates for humans. Hence, no risk ratio could be calculated.

Regarding substances for which it was possible to calculate a ratio, it was observed that in almost all cases (including PEs such as DEHP, DINP and DIDP), the risk ratio was below 1, indicating low risk. The only exception was ESBO, for which a ratio of 2.5 was calculated based on the maximum intake rate for infants. Similarly, a risk ratio of 3.4 was calculated for DPHP for children and mouthing of toys as the intake

**Table 6**

Intake rates, limit values and risk ratios of phthalates and alternative plasticizers. Limit values taken from ECHA represent DNELs, where the lower value was selected (dermal or oral).

Substance	Intake [µg/kg/day]	Limit value [µg/kg/d]	Risk ratio
<i>Phthalate plasticizers</i>			
DEHP	2.7	50 <sup>f</sup>	0.05 <sup>d</sup>
DINP + DIDP	1.6	150 <sup>g</sup>	0.01
DPHP	135	40 <sup>h</sup>	3.4
<i>Alternative plasticizers</i>			
<i>Adipates</i>			
DBA	No data	No hazard <sup>b</sup>	–
DEHA	0.46	300 <sup>d</sup>	1.5 × 10 <sup>-3</sup>
	2.35, infants		0.01
	1.0, children		3.3 × 10 <sup>-3</sup>
	0.67, adults		2.0 × 10 <sup>-3</sup>
DINA	No data	1700 <sup>b</sup>	–
DIDA	2.92	19,600 <sup>b</sup>	1.5 × 10 <sup>-4</sup>
<i>Benzoates</i>			
DEGDB	No data	800 <sup>b</sup>	–
DPGDB	4.36 × 10 <sup>-3</sup>	220 <sup>b</sup>	2.0 × 10 <sup>-5</sup>
<i>Citrates</i>			
ATBC	4.36 × 10 <sup>-3</sup>	1000 <sup>c</sup>	4.4 × 10 <sup>-6</sup>
	60.0, children using teething rings		0.06
	0.02		2.0 × 10 <sup>-5</sup>
<i>Cyclohexane dicarboxylic acids</i>			
DINCH	8.10	400 <sup>c</sup>	0.20
<i>Phosphate esters</i>			
DEHPA	4.36 × 10 <sup>-3</sup>	250 <sup>b</sup>	1.7 × 10 <sup>-5</sup>
TEHPA	2.86	25,000 <sup>b</sup>	1.1 × 10 <sup>-4</sup>
TCP	0.14	50 <sup>b</sup>	2.9 × 10 <sup>-3</sup>
<i>Sebacates</i>			
DBS	No data	No hazard <sup>b</sup>	–
DOS	4.36 × 10 <sup>-3</sup>	No hazard <sup>b</sup>	–
<i>Terephthalates</i>			
DEHT	0.29	3950 <sup>b</sup>	7.3 × 10 <sup>-5</sup>
<i>Trimellititates</i>			
TOTM	1.62 × 10 <sup>-13</sup>	1130 <sup>b</sup>	1.4 × 10 <sup>-16</sup>
<i>Vegetable oil derivatives</i>			
COMGHA	No data	No hazard <sup>b</sup>	–
ESBO	84.0, adults	1000 <sup>e</sup>	0.08
	2.30, children		2.3 × 10 <sup>-3</sup>
	340–4650, infants		2.5
<i>Others</i>			
ASE	No data	470 <sup>b</sup>	–
GTA	110	2500 <sup>b</sup>	0.04
TXIB	7.30 µg/m <sup>3</sup>	32,600 µg/m <sup>3b</sup>	2.2 × 10 <sup>-4</sup>

<sup>a</sup> Stuer-Lauridsen et al. (2001).

<sup>b</sup> ECHA (2014b).

<sup>c</sup> NICNAS (2011).

<sup>d</sup> EFSA (2004).

<sup>e</sup> EUC, (2002).

<sup>f</sup> EFSA, (2005a).

<sup>g</sup> EFSA (2005b).

<sup>h</sup> BfR, (2011).

route. This highlights the importance of differentiating between age groups when estimating intake rates as children or infants could potentially be a high risk group, especially for plasticizers used in children's articles. Unfortunately this was only done for DEHA, ATBC and ESBO. Considering their use and application, there is a need for TXIB, DEHT and DINCH intake estimations for children, which is currently not the case.

Dietary exposure of DINCH was estimated to be 0.081 mg/kg/day for the Australian population, roughly 20% of the tolerable daily intake (TDI) of 0.4 mg/kg/day (NICNAS, 2011) and resulting in a ratio of 0.2, which was the value closest to 1 (besides ESBO for infants). Considering that other exposure routes were not included and that e.g. dermal

exposure may be a significant pathway (NICNAS, 2011), this indicates that total exposure to DINCH may be close to the TDI. Although an oral reference dose (RfD) of 700 µg/kg/d exists (Bhat et al., 2014), we found that a more conservative risk estimation using the TDI from the NICNAS report is more appropriate. Furthermore, no special consideration was given to sources such as dust or children's toys and current studies do not represent high risk groups e.g. children. This is an important aspect as DINCH is used as an alternative plasticizer in children's toys. Therefore, children's exposure to DINCH should be investigated in more detail and exposure to the general population should be closely monitored.

## 9. Persistence, bioaccumulation and toxicity (PBT) properties

Because the selected chemicals are listed as HPV substances, PBT assessments are necessary and available in the ECHA database for registered substances. PBT properties describe more general characteristics of a chemical, considering both humans and the environment. For instance, the toxicity criteria includes toxicological as well as ecotoxicological tests. A summary is given in Table 7. None of the selected alternative plasticizers displayed a PBT or very persistent, very bioaccumulative (vPvB) profile according to the REACH criteria (ECHA, 2014a). With the exception of TEHPA and TCP, none can be considered persistent, bioaccumulative or toxic although there is a need of more experimental data regarding the persistence of TOTM and the bioaccumulation potential of DEGDB and DPGDB. The scientific justification for the benzoates being non-bioaccumulative was based on estimations using their log  $K_{OW}$  values which can be regarded as plausible. Nevertheless, experimental bioaccumulation studies are recommended. TEHPA fulfilled the criteria of a persistent chemical and TCP could be considered toxic according to the REACH criteria. Although most alternatives are not

environmentally persistent in the conventional sense, it is likely that these chemicals fulfill the criteria of being “pseudo-persistent” or continuously present (Mackay et al., 2014) due to their continuous production and release into the environment, leading to continuous environmental and human exposure. Clearly, even more attention should be paid to continuously released and persistent chemicals such as TEHPA and to potentially toxic substances such as TCP, not only from a human risk perspective but also from an environmental point of view. It should also be noted that the toxicity criterion includes acute and chronic toxicity as well as carcinogenicity, mutagenicity and reproductive toxicity, but other non-standard endpoints such as early developmental toxicity or endocrine disruption are not included.

## 10. Concluding remarks

Alternative plasticizers include chemical substances with a large variation of physicochemical properties. Similarities to the selected PEs could be observed for some substances such as DINA and DINCH, which are located close to the PEs on the chemical space map (Fig. 5). In contrast to the established PEs like DEHP, alternative plasticizers do not have many measurements available for important properties such as vapor pressure, solubility in water or log  $K_{OW}$ . This makes determining the reliability of a property value difficult as not many studies exist for comparison. On the other hand, estimations such as those from EPISuite sometimes vary more than 2 orders of magnitude from experimental results. As a consequence, values selected for modeling indoor fate may be erroneous. Additional experimental measurements of these key properties are necessary for a more reliable fate assessment. Nevertheless, we are confident that the majority of the alternative plasticizers are likely to partition to organic matter on surfaces and airborne particles in the indoor environment. Their hydrophobicity means that settled dust and/or food could be important sources of exposure. Indeed, measured concentrations, especially for important alternatives like DINCH, are mostly present for food and dust.

A reason for concern is that all of the selected substances are chemicals with high production volumes and widespread use in consumer products, including children's articles. The availability of human exposure data is currently limited, which hinders strong conclusions to be drawn as well as adequate human risk assessments for some alternatives. In the case of DINCH, production, use and human exposure data indicate strong increases during the last few years. As mentioned, measured concentrations of alternatives generally agree with the indoor fate assessment, showing the detection of many hydrophobic alternatives in dust or food. Additionally, TXIB, which was predicted to partition to air according to the indoor fate model, has been mainly detected in air. However, the availability of information regarding human exposure cannot be considered satisfactory. In particular, more studies attempting to elucidate the relative importance of various uptake pathways will be crucial for more accurate exposure assessments. Also, further consideration of high risk groups such as infants and children will improve human risk assessment because different age groups are expected to have different exposure patterns. For example, hand-to-mouth exposure (leading to dust ingestion) and uptake via mouthing of objects have been thoroughly discussed for phthalates (Babich et al., 2004; Guo and Kannan, 2011; Wormuth et al., 2006). Hand-to-mouth exposure has also been addressed in studies investigating polybrominated diphenyl ethers (PBDE) (Stapleton et al., 2008; Watkins et al., 2011), which are used as flame retardants. In contrast to alternative plasticizers, phthalates are a chemical group for which human exposure is well studied. Much information exists regarding the relative importance of uptake pathways and sources of exposure (Guo and Kannan, 2011; Weschler and Nazaroff, 2012, 2014; Wormuth et al., 2006) and potential high risk groups (Beko et al., 2013; Langer et al., 2014). Ideally, the detail of information available for alternative plasticizers should be equal to that of traditional phthalates like DEHP in

**Table 7**  
Persistence, bioaccumulation and toxicity of the selected alternative plasticizers, taken from the ECHA database (ECHA, 2014b).

Substance	Persistent	Bioaccumulative	Toxic
<i>Adipates</i>			
DBA	No	No	No
DEHA	No	No	No
DINA	No	No	No
DIDA	No	No	No
<i>Benzoates</i>			
DEGDB	No	No (based on estimation)	No
<i>Citrates</i>			
ATBC	No	No	No
<i>Cyclohexane dicarboxylic acids</i>			
DINCH	No	No	No
<i>Phosphate esters</i>			
DEHPA	No	No	No
TEHPA	Yes	No	No
TCP	No	No	Yes
<i>Sebacates</i>			
DBS	No	No	No
DOS	No	No	No
<i>Terephthalates</i>			
DEHT	No	No	No
<i>Trimellitates</i>			
TOTM	Needs more experimental data	No	No
<i>Vegetable oil derivatives</i>			
COMGHA	No	No	No
ESBO	No	No	No
<i>Others</i>			
ASE	No	No	No
GTA	No	No	No
TXIB	No	No	No

the future, especially for important high production alternatives such as DINCH.

Toxicity profiles were extensive but still showed data gaps, mostly regarding carcinogenicity and endocrine disruption (Table 1A). According to current knowledge, the use of alternative plasticizers seems to be of low risk for humans as calculated risk ratios were mostly well below 1. Also, none of the selected alternatives are PBT or vPvB substances although TEHPA could be considered persistent and TCP toxic. However, for plasticizers in particular, constant production and emission can lead to continuous exposure and pseudo-persistence. Attention should be paid to TEHPA, ESBO and TCP due to persistence, high exposure (to infants) and toxicity, respectively. Furthermore, DINCH is a plasticizer with rapidly increasing use and concentration in humans in recent years, hence the risk ratio will not stay constant but is very likely to increase. Close and careful biomonitoring of this chemical as well as all other substances for which an increasing exposure can be expected is needed. Finally, a problem often encountered is the lack of analytical tools and methods that would provide a more thorough understanding of the (human) metabolic pathways of certain chemicals. To ensure better human exposure assessment, prospectively and retrospectively, we also encourage the development and validation of analytical methods and identification of biomarkers for substances where these are lacking in human matrices.

### Conflict of interest

The authors declare no conflict of interest.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.scitotenv.2015.09.036>.

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