Assessing human exposure to phthalates, alternative plasticizers and organophosphate esters

Tuong Thuy Bui

Academic dissertation for the Degree of Doctor of Philosophy in Applied Environmental Science at Stockholm University to be publicly defended on Thursday 1 June 2017 at 13.00 in William-Olssonsalen, Geovetenskapens hus, Svante Arrhenius väg 14.

Abstract

Phthalate esters (PEs) and organophosphate esters (OPEs) are common indoor pollutants frequently detected in environmental (dust, air), personal (hand wipes, diet) and human matrices (urine, serum etc.). In this thesis, mathematical models were used to establish links between intake and body burden for a comprehensive dataset based on a Norwegian study population. Also, the relative importance of different PE uptake pathways was assessed and discussed. Furthermore, the suitability of human nails as an alternative, non-invasive biomonitoring matrix for PEs was investigated. Additionally, information regarding alternative plasticizers to PEs was collected and presented extensively. Results showed that for PEs (paper II), daily intakes based on external exposure media agree with back-calculations using urinary metabolite concentrations, leading to the conclusion that human exposure for the general adult population is well understood and that the most important uptake routes were captured. Overall intake levels are comparable or lower than level presented in recent comprehensive studies and hazard quotients were well below 1 (low risk). As expected, diet was found to be the most important uptake route for all PEs. For lower molecular weight PEs, inhalation becomes a strong contributing pathway whereas for higher molecular weight PEs, dust ingestion was also important. Daily intake based on hand wipes was found to be much lower than the estimated total dermal intake based on air, dust and personal care products, questioning the relevance of hand wipes to represent total dermal exposure. Human nails were found to be unsuitable for replacing urine as a biomonitoring matrix for PEs as internal intake (from blood) cannot explain measured nail concentrations and uptake from air is too slow to reach observed concentrations within a realistic time frame (paper III). Hence, the kinetic links between intake and nail concentrations could not be established. Although exposure to traditional PEs is decreasing, use and body burden of some alternatives are increasing (paper I). Fortunately, most alternative plasticizers have favorable toxicological properties, resulting in low risk for humans. In contrast to PEs, OPEs still remain a group of poorly studied substances in terms of human exposure (paper IV). Due to lack of information regarding human metabolism, reliable links between intake and concentrations in serum and urine could not be established. Modelling results showed that concentrations in serum, and to some extent, urine, were underestimated for 2 compounds. It is likely that a combination of missing intake and suboptimal biomarkers were the cause for this under-prediction. Because of this, further studies regarding human metabolism should be performed for OPEs and potentially more specific biomarkers identified in the future. For PEs, there is a need for more comprehensive datasets to study exposure for high risk groups such as infants and children. Furthermore, dermal uptake remains poorly understood and the uptake of PEs into human nails should be studied in more detail to establish the kinetic links between exposure and body burden.

Keywords: *Human exposure, phthalates, organophosphates, plasticizers, flame retardants, modelling.*

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Abstract

Phthalate esters (PEs) and organophosphate esters (OPEs) are common indoor pollutants frequently detected in environmental (dust, air), personal (hand wipes, diet) and human matrices (urine, serum etc.). In this thesis, mathematical models were used to establish links between intake and body burden for a comprehensive dataset based on a Norwegian study population. Also, the relative importance of different PE uptake pathways was assessed and discussed. Furthermore, the suitability of human nails as an alternative, non-invasive biomonitoring matrix for PEs was investigated. Additionally, information regarding alternative plasticizers to PEs was collected and presented extensively. Results showed that for PEs (paper II), daily intakes based on external exposure media agree with back-calculations using urinary metabolite concentrations, leading to the conclusion that human exposure for the general adult population is well understood and that the most important uptake routes were captured. Overall intake levels are comparable or lower than level presented in recent comprehensive studies and hazard quotients were well below 1 (low risk). As expected, diet was found to be the most important uptake route for all PEs. For lower molecular weight PEs, inhalation becomes a strong contributing pathway whereas for higher molecular weight PEs, dust ingestion was also important. Daily intake based on hand wipes was found to be much lower than the estimated total dermal intake based on air, dust and personal care products, questioning the relevance of hand wipes to represent total dermal exposure. Human nails were found to be unsuitable for replacing urine as a biomonitoring matrix for PEs as internal intake (from blood) cannot explain measured nail concentrations and uptake from air is too slow to reach observed concentrations within a realistic time frame (paper III). Hence, the kinetic links between intake and nail concentrations could not be established. Although exposure to traditional PEs is decreasing, use and body burden of some alternatives are increasing (paper I). Fortunately, most alternative plasticizers have favorable toxicological properties, resulting in low risk for humans. In contrast to PEs, OPEs still remain a group of poorly studied substances in terms of human exposure (paper IV). Due to lack of information regarding human metabolism, reliable links between intake and concentrations in serum and urine could not be established. Modelling results showed that concentrations in serum, and to some extent, urine, were underestimated for 2 compounds. It is likely that a combination of missing intake and suboptimal biomarkers were the cause for this under-prediction. Because of this, further studies regarding human metabolism should be performed for OPEs and potentially more specific biomarkers identified in the future. For PEs, there is a need for more comprehensive datasets to study exposure for high risk groups such as infants and children. Furthermore, dermal uptake remains poorly understood and the uptake of PEs into human nails should be studied in more detail to establish the kinetic links between exposure and body burden.

Sammanfattning

Ftatalatestrar (FE) och organofosfatestrar (OFE) är vanligt förekommande föroreningar i inomhusluft som också ofta detekteras miljöprover (dam, luft), samt i person- (servetter, diet) och human-matriser (urin, serum etc.). I denna doktorsavhandling användes matematiska modeller för att klarlägga kopplingar mellan intag av FE och OFE med uppmätta mängder i människokroppen i ett omfattande dataset från en Norsk kohort. Den relativa betydelsen av olika upptagsvägar för olika FE behandlades och diskuterades också. Vidare undersöktes naglars användbarheten som en alternativ, icke-invasiv, provmatris för övervakning av ftalatestrar i humant material. Utöver detta sammanfattades och presenterades omfattande information om alternativa mjukgörare. Resultaten visade att det uppmätta dagliga intaget av FE, baserat på extern exponeringsmedia, överensstämmer med den beräknade exponeringen när koncentrationer av urinmetaboliter användes (paper II). Detta leder till slutsatsen att exponering av vuxna individer i en generell population är välbeskriven och att de viktigaste exponeringsvägarna var inkluderade. Överlag är nivåerna för det totala upptaget jämförbara eller lägre än nivåer som nylige presenterats i omfattande studier samt riskkvoter var långt under 1 (låg risk). Som förväntat var dieten den viktigaste rutten för upptag för alla FE. För FE med låg molekylvikt var inhalation en viktig exponeringsväg, medan för högmolekylvikt FE var inandning av dam också av betydelse. Dagligt intag baserat på analys av handservetter var mycket lägre än det uppskattade totala dermala intaget baserat på luft, dam, personvårdsprodukter, vilket ifrågasätter relevansen hos handservetter som representativ provmatris för att beskrivande den totala dermala exponeringen. Naglar som provmatris är inte lämpliga ersättare till urin för övervakning av FE i humant material, då invärtes upptag (från blod) inte kan förklara uppmätta koncentrationer i naglar samt upptaget från luft är för långsamt för att förklara de uppmätta koncentrationerna inom en realistisk tidsram (papper III). Således, kinetiken mellan upptag via luft och koncentrationer i naglar kunde inte etableras. Exponering av traditionella FE minskar, användandet och uppmätta mängder i människokroppen av några alternativa FE ökar således (Papper I). Lyckligtvis har de flesta alternativa mjukgörarna fördelaktiga toxikologiska egenskaper, vilket leder till en lägre risk för människor. I motsats till FE så är OFE fortfarande en grupp kemikalier som inte har studerats utförligt när det kommer till exponering av människor (papper IV). På grund av bristande information kring metabolism av dessa ämnen i människor kunde inte tillförlitliga kopplingar mellan intag och serumkoncentrationer fastställas. Dock så visade modellering att serumkoncentrationer, och i viss utsträckning också urinkoncentrationer, var underskattade för 2 ämnen. Denna underskattning är troligen ett resultat av bristande information kring upptag och suboptimala biomarkörer. På grund av detta bör studier av humanmetabolism av OFE utföras, samt bör bättre biomarkörer för dessa ämnen tas fram. För FE finns det ett behov av mer omfattande data för att kunna studera exponering av högrisk grupper så som spädbarn och barn.

Vidare, är förståelsen för det dermala upptaget begränsat och upptaget av FE i naglar bör studeras vidare i detalj för att fastställa kinetiken mellan exponering och uppmätta mängder i människokroppen.

List of papers

Paper I

Bui TT*, Giovanoulis G*, Palm Cousins A, Magner J, Cousins IT, de Wit CA. 2016. Human exposure, hazard and risk of alternative plasticizers to phthalate esters. Science of the Total Environment 541:451-467

* Shared first authorship

Paper II

Giovanoulis G*, Bui, TT*, Xu F, Covaci A, Palm Cousins A, Magner J, Cousins IT, de Wit CA. Multi-pathway human exposure assessment of phthalate plasticizers and DINCH. Submitted manuscript.

* Shared first authorship

Paper III

Bui TT, Alves A, Palm Cousins A, Voorspoels S, Covaci A, Cousins IT. 2017. Estimating uptake of phthalate ester metabolites into the human nail plate using pharmacokinetic modelling. Environment International Elsevier. p 148-155

Paper IV

Bui TT, Xu F, Van den Eede N, Palm Cousins A, Covaci A, Cousins IT. Probing the relationship between external and internal human exposure of organophosphate flame retardants using pharmacokinetic modelling. Submitted manuscript.

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Author contributions

I, T.T. Bui, made the following contributions to the papers presented in this thesis:

Paper I

Involved in planning of the manuscript together with co-authors. Investigated and summarized physicochemical properties, use patterns, indoor fate and toxicological information of alternative plasticizers. Performed risk assessment for adults and children. Jointly led the writing of the manuscript with G.Giovanoulis.

Paper II

Involved in planning of the manuscript together with G.Giovanoulis. Performed multi-pathway exposure assessment for phthalates and DINCH, compared it to biomonitoring approach and performed risk assessments for the study population. Jointly led the writing of the manuscript with G.Giovanoulis.

Paper III

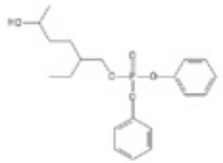
Planned the study together with A.Alves. Designed and performed pharmacokinetic, partitioning and air-to-nail modelling. Led the writing of the manuscript.

Paper IV

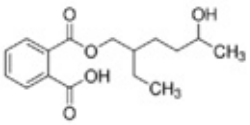
Initially planned the study together with F.Xu. Designed and performed pharmacokinetic modelling. Led the writing of the manuscript.

Abbreviations

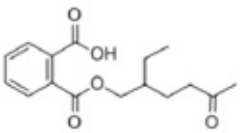
5OH –EHDPHP – 5-hydroxy 2-ethylhexyl diphenyl phosphate



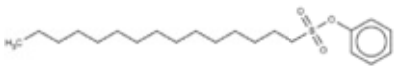
5OH-MEHP - Mono-(2-ethyl-5-hydroxyhexyl) phthalate



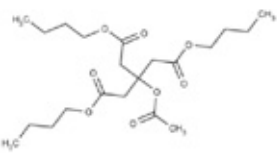
5oxo-MEHP - Mono-(2-ethyl-5-oxohexyl) phthalate



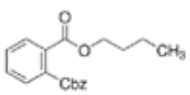
ASE - Alkylsulfonic phenyl ester



ATBC – Acetyl tributyl citrate



BBzP- Benzyl-butyl phthalate

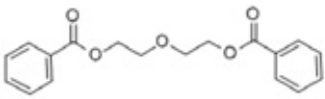


COMGHA – Glycerides, caster oil-mono, hydrogenated, acetates

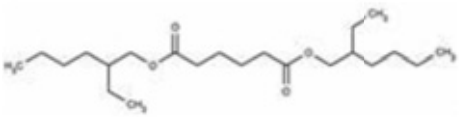
DBA – Dibutyl adipate

DBS – Dibutyl sebacate

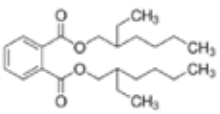
DEGDB – Di(ethylene glycol) dibenzoate



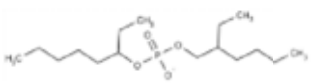
DEHA – Bis(2-ethylhexyl) adipate



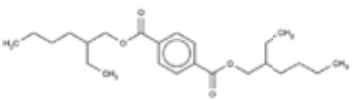
DEHP - Bis-2-ethylhexyl phthalate



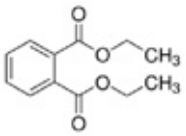
DEHPA – Bis(2-ethylhexyl) phosphate



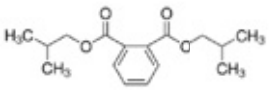
DEHT – Bis(2-ethylhexyl) terephthalate



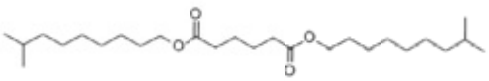
DEP – Diethyl phthalate



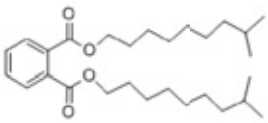
DiBP – Diisobutyl phthalate



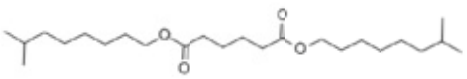
DIDA – Diisodecyl adipate



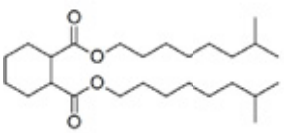
DIDP – Diisodecyl phthalate



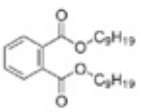
DINA – Diisononyl adipate



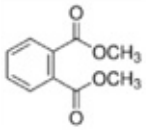
DINCH - 1,2-Cyclohexane dicarboxylic acid diisononyl ester



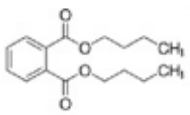
DINP – Diisononyl phthalate



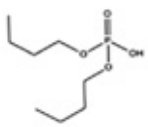
DMP – Dimethyl phthalate



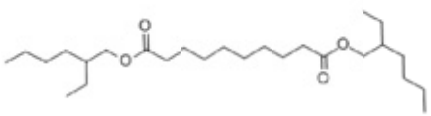
DnBP (PE) – Di-n-butyl phthalate



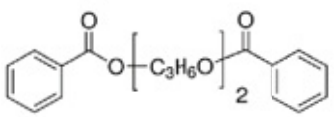
DNBP (OPE) – Di-n-butyl phosphate



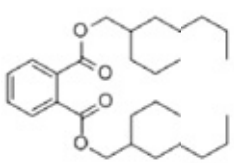
DOS – Bis(2-ethylhexyl) sebacate



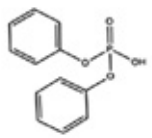
DPGDB – Di(propylene glycol) dibenzoate



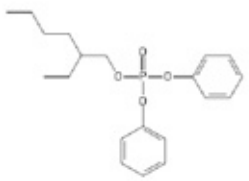
DPHP (PE)- Bis(2-propylheptyl) phthalate



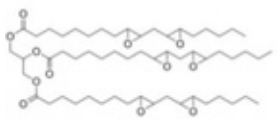
DPHP (OPE)– Diphenyl phosphate



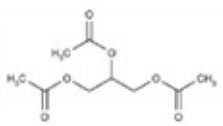
EHDPHP – 2-ethylhexyl diphenyl phosphate



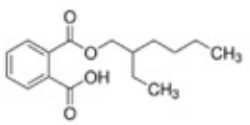
ESBO – Epoxidized soybean oil



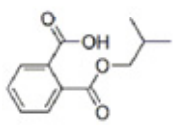
GTA – Glycerin triacetate



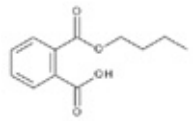
MEHP – Mono-(2-ethylhexyl) phthalate



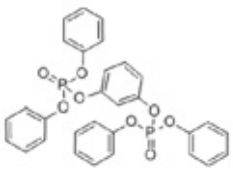
MiBP – Monoisobutyl phthalate



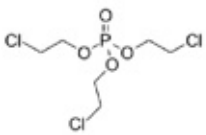
MnBP - Mono-n-butyl phthalate



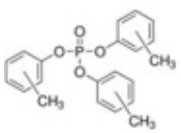
RDP – Resorcinol bis(diphenylphosphate)



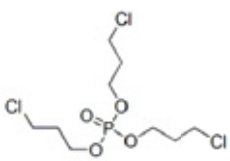
TCEP – Tris(2-chloroethyl) phosphate



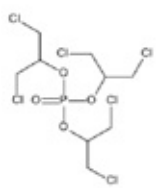
TCP – Tricresyl phosphate



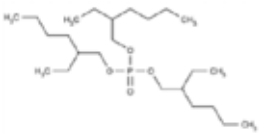
TCPP – Tris(chloropropyl) phosphate



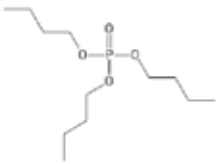
TDCPP – Tris-(2-chloro-, 1-chloromethyl-ethyl)-phosphate



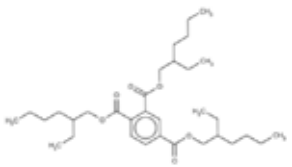
TEHPA – Tris(2-ethylhexyl) phosphate



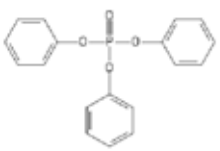
TNBP – Tri-n-butyl phosphate



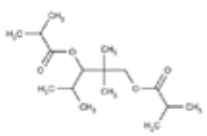
TOTM – Tris-2-ethylhexyl trimellitate



TPHP – Triphenyl phosphate



TXIB – Trimethyl pentanyl diisobutyrate



BW – Bodyweight

GM – Geometric mean

HQ – Hazard quotient

K_{OW} – Octanol-water partitioning coefficient

OPE – Organophosphate ester

PBDE – Polybrominated diphenyl ether

PCP – Personal care product

PE – Phthalate ester

PFR – Phosphorous flame retardant

PK – Pharmacokinetic

RfD – Reference dose

TDI – Tolerable daily intake

1 Introduction

1.1 Background

Humans typically spend more than half the day in the indoor environment (USEPA, 2011). Consequently, they can be exposed to a variety of chemicals from consumer products or other indoor sources. Among others, phthalate esters (PEs) and organophosphate esters (OPEs) are common indoor pollutants (Wensing et al., 2005) and are mostly used as plasticizers (Murphy, 2001) and flame retardants (EHC-192, 1997) respectively.

Plasticizers are chemicals added into polymers to ensure flexibility and durability of the product (Wilkes et al., 2005). PEs are the most prominent group of plasticizers and the general structure consists of a benzene ring with two alkyl side-chains in ortho position, connected via esterification (Fig1). Since these side chains can be substituted by a variety of different chemical groups, physicochemical properties vary immensely (Staples, 2003). Higher molecular weight PEs such as benzyl-butyl phthalate (BBzP), bis-2-ethylhexyl phthalate (DEHP), diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP) are mostly used as plasticizers in polyvinyl chloride flooring and plastics, building materials, medical devices, cables and toys (Heudorf et al., 2007; Murphy, 2001) whereas lower molecular weight PEs such as di-ethyl phthalate (DEP) or diisobutyl phthalate (DiBP)/di-n-butyl phthalate (DnBP) are also used as additives and solvents in personal care products (PCPs) (Heudorf et al., 2007; Schettler, 2006).

Flame retardants are used to inhibit the spread of fire (EHC-192, 1997). OPEs belong to the group of phosphorus flame retardants (PFRs), more specifically, organic PFRs. They can be either reactive and chemically binding to the final product, or additive and mixed into the polymer (van der Veen and de Boer, 2012). Additionally, halogenation of these chemicals is common to increase their lifetime in the product (Fisk et al., 2003). Generally, OPEs consist of a phosphate backbone with 3 side chains connected via esterification (Fig 1). They represent a group of flame retardants introduced as alternatives for polybrominated diphenyl ethers (PBDEs), which are regarded as persistent, bioaccumulative and toxic (UN, 2011). OPEs are widely used chemicals with an annual production volume of about 90 000 tonnes in Europe in 2006 (van der Veen and de Boer, 2012). Applications include, among others, plastics,

rubber, foam and textiles (Mendelsohn et al., 2016; Poma et al., 2017; van der Veen and de Boer, 2012; Xu et al., 2016).

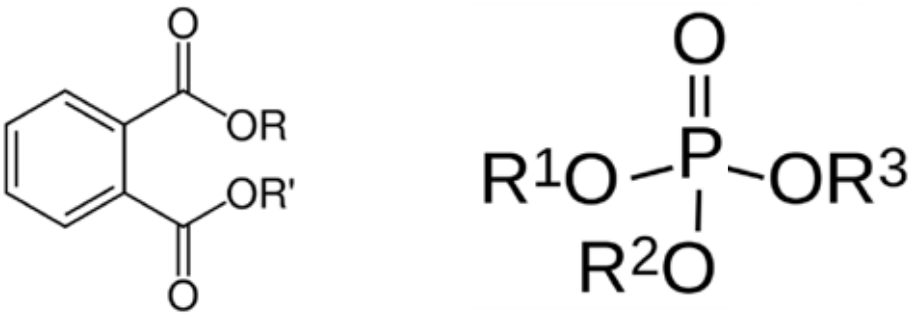


Figure 1 General structure of phthalate esters (left) and organophosphate esters (right).

1.2 Reasons for concern

Due to the fact PEs are not covalently bound to the material they are added to, release into the environment can occur by volatilization, abrasion, leaching and direct diffusion to exposure matrices i.e. dust (Afshari et al., 2004; Fromme et al., 2004; Fujii et al., 2003; Rudel et al., 2003). Additionally, widespread use has led to ubiquitous presence in the indoor environment (Peters, 2003; Rudel et al., 2003). Exposure to these chemicals has been found to cause several adverse effects in animal studies, where reproductive toxicity and endocrine disruption are the most commonly observed effects (Culty et al., 2008; Hauser, 2008; Hauser et al., 2006; Ventrice et al., 2013; Matthias Wittassek et al., 2007; Wittassek et al., 2011). Regarding humans, a decreased anogenital index has been associated with exposure to PEs (Bustamante-Montes et al., 2013). Furthermore, DEHP is listed as a potential carcinogen based on animal data (UNECE, 2011). Awareness of the potential health risks became apparent after certain PEs, including di-isononyl phthalate (DINP) and di-isodecyl phthalate (DIDP) were prohibited in the EU, US and Canada in sensitive applications such as children's toys and other childcare articles (EC, 2009, 2008, 2007; Kim et al., 2007). Since 2015, DiBP, DnBP, BBzP and DEHP are also included in Annex XIV of REACH (EC, 2013), requiring authorization for any application.

Similarly to PEs, many OPEs are additives and not chemically bonded to the final products, which leads to an easy release into the environment (Rodríguez et al., 2006). Toxicological information show that some compounds, for example tricresyl phosphate (TCP), triphenyl phosphate (TPHP) tris(2-chloroethyl) phosphate (TCEP), tris(chloropropyl) phosphate (TCPP) and tris-(2-chloro-, 1-chloromethyl-ethyl)-phosphate (TDCPP) have been reported to be (potentially) carcinogenic, neurotoxic, reproductively toxic or obesogenic (Pillai et al., 2014; van der Veen and de Boer, 2012). Both PEs and OPEs have been detected in various indoor matrices (e.g. air, dust, food) and can enter the human body via inhalation, ingestion or dermal uptake (Clark et al., 2011; van der Veen and de Boer, 2012; Wormuth et al., 2006; Xu et al., 2016).

1.3 State of the art in human indoor exposure assessment

Human exposure is determined by the intake, which is the amount of a chemical that ultimately enters the body at a certain rate and potentially causing adverse health effects. Hence, we are most interested in accurately determining intake rates for the studied chemicals. In general, there are two distinct methods (Fig 2) to assess human intake (Clark et al., 2011):

1) By measuring concentrations of the chemical in various external media such as dust and air, estimating intake rates (also called indirect method)
2) By measuring the human body burden of the chemical (or its metabolites) and back-calculating intake rates (also called direct method)

Each method has its own advantages and disadvantages, for example, the first method (based on external exposure media) is preferable to identify sources of exposure whereas the biomonitoring approach is often more accurate in determining the total intake.

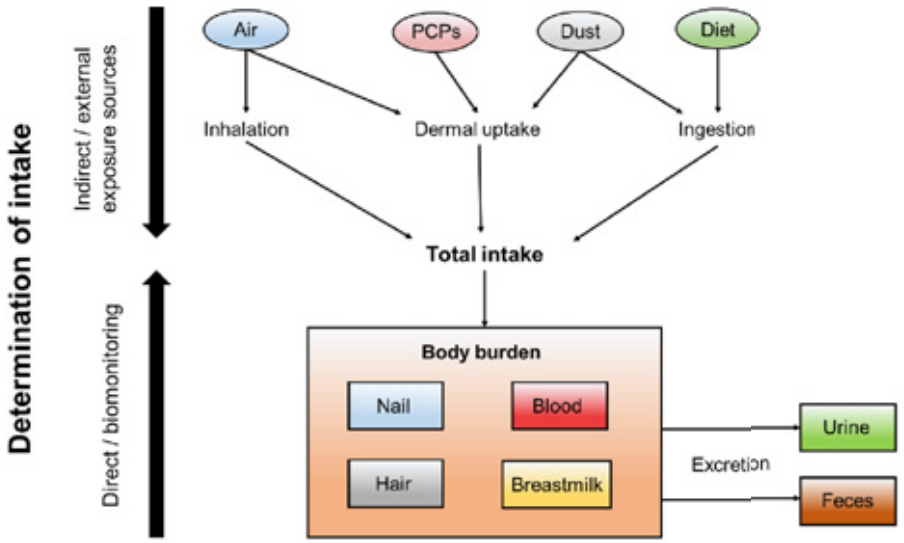


Figure 2 Schematic overview of human indoor exposure and the two approaches for assessing human exposure. Exposure media are shown at the top (in ovals) and can contribute to one or more exposure pathways (inhalation, dermal uptake or ingestion), leading to an intake rate that affects the human body burden, represented by different internal matrices. At the end, the chemical itself and/or its metabolites can be excreted in urine or feces.

For PEs, both methods have been performed extensively. For example, DMP, DEP, DiBP/DnBP, BBzP, DEHP, DINP and DIDP have been detected and quantified in air (Das et al., 2014; Ma et al., 2014; Martine et al., 2013; Tran and Kannan, 2015; Zhu et al., 2016), dust (Das et al., 2014; Gevao et al., 2013; Guo and Kannan, 2011; Kang et al., 2012), food (Bradley et al., 2013; Cheng et al., 2016; Das et al., 2014; Fierens et al., 2012; Heinemeyer et al., 2013; Sakhi et al., 2014; Schecter et al., 2013; Sioen et al., 2012; Sui et al., 2014) and PCPs (Bao et al., 2015; Koo and Lee, 2004). The relative importance of each uptake pathway is relatively well studied. Food seems to be the major contributor to PE exposure, in particular in case of higher molecular weight phthalates such as DEHP, DINP and DIDP (Cao et al., 2016; Guo and Kannan, 2011; Ji et al., 2014; Martine et al., 2013; Wormuth et al., 2006). Dermal absorption or inhalation was found to be important for smaller PEs such as DMP, DEP, DiBP and DnBP (Guo and Kannan, 2011; Ji et al., 2014; Wormuth et al., 2006). Furthermore, biomonitoring of PEs has been commonly performed. As rapidly metabolized substances, they are usually measured in urine and hence, excretion

factors of biomarkers (metabolites) are necessary to back-calculate the intake of their respective parent compound. Fortunately, studies have measured the metabolism and kinetics of PEs in humans *in vivo*, which allowed the estimation of such excretion factors (Anderson et al., 2001; Gries et al., 2012; Koch et al., 2013, 2012; Koch and Angerer, 2011; Leng et al., 2014). As a result, biomonitoring has become a well-used tool to determine total human exposure (Ait Bamai et al., 2015; Calafat and McKee, 2006; Chen et al., 2008; Dewalque et al., 2014; Fromme et al., 2007; Gao et al., 2016; Hartmann et al., 2015; Itoh et al., 2007; Kao et al., 2012; Koch et al., 2003; Saravanabhavan et al., 2013; Schütze et al., 2015; M Wittassek et al., 2007). PEs are also used in children's articles and infants/toddlers are recognized as a high risk group because of lower body weight and higher relative body surface (relevant e.g. for dermal uptake) compared to adults. Furthermore, infants and toddlers are usually in closer contact to the floor and are more likely to be exposed via dust, hand-to-mouth behavior and mouthing of products (Beko et al., 2013; M Wittassek et al., 2007; Wormuth et al., 2006). Nevertheless, use of PEs and thus exposure has been decreasing due to the legislative actions taken based on the precautionary principle (Giovanoulis et al., 2016; SPIN, 2016). For this reason, alternative phthalate or non-phthalate plasticizers have been introduced roughly within the last 15 years. Among those alternative plasticizers, bis(2-propylheptyl) phthalate (DPHP) and 1,2-cyclohexane dicarboxylic acid diisononyl ester (tradename Hexamoll DINCH) belong to the most widely used substances, directly substituting DEHP (SPIN, 2016). Biomonitoring studies and metabolism studies regarding DPHP and DINCH have recently been published, showing an increasing trend in human body burdens (Koch et al., 2013; Leng et al., 2014; Nagorka et al., 2011a; Schutze et al., 2014; Schütze et al., 2015).

In contrast to PEs, human exposure to OPEs is far less studied. They have been measured in indoor air, dust and food (Eulaers et al., 2014; van der Veen and de Boer, 2012; Xu et al., 2016, 2015) and their metabolites were found in human matrices, including urine, blood and breast milk (Kim et al., 2014; Van den Eede et al., 2015; Zhao et al., 2016). Initially, dust ingestion was considered to be the major intake pathway (de Boer et al., 2016), however, a more diverse exposure pattern has been suggested recently, depending on the specific compound. For example, dietary intake

can be at least as important as dust intake (e.g. for 2-ethylhexyl diphenyl phosphate, EHDPHP) (Poma et al., 2017; Xu et al., 2017; Zheng et al., 2016) or inhalation of air can be a significant contribution to human exposure for TCPP (Xu et al., 2016). Similarly to PEs, human body burden is measured using urinary metabolites as biomarkers (Butt et al., 2016; Dodson et al., 2014; Van den Eede et al., 2015), while few recent studies also measured their presence in serum, hair and nails (Alves et al., 2016a; Kucharska et al., 2015; Zhao et al., 2016). Although studies on metabolism of OPEs exist (Ballesteros-Gómez et al., 2015a; Cooper and Stapleton, 2011; Su et al., 2014; Van den Eede et al., 2016b), no excretion factors have been established for any specific compound yet.

Recently, non-invasive human matrices such as hair and nails have been proposed to represent an alternative to current biomonitoring methods for both PEs and OPEs (Alves et al., 2016b, 2016c, 2014; Giovanoulis et al., 2016). Various advantages of using these matrices exist, including ease of sampling and relative stability of samples. Disadvantages are potential external contamination and yet unclear uptake kinetics.

1.4 A-TEAM sampling campaign

The work presented in this thesis is a part of the "A-TEAM" (Advanced tools for exposure assessment and biomonitoring) project, which aims to investigate human exposure to various consumer chemicals. The study cohort consists of 61 adults, age 20 to 66 with 16 males and 45 females living in the Oslo area (Norway). Participants were recruited from the Norwegian Institute of Public Health (NIPH) staff members and were invited by an electronic announcement on the website of the institute. Sampling was performed during winter 2013/2014, where air, dust, food, hand-wipes, urine and blood samples were taken. Additionally, information about the home environment as well as personal and lifestyle data were collected. Further details regarding the whole sampling campaign are presented in Papadopoulou et al. (2015). For this thesis, a brief summary of the relevant sampling methods for PEs and OPEs is given below because these methods represent the foundation of the work done in **papers II-IV**.

Indoor air samples were taken using two different methods. The first method involved stationary pumps which were placed in the living rooms of participants for 24 h and connected to ENV+ SPE cartridges (200 mg, 6 ml). The second method used personal air samplers, which were portable pumps connected to an ENV+ SPE cartridge (1 g, 25 ml) and were worn by the participants for 24 h. For dust, the sampling of floor and vacuum bag dust was conducted. Floor dust was taken from the living rooms of participants using a vacuum cleaner equipped with a forensic nozzle and a dust filter. Vacuum bag dust was provided directly by the participants. Food samples were also provided by the participants which were duplicate portions of all foods (solid and liquid) consumed within a 24 h period. Hand-wipes were collected by wiping from wrist to fingertips of both hands (palm and back of the hand) using a piece of glass wool rinsed with 3 ml of isopropanol for PEs and using sterile gauze pads for OPEs. Participants were advised not to wash their hands 1 h prior to collection of samples. Urine samples were provided by the participants and consisted of 3 samples, one morning urine spot and 2 evening urine spots. For serum, venous blood samples were collected by a research nurse in 1 ml plastic serum tubes. For fingernail sampling, participants were asked not to cut their nails for 2-3 weeks prior to collection. Also, they were asked to remove any nail polish, dirt, debris and artificial nails. Nails from both hands were provided by the participants.

1.5 Research gaps and thesis objectives

As a group of well-studied chemicals, human exposure to PEs has been investigated extensively. However, some aspects are still uncertain. Firstly, the relative importance of uptake pathways has always been estimated using measured concentrations that have temporal or geographical differences (different study groups, different times of sampling) and inter-laboratory differences in general should also not be underestimated. Furthermore, comparisons with biomonitoring data from a different study population or at a different time might not reflect immediate exposure but rather intake from a different time-span. Especially for PEs, where changes in exposure reflects body concentrations rather quickly (as these chemicals are rapidly eliminated), it is difficult to relate concentrations in external media to human body burden. Secondly, some uptake pathways are less well studied than others. For

example, food is a very well-studied matrix as the majority of the exposure is likely affected by dietary intake. On the other hand, dermal exposure is not as extensively investigated. Chemical-specific parameters such as dermal absorption fractions are unknown. Direct contact with products containing PEs (dermal uptake) or hand-to-mouth exposure (ingestion) is extremely difficult to estimate and remains mostly unknown. Lastly, the introduction of alternative plasticizers with evidence of increasing human exposure requires further monitoring in environmental media and the human body. Unfortunately, not much is known regarding their concentrations in the indoor environment as well as in consumer products.

For OPEs, there is a severe lack of information regarding metabolism and kinetics *in vivo*, particularly for humans, in order to derive excretion factors for exposure assessment purposes. The relative importance of uptake pathways is not well studied and links to internal concentrations have not yet been established.

Regarding non-invasive matrices, their suitability as urine/serum alternatives have yet to be sufficiently addressed. In particular, it is unknown what nail or hair concentrations represent in terms of intake or exposure to PEs. Accurate kinetics are necessary to relate uptake and concentration in order to back-calculate daily intake for humans.

The overall aim of this thesis is to improve the knowledge regarding human exposure to PEs and OPEs in the indoor environment using mathematical modelling tools. Pharmacokinetic models have been proven as powerful methods to complement exposure assessment (Cahill et al., 2003; Clewell et al., 2008). For this, the comprehensive dataset described above, which included measured concentrations of PEs and OPEs in indoor matrices (i.e. air, dust), personal samples (hand wipes, food) and human matrices (urine, serum) is available. Since both studied substance classes are very different in terms of available literature information, objectives have to be specified for each group separately. For PEs, the thesis aims to 1) relate external concentrations to human body burden **(Paper II)**, 2) study the relative importance of different uptake pathways **(Paper II)** 3) provide and summarize information on use, exposure, health effect and risk regarding alternative plasticizers **(Paper I)** and 4) investigate the suitability of non-invasive matrices, in particular human nail **(Paper**

III). For OPEs, this work will use existing literrature data and results from the A-TEAM study population to attempt linking external and internal concentrations in order to evaluate current knowledge and identify further research needs regarding human exposure assessment **(Paper IV)**.

The specific objectives of **papers I-IV** are summarized as follows:

Paper I

The objective of this study was to collect information on use and application, human exposure, health effects and risk of several alternative plasticizers. Another goal was to specify research gaps and future perspectives in order to carefully monitor these chemicals with an expected increase in exposure.

Paper II

This work was performed in order to establish links between external and internal concentration of PEs and DINCH using a comprehensive dataset. We also aim to provide solid information on the relative importance of several uptake pathways. The last goal of this study was to provide an overview of human risk based on established health limit values and estimated intake rates.

Paper III

The overall aim of this study was to evaluate the suitability of human nails biomonitoring of PEs. More specifically, this work aims to test the hypothesis that internal intake (from blood) is the dominant pathway determining nail concentrations, which would provide an indication that nails are indeed suitable for biomonitoring purposes.

Paper IV

The objective of this study was to investigate the links between internal concentrations (serum, urine) and external concentrations (represented by total intake) for OPEs. In particular, we aim to exploit a comprehensive dataset and use pharmacokinetic model that quantitatively links external exposure (intake) with internal levels of OPEs and metabolites, derive parameters needed to estimate human *in vivo* metabolism and explore uncertainties and data gaps in our understanding of human exposure of OPEs.

2 Methods

2.1 Chemicals

In this thesis, a variety of chemicals i.e. phthalate and non-phthalate plasticizers and organophosphate flame retardants were studied. **Paper I** investigated the physicochemical properties, use, exposure and toxicological information of several alternative non-phthalate plasticizers, which are very diverse and represent several groups of substances (Table 1). **Paper II and III**, on the other hand, assessed mainly phthalates and **paper IV** addressed 3 commonly used OPEs (Table 2).

Table 1 Alternative plasticizers assessed in **paper I**. Values of log K_{OW} were estimated using EPIWEB 4.1 (USEPA, 2012) unless otherwise noted.

Substance	CAS Number	Molar weight [g/mol]	Log K_{OW} (25°C)
Dibutyl adipate (DBA)	105-99-7	258.35	4.33
Bis(2-ethylhexyl) adipate (DEHA)	103-23-1	370.57	8.94[a]
Diisononyl adipate (DINA)	33703-08-1	398.62	9.24
Diisodecyl adipate (DIDA)	27178-16-1	426.67	10.08
Di(ethylene glycol) dibenzoate (DEGDB)	120-55-8	314.33	3.04
Di(propylene glycol) dibenzoate (DPGDB)	2738-31-4	342.39	4.3[a]
Acetyl tributyl citrate (ATBC)	77-90-7	402.48	4.29
Cyclohexane-1,2-dicarboxylate diisononyl ester (DINCH)	1166412-78-8	424.65	10[a]
Bis(2-ethylhexyl) phosphate (DEHPA)	298-07-7	322.42	2.67[a]
Tris(2-ethylhexyl) phosphate (TEHPA)	78-42-2	434.63	9.49
Tricresyl phosphate (TCP)	1330-78-5	368.37	5.11[b]
Dibutyl sebacate (DBS)	109-43-3	314.46	6.3
Bis(2-ethylhexyl) sebacate (DOS)	122-62-3	426.67	10.08
Bis(2-ethylhexyl) terephthalate (DEHT)	6422-86-2	390.56	8.39
Tris-2-ethylhexyl trimellitate (TOTM)	3319-31-1	546.78	8[a]

Glycerides, castor oil-mono, hydrogenated, acetates (COMGHA)	736150-63-3	500.5	6.4[a]
Epoxidized soybean oil (ESBO)	8013-07-8	1000	14.84
Alkylsulfonic phenyl ester (ASE)	91082-17-6	368.57	3.88
Glycerin triacetate (GTA)	102-76-1	218.2	0.25[a]
Trimethyl pentanyl diisobutyrate (TXIB)	6846-50-0	268.41	4.91

[a](ECHA, 2016)

[b](Saeger et al., 1979)

Table 2 Phthalates and organophosphate esters studied in **paper II-IV**. Values of log K_{OW} were estimated using EPIWEB 4.1 (USEPA, 2012) unless otherwise noted.

Substance	**CAS Number**	**Molar weight [g/mol]**	**Log K_{OW} (25°C)**
Phthalate esters (Paper II&III)			
Dimethyl phthalate (DMP)	131-11-3	194.18	1.53[b]
Diethyl phthalate (DEP)	84-66-2	222.24	2.39[b]
Diisobutyl phthalate (DiBP)	84-69-5	278.34	4.61[b]
Di-n-butyl phthalate (DnBP)	84-74-2	278.34	4.61[b]
Benzyl-butyl phthalate (BBzP)	85-68-7	312.37	4.91[b]
Bis-2-ethylhexyl phthalate (DEHP)	117-81-7	390.56	7.45[a]
Bis(2-propylheptyl) phthalate (DPHP)	53306-54-0	446.66	10.36
Diisononyl phthalate (DINP)	28553-12-0	418.61	9.52
Diisodecyl phthalate (DIDP)	26761-40-0	446.74	9.46
Organophosphate esters (Paper IV)			
2-ethylhexyl diphenyl phosphate (EHDPHP)	1241-94-7	362.4	5.87[a]
Tri-n-butyl phosphate (TNBP)	126-73-8	266.32	3.82
Triphenyl phosphate (TPHP)	115-86-6	326.29	4.7

[a](ECHA, 2016)

[b](Schwarzenbach, 2005)

2.2 Exposure modelling of phthalates

In order to determine human intake of PEs and the relative importance of each uptake pathway (Fig 2), exposure was modelled using concentrations in external media. Detailed methodology, equations and assumptions are presented in **paper II**. In summary, inhalation of PEs in bulk air was estimated using stationary air concentration c_{air} [ng/m³], inhalation rate IR [m³/d/kg bodyweight] and indoor residence time fraction T [-]:

$$DI_{inh} = C_{air} \times IR \times T \quad (1)$$

Dietary uptake was assessed using concentrations in food c_{diet} [ng/g food] and considering the amount of food consumed in the last 24h I_{diet} [g food/d]:

$$DI_{diet} = \frac{C_{diet} \times I_{diet}}{BW} \quad (2)$$

BW describes the bodyweight in kg. Dust ingestion was calculated using concentrations in vacuum cleaner bag dust c_{bd} [ng/mg dust] and the daily dust ingestion rate for adults [mg dust/d]:

$$DI_{dust_i} = \frac{C_{bd} \times I_{dust}}{BW} \quad (3)$$

Dermal exposure based on hand wipe samples was estimated using hand wipe concentrations c_{hw} [ng/m²], the hand surface area A_{hands} [m²] and dermal absorption fractions f_A [-]:

$$DI_{hw} = \frac{C_{hw} \times A_{hands} \times f_A}{BW} \quad (4)$$

These were compared to other sources of dermal exposure such as air (DI_{dermal_gas}), dust (DI_{dermal_dust}) and PCPs (DI_{dermal_PCP}):

$$DI_{dermal_gas} = \frac{C_{gas} \times k_{pg} \times A_{f,h} \times T}{BW} \quad (5)$$

$$DI_{dermal_dust} = \frac{C_{bd} \times A_{hands} \times M_S \times f_A \times 0.15}{BW} \quad (6)$$

$$DI_{dermal_PCP} = \frac{\sum_{i=1}^{n} c_{PCP} \times f_{PCP} \times m_U \times M_A \times r}{BW} \quad (7)$$

where c_{gas} is the PE concentration in vapour phase [ng/m³], k_{pg} the indoor air transdermal permeability coefficient [m/h], $A_{f,h}$ the surface area of both hands and the face [m²], M_S the amount of dust adhered to the skin [g dust/m²], C_{PCP} the concentration in a particular PCP [ng/g], f_{PCP} the daily use frequency of a product [1/d], m_U the amount used per application [g], M_A the mass absorption fraction of a compound [-] and r the retention fraction of a product [-].

Exposure factors (i.e. inhalation rates, body surface estimation, PCP concentrations etc.) necessary for assessing intake were taken from various sources (CTFA, 1983; Du Bois and Du Bois, 1916; Guo and Kannan, 2013, 2011; Llompart et al., 2013; Loretz et al., 2006, 2008, 2005; O'Sullivan and Schmitz, 2007; Schwarzenbach, 2005; Staples, 2003; USEPA, 2011, 2003; Weschler and Nazaroff, 2014; Wormuth et al., 2008, 2006; Yu et al., 2008).

2.3 Modelling uptake of PEs from blood into nail

Paper III aimed to provide an understanding of the links between intake of PEs and their concentration in nail in order to evaluate the suitability of nails as a biomonitoring matrix. An important key assumption made in this study was to assume that uptake into the nail plate occurs only from the blood stream since the nail plate is surrounded by richly perfused tissues. External sources of exposure such as PCPs were therefore not considered. Unfortunately, no blood/serum measurements of PEs were available and concentrations had to be estimated. For this purpose, an empirical two-box pharmacokinetic (PK) model by Lorber et al. (2010; 2013) was used. This PK model is able to predict serum concentrations of DEHP and DnBP/DiBP metabolites following oral intake of their respective parent compounds. The intake, which is used as an input parameter, is based on biomonitoring results using the creatinine-model and presented in Giovanoulis et al. (2016) for the same study population. This method is well established and able to accurately reflect total intake. In the Lorber model, intake of DEHP and DiBP/DnBP occurs orally, followed by formation of metabolites at a certain rate (k) and fraction (f). These metabolites can be further metabolized or directly excreted in urine (Fig 3). This model does not

represent a mechanistic mass balance model and was calibrated using accurate dosing experiments (Koch et al., 2012, 2005, 2004). Simulations were run in 15 min steps and end after 30 days to ensure steady state conditions.

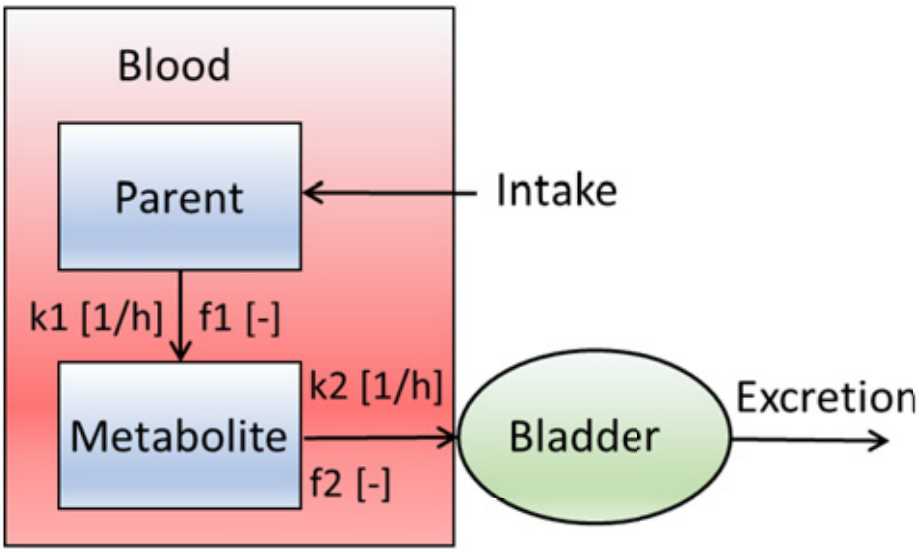


Figure 3 General scheme of the Lorber PK model. k is the elimination rate constant [1/h] and f a dimensionless fraction.

Based on the steady state serum concentrations obtained in the Lorber PK model, uptake into nail was modeled conservatively using a simple equilibrium partitioning model (Eq 8).

$$c_n = k_{nb} \times c_b \qquad (8)$$

where k_{nb} is the nail-blood equilibrium partitioning coefficient [-], c_n the PE concentration in nail [ng/g nail] and c_b the PE concentration in blood [ng/ml].

Nail and blood were considered separate compartments and uptake of PEs into the nail was assumed to occur via passive diffusion. Because no information regarding the partitioning of chemicals into nails exist, it was considered to be a tissue compartment. To estimate partitioning between blood and body tissues, a simplified equation presented by DeJongh et al. (1997) was used:

$$k_{nb} = \frac{V_{l,n} \times K_{OW}^{A} + V_{w,n}}{V_{l,b} \times K_{OW}^{A} + V_{w,b}} + B \quad (9)$$

where V_l and V_w is the lipid and water content fraction respectively, K_{OW} the octanol-water partition coefficient and A and B additional calibrated parameters for a certain tissue-blood relationship. Due to similar water/lipid content, values for the muscle tissue were assigned to the nail compartment for A and B.

2.4 Assessing the links between external and internal concentrations of OPEs

In **Paper IV**, the aim was to establish links between intake based on measured concentrations in exposure media and internal concentrations (serum and urine). Because metabolism of OPEs has not been as well studied as PEs, the links between external and internal concentrations can only be estimated using modelling. The model used in this study is conceptually very similar to the model used in **paper III** (Lorber model) and was chosen because of its simplicity and low number of parameters. A key advantage of such a simple model over physiologically based models is the reduction of processes involved. For example, the simple model does not require further chemical-specific parameters for blood-tissue distribution and renal filtration. As a consequence, only 4 parameters are needed to describe the kinetics in the whole model: k1 (parent compound elimination rate), f1 (metabolite formation fraction), k2 (metabolite elimination rate) and f2 (metabolite excretion fraction). In this study, we investigated EHDPHP, Tri-n-butyl phosphate (TNBP) and TPHP as it was possible to detect their metabolites in both serum and urine for the study population. Results from a literature research to find information regarding the above mentioned parameters is presented in Table 3. Those remaining unknown were fitted by the model via the least squared residuals method, using biomonitoring data (serum, blood, unpublished data) and daily intake values from the publication by Xu et al. (2016), which were calculated based on measurements in exposure media for the same Norwegian study population. Then, the model was run using literature and fitted parameters, where predicted metabolite concentrations in serum/urine (at steady state) were compared to observed data.

Table 3 Parameters in the OPE model based on literature data.

Compound/ Metabolite	Parameter	Study type	Reference
EHDPHP/5OH-EHDPHP	Not available	Not available	not available
TNBP/DNBP	k1 = 0.533/h	Rat *in vivo*	(ECHA, 2016)
	f1 = 0.14	Herring gull liver microsomes	(Greaves et al., 2016)
	f2 = 0.47	Rat *in vivo*	(Suzuki et al., 1984)
TPHP/DPHP	k1 = 2.886/h	Human hepatic cells *in vitro*	(Van den Eede et al., 2016a)
	f1 = 0.17; 0.15	Chicken embryonic hepatocytes; Herring gull liver microsomes	(Su et al., 2014); (Greaves et al., 2016)

3 Results and discussion

3.1 Temporal trends and risk of alternative plasticizers

In **paper I**, alternative plasticizers were studied in terms of use, physicochemical properties, toxicological information, exposure and ultimately, risk. Figure 4 shows the temporal use trend of plasticizers ("traditional" phthalates, DPHP and alternative plasticizers) in Sweden from 1999 to 2012 (SPIN, 2016). It became obvious that there has been a shift from traditional phthalates to alternative plasticizers, including DPHP and other alternatives (see Table 1 for a list of studied compounds), in particular starting from 2010. This was expected as we already mentioned above that most PEs (i.e. DEHP) are restricted and currently undergo phase out. A closer look revealed that DINCH contributed to over 70% of the use of alternative plasticizers.

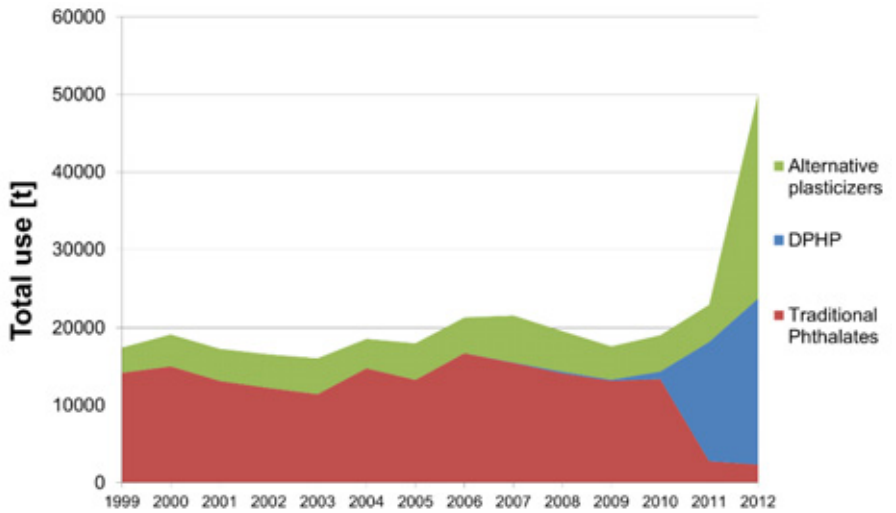


Figure 4 Total use of "traditional phthalates" (sum of DEP, DnBP, DiBP, BBzP, DEHP, DINP and DIDP) and the more recently occurring DPHP compared to the use of alternative plasticizers (sum of substances listed in Table 1 excluding COMGHA) in Sweden from 1999 to 2012.

To determine the risk coming from those alternative plasticizers, information on human intake was collected and compared to health based limit values (Table 4). Although some alternatives did not show any hazardous properties (hence, no limit value could be estimated), health limit values have been established for other alternatives. However, estimated intake values were mostly at least one order of

magnitude lower, which indicated low risk for the general population. Exceptions were DINCH, DPHP and ESBO with risk ratios of 0.2, 3.4 and 2.5 respectively. In case of DPHP and ESBO, where intake exceeded health limits, children or infants were identified as being at high risk. Nevertheless, it could be observed most alternatives are less toxic than DEHP or DINP/DIDP which they replaced. In **paper I**, ESBO, DPHP and DINCH were identified as potentially important for future studies, either because of relatively high risk or increasing use trend. Indeed, DINCH was not only detected in dust (Nagorka et al., 2011a, 2011b) but also in human urine as metabolites with increasing trends (Giovanoulis et al., 2016; Schutze et al., 2014; Silva et al., 2013). Consequently, exposure to DINCH is likely to increase in the future. Similarly, Schütze et al. (2015) have shown that the general German population is increasingly exposed to DPHP, supporting the findings presented in Fig 4.

Table 4 Intake rates, limit values and risk ratios of alternative plasticizers presented in **paper I**. Limit values taken from ECHA represent DNELs, where the lower value was selected (dermal or oral). In case of multiple intake estimates, the highest value was taken to determine risk ratio.

Substance	Intake [µg/kg/d]	Limit value [µg/kg/d]	Risk ratio
DPHP	135, children[b]	40[b]	3.4
DBA	No data	No hazard [j]	-
DEHA	2.35, infants[c]	300 [a]	0.01
DINA	No data	1700 [j]	-
DIDA	2.92[d]	19600 [j]	1.5×10^{-4}
DEGDB	No data	800 [j]	-
DPGDB	4.36×10^{-3} [a]	220 [j]	2.0×10^{-5}
ATBC	60.0, children (teething ring)[a]	1000 [j]	0.06
DINCH	81[e]	400 [c]	0.20
DEHPA	4.36×10^{-3} [a]	250 [j]	1.7×10^{-5}
TEHPA	2.86 [a]	25000 [j]	1.1×10^{-4}
TCP	0.14 [d]	50 [j]	2.9×10^{-3}
DBS	No data	No hazard [j]	-
DOS	4.36×10^{-3} [a]	No hazard [j]	-
DEHT	0.29 [d]	3950 [j]	7.3×10^{-5}
TOTM	1.62×10^{-13} [a]	1130 [j]	1.4×10^{-16}
COMGHA	No data	No hazard [j]	-
ESBO	340-4650, infants[f]	1000 [k]	2.5
ASE	No data	470 [j]	-
GTA	110 [g]	2500 [j]	0.04
TXIB	7.30 µg/m³ [d]	32600 µg/m³ [j]	2.2×10^{-4}

[a](Wittassek and Angerer, 2008), [b](BfR, 2011) [c](Liang and Xu, 2014), [d](Bui et al., 2016), [e](NICNAS, 2011), [f](EFSA, 2004), [g](OECD, 2002), [h](EFSA, 2005a), [i](EFSA, 2005b), [j](ECHA, 2014), [k](EUC, 2002)

3.2 Human exposure and risk of phthalates and DINCH

Human exposure was assessed in this thesis (**Paper II**) using concentrations in external matrices (Eq 1-7). Based on the findings in **paper I**, DINCH and DPHP were found to be highly relevant for human exposure as they directly replace phthalate plasticizers such as DEHP and their presence in humans was shown in other studies (Schutze et al., 2014; Schütze et al., 2015), indicating increasing exposure trends. Therefore, those two substitutes were included in the study. Compared to the direct method using biomonitoring data, total intake based on external media did not show large differences (Figure 5). This illustrates a good understanding of important uptake pathways adults and that they were captured during the sampling process. However, significant differences were found for DMP, DiBP/DnBP, BBzP and DEHP which could be explained by the conservative approach of the indirect exposure estimation. Unfortunately, no comparisons were available for DINP, DIDP and DPHP because no metabolites were measured.

In **paper II**, total intake of DEHP was estimated to be the highest, followed by DiBP, DnBP, DEP, DINP, DINCH, DIDP, BBzP, DPHP and DMP in decreasing order. The range of geometric means (GM) was 39.5 ng/kg/d (DMP) to 1580 ng/kg/d (DEHP). Compared to the literature, these intakes were found to be either similar or lower with the exception of DIDP, where Wormuth et al. (2006) calculated a total intake of 10 in contrast to 295 ng/kg/d estimated in this study. Overall, intakes of traditional PEs were found to be low and, in combination with literature information (SI of **paper II**) following a decreasing trend as expected. For DINCH, both the intake estimated in this work and the biomonitoring approach in Giovanoulis et al. (2016) were found to be similar to the direct method applied in other studies from Germany and the US (Schutze et al., 2014; Silva et al., 2013). Also, an intake of 49 ng DPHP/kg/d (GM) in this study lies within the range of 25-314 ng/kg/d calculated by Schütze et al (2015).

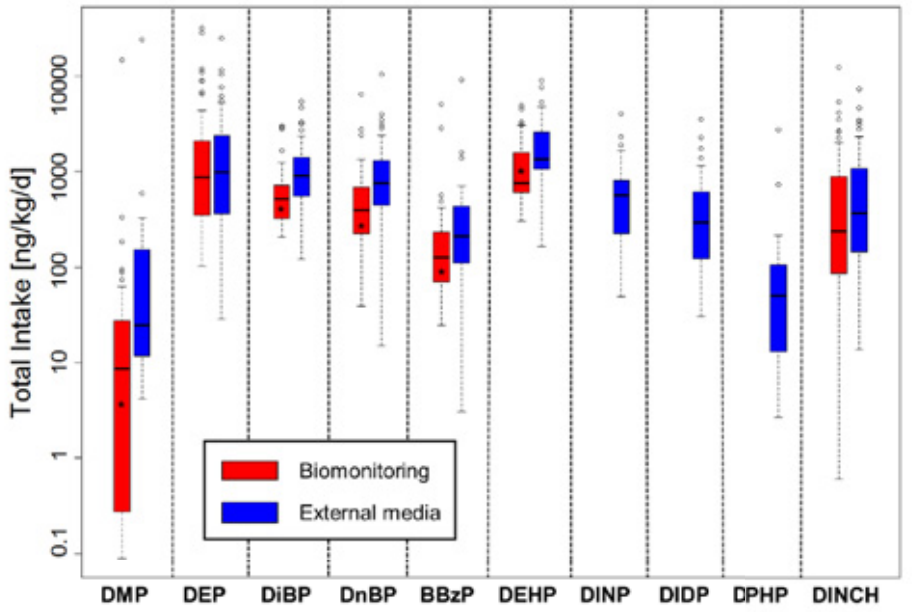


Figure 5 Box-Whisker plots of daily intakes [ng/kg/d], comparing exposure based on biomonitoring data (red) and external exposure (blue). Boxes represent 25th, 50th (shown by the horizontal line) and 75th percentiles. Whiskers indicate maximum and minimum values within 1.5x the inter-quartile range and circles show outliers. Indirect exposure is calculated using Eq 1-7 and direct exposure using the method described in Giovanoulis et al. (2016). A * indicates a significant difference between the two datasets in a Mann-Whitney-U test ($p < 0.05$).

A closer look into the contributions of each uptake pathways (Figure 6) indicated that for all studied compounds, dietary intake was estimated to be the dominant route of exposure (at least 50% contribution). However, for lower molecular weight phthalates, inhalation was also estimated to be relatively important with a contribution of 45% for DMP and 10% for DEP, DiBP and DnBP. Dermal uptake was determined to be negligible with the exception of DEP, where it contributed to approximately 10% of the total intake. This is not surprising as DEP is commonly used and also detected in PCPs (Koniecki et al., 2011). Dust ingestion was more significant for higher molecular weight phthalates, where its contribution was 40% for DINP, 10% for DEHP, DIDP, DPHP and DINCH and 5% for BBzP. These findings are mostly in agreement with other studies that found diet to be the main contributor to intake (Cao et al., 2016; Das et al., 2014; Guo and Kannan, 2011; Ji et al., 2014; Martine et al., 2013), although the large extent and observation also for very low molecular weight

PEs was surprising. For example, the study by Wormuth et al. (2006) found inhalation to be more important for DMP, DEP, BBzP and DINP.

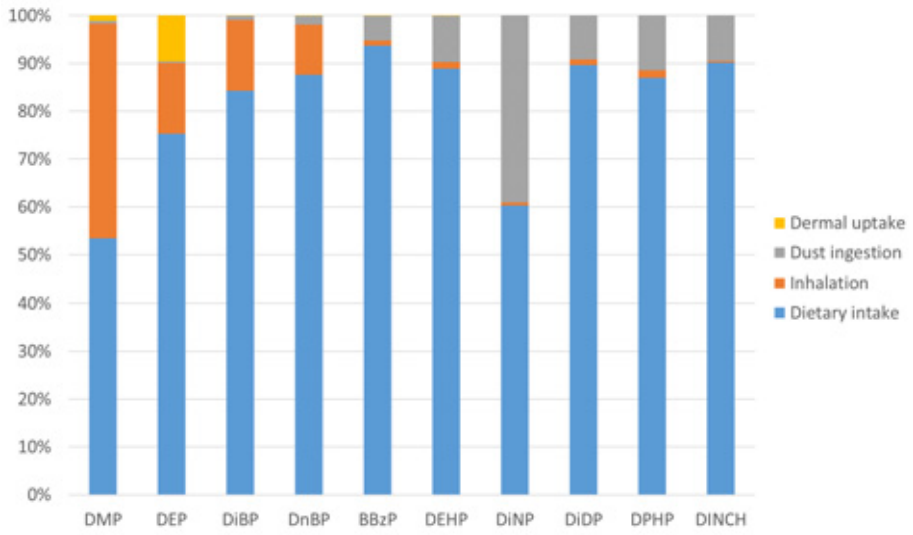


Figure 6 Relative importance of different uptake pathways, comparing the geometric means of each intake. Dermal uptake was assessed using hand wipe samples (DI_{hw}). Since no hand wipe results were available for DINCH, $DI_{dermal_gas} + DI_{dermal_dust}$ was used instead.

Comparing different dermal uptake routes and methods (Figure 7), it could be observed that air was a negligible source and that dust was only a very small contributor. GMs of dermal uptake via dust was found to be larger than uptake via air by factors ranging from 3 (DiBP) to 9 x 10^5 (DIDP). On the other hand, exposure via PCPs was estimated to be relatively high and in case of DMP and DEP, much higher than intake calculated based on hand wipe samples (median: up to a factor of 2000). For a more realistic comparison, dermal uptake via PCP only used on hands showed that there was not much difference to total PCP exposure except for DEP and DEHP. For these compounds, we concluded that the majority of PCP exposure occurred via products that were not applied to hands, such as deodorants and perfumes. Still, the difference between PCP intake and hand wipe intake remained large for DEP. No concentrations of DINP, DIDP and DINCH were reported in PCPs and therefore, no intakes could be estimated. Overall, the use of hand wipes to represent total dermal intake should be regarded with care and likely underestimates the integrative dermal

exposure. This is especially true for DMP and DEP, where differences between hand wipes and PCPs were very high. Lastly, it should be mentioned that dermal absorption factors were taken from literature and are likely underestimating dermal uptake as recent studies have shown that DEHP and DnBP are first metabolized in the skin and subsequently absorbed at a high fraction (Beydon et al., 2010; Hopf et al., 2014)

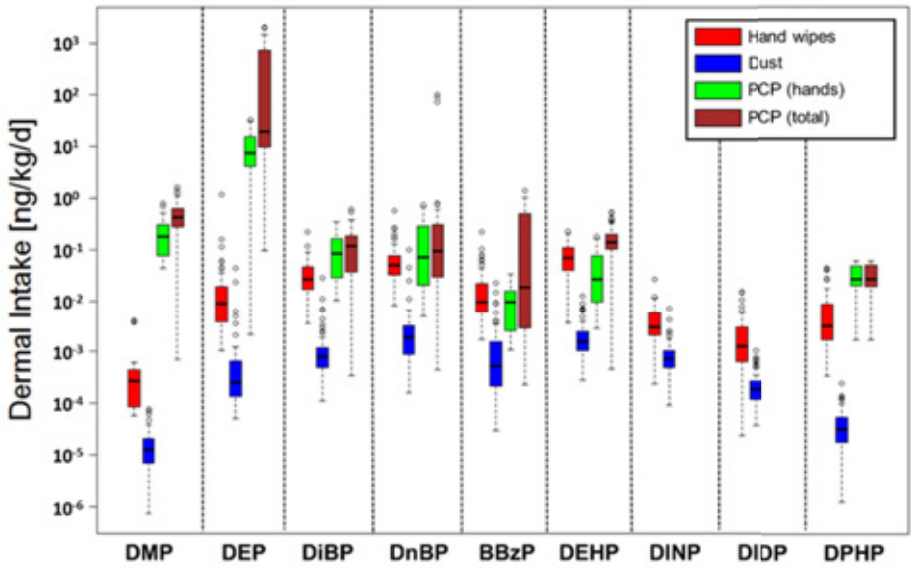


Figure 7. Box-Whisker plots of dermal daily intakes [ng/kg/d], comparing hand wipes (red), dust (blue), PCPs (hand products only) (green) and PCPs (all products) (brown). Boxes represent 25th, 50th (shown by the horizontal line) and 75th percentiles. Whiskers indicate maximum and minimum values within 1.5x the inter-quartile range and circles show outliers. Uptake via air for not included because of negligible contribution (see main text).

Finally, the risk of PEs and DINCH was assessed with hazard quotients (HQs). These values were calculated by dividing the total daily intake with an established health limit value. HQs were below 1 for all studied compounds and indicate low risk for the adult general population. The highest HQs were calculated for DiBP/DnBP and DEHP with medians ranging from 0.005-0.091 and 95th percentiles ranging from 0.018 to 0.36 respectively. Exposure to traditional PEs will likely continue to decrease due to restrictions and phase-out, hence risk will probably remain low. However, alternatives such as DPHP and DINCH are showing an increase in exposure and therefore, should be closely monitored in the future.

3.3 Human nails as an alternative, non-invasive biomonitoring matrix for PEs

Internal uptake of DiBP/DnBP and DEHP metabolites from blood into nail was predicted and compared to measured data in **paper III** (Figure 8). Nail concentrations were underestimated by 1 to 3 orders of magnitude. These difference were substantial and led to the conclusion that although the calculations were highly conservative (equilibrium partitioning), uptake from blood cannot explain observed nail concentrations in the study population and the hypothesis that nail concentrations mainly reflect internal uptake should be rejected. Therefore, it is likely that other sources of exposure play an important role in determining the concentrations in nail. Examples include uptake via air, dust and PCPs. An uncertainty analysis showed that the underestimations cannot be attributed to uncertainties in the input parameters. To take one step further, gaseous diffusive uptake was modeled dynamically (shown in **paper III)** and results revealed very slow uptake. Although equilibrium concentrations between air and nail could explain the biomonitoring data, uptake was found to be too slow to reach equilibrium conditions in reality. Hence, uptake from air could not explain measured data either and other potential uptake routes (direct contact with plastics, PCPs) should be investigated. Due to the fact that we do not know the kinetic processes between intake and nail concentrations, it is not possible to back-calculate total intake similar to what can be done with urinary metabolite concentrations.

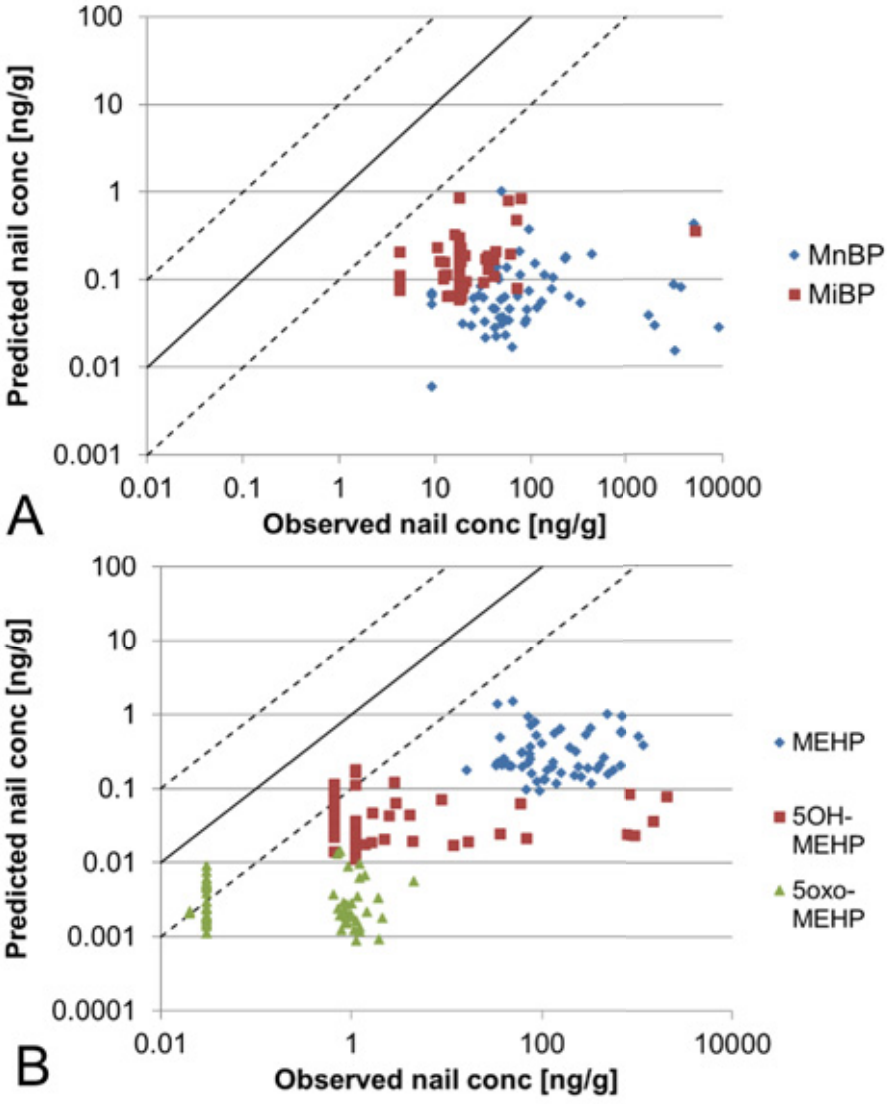


Figure 8 Observed versus predicted nail concentration for DnBP and DiBP (A), DEHP (B) metabolites.

3.4 Links between external and internal concentrations of OPEs

The parameters describing metabolism and excretion of the studied OPEs in **paper IV** are shown in Table 5. These include parameters shown above (Table 3) and model-fitted parameters. It has been found during additional simulations that the parameter k1 is of low importance for the overall result of the model output and mainly affects the time to reach steady-state concentrations. Although k1 is an important parameter for understanding human metabolism *in vivo*, it was not found to be relevant for determining the actual steady-state concentrations. For EHDPHP, a high f1 of 0.91 seems plausible as it was shown that 5OH-EHDPHP might be one of the dominant EHDPHP metabolites (Ballesteros-Gómez et al., 2015a). Also, a low 5OH-EHDPHP elimination rate could be explained by the fact that it undergoes phase II metabolism (glucuronide-conjugation) as it is relatively hydrophobic. A low urinary excretion fraction of 13%is in agreement with another study (Treon et al., 1953), which found 10% excretion in human urine. For TNBP, a fast elimination of its metabolite DNBP is quite possible considering the relatively small size and high hydrophobicity as a strong acid. However, a k2 of 72/h or a half-life of less than one minute leads to the conclusion that elimination was certainly overestimated, which could also be said for an estimated k2 of 97.6/h for TPHP/DPHP. A high f2 of 0.7 on the other hand could be expected as similarly to DNBP, DPHP exists mainly in dissociated form at physiological pH as it has strong acidic properties.

Table 5 Kinetic parameters in the simple PK model for EHDPHP, TNBP and TPHP.

Chemical	Parameter	Value [unit]
EHDPHP	k1*	28.3 [1/h]
	f1*	0.91 [-]
	k2*	0.03 [1/h]
	f2*	0.13 [-]
TNBP	k1[a]	0.533 [1/h]
	f1 [b]	0.14 [-]
	k2*	72.1 [1/h]
	f2 [c]	0.47 [-]
TPHP	k1 [d]	2.886 [1/h]
	f1 [b,e]	0.16 [-]
	k2*	97.6 [1/h]
	f2*	0.70 [-]

*fitted by the model ; [a](ECHA, 2016), [b](Greaves et al., 2016), [c](Suzuki et al., 1984), [d](Van den Eede et al., 2016a), [e](Su et al., 2014)

Comparing model predictions to biomonitoring data (Table 6), we can see that a good fit was achieved for EHDPHP with the GM of ratios between predictions and observations being close to 1 (0.82 and 0.5 for urine and serum respectively). For TNBP and TPHP, urine concentrations (GMs) differed from observed data by 4-10-fold. However, serum concentrations (GMs) deviated from observed data by a factor of approximately 500 for TNBP and 1000 for TPHP. This showed that using the mentioned parameters, it was not possible to accurately predict body burderns of TNBP and TPHP metabolites. We ran additional simulations to investigate whether fitting all 4 parameters (k1, f1, k2, f2) could lead to a better fit and found this to be the case only for TNBP (shown in the SI of **paper IV**). Still, urine concentrations were underestimated by a factor of 10. For TPHP, no improvements could be observed. This means that the good fit observable for EHDPHP could not be achieved for TPHP with any combination of k and f within the constraints set in the model. Therefore, it is likely that intake was underestimated for TNBP and TPHP to a certain degree. Another reason for the poor fit could lie in unspecific biomarkers. For example, direct exposure to DNBP is possible as the substance itself is produced in volumes of 100-1000 tonnues per year in the EU (ECHA, 2016). Furthermore, DPHP is also a metabolite of EHDPHP and resorcinol bis(diphenylphosphate) (RDP) (Ballesteros-Gómez et al., 2015a, 2015b) and was detected in dust (Ballesteros-Gómez et al., 2016; Mendelsohn et al., 2016). Hence, DPHP might not be the optimal biomarker for TPHP, although no better alternative was suggested. However, it is currently unknown which source of uncertainty (intake or biomarkers) is dominant.

Therefore, a second modelling exercise was performed in order to 1) investigate the magnitude of missing intake that was hypothesized above (results shown in **paper IV**) and 2) determine the likelyhood if missing intake alone could be a plausible explanation for the poor model fit for TNBP and TPHP. Here, the original intake values from Xu et al. (2016) were multiplied with increasing factors until a good fit, define as deviations < 10-fold, was reached. The analysis showed that we probably underestimated total intake for TNBP by a factor of approximately 40 to 200, whereas for TPHP the underestimation of intake was at least 40-fold. These underestimations are fairly high in magnitude and considering a total intake of 2.61 and 4.41 ng/kg/d for TNBP and TPHP respectively, are unlikely to be realistic. Therefore, missing

intake alone is not likely to explain the poor fit for TNBP and TPHP and the selection of biomarker probably plays an important role as well.

Table 6 Geometric means of predicted and observed concentrations of 5OH-EHDPHP, DNBP and DPHP. The range is shown in brackets.

Chemical	Predicted [ng/ml]		Observed [ng/ml]	Ratio Predicted/Observed [-]		
	Urine	Serum	Urine	Serum	Urine	Serum
5OH-EHDPHP	0.06 (5 × 10^{-4}-0.31)	0.08 (5 × 10^{-4}-0.28)	0.07 (0.02-1.3)	0.15 (0.08-0.45)	0.82 (0.03-7.02)	0.5 (0.004-3.36)
DNBP	0.09 (0.007-0.27)	5.5 × 10^{-4} (1.9 × 10^{-5}-0.002)	1.01(0.21-3.76)	0.34 (0.22-0.73)	0.09 (0.006-0.48)	0.002 (5.9 × 10^{-5}-0.008)
DPHP	0.22 (0.06-23.9)	4.6 × 10^{-4} (1.6 × 10^{-4}-0.05)	0.93 (0.21-3.76)	0.33 (0.22-4.99)	0.24 (0.03-65.8)	0.001 (7.5 × 10^{-5}-0.14)

In conclusion, no accurate links between external and internal concentrations for TNBP and TPHP could be established because of missing intake/exposure routes and unspecific biomarkers. It has to be mentioned that although the fit for EHDPHP was regarded as good, uncertainty analysis revealed high uncertainties in the model output (urine and serum concentrations) so results should be regarded with care.

4 Conclusions

The work in this thesis demonstrated that exposure to indoor pollutants such as PEs and OPEs remains an important field to be studied, especially regarding the exposure to alternative plasticizers. **Paper I** showed that traditional phthalate plasticizers are being replaced by alternative plasticizers with more favorable toxicological properties. Nevertheless, their exposure is expected to increase and increasing trends in both use and body burden have been reported, especially for DINCH and DPHP. Human exposure to PEs and DINCH was assessed in **paper II** and it was shown to be relatively well understood for adults in the general population. Intake was estimated to occur mostly via diet, although inhalation and dust ingestion were estimated to be relevant to a certain degree depending on the use and physicochemical properties of PEs. However, dermal exposure was shown to be not well understood and the suitability of hand wipes to represent total dermal uptake needs further investigation. As an alternative, non-invasive matrix, human nails were shown in **paper III** to be unsuitable for replacing urine as a biomonitoring matrix, at least with the current understanding of the links between intake and body burden. Exposure to OPEs, in contrast to PEs, was shown to be still poorly studied and understood (see also conclusions for **paper IV**). Links between external and internal concentrations could not be reliably established for EHDPHP, TNBP and TPHP due to high uncertainties in model parameters and poor fit using literature information based on animal and *in vitro* studies. The reasons for that lay mostly in a combination of missing intake information and unspecific biomarkers. Overall, it became clear that there are large difference between PEs and OPEs regarding the scientific understanding and progress of exposure assessments. Being a group of well-studied compounds, the progress of elucidating key aspects in exposure to PEs in the indoor environment is advanced, whereas understanding exposure to OPEs is still at an early stage.

5 Future perspectives

Although PEs were concluded to be a group of well-studied compounds, there are still aspects to be improved. Firstly, due to the nature of the study population (only adults, age 20-66), conclusions were drawn for the adult general population only. Certainly, a comprehensive dataset with biomonitoring data for high risk groups such as infants or children will be very valuable for future studies as they are likely to be exposed to higher doses and have different uptake patterns as well. This applies not only for PEs but also for OPEs. Secondly, the presence of alternative plasticizers, in particular DPHP and DINCH, should be routinely monitored in environmental, indoor and human matrices because exposure can be expected to increase. Of particular interest are concentrations in PCPs/hand-wipes due to the lack of measurements in general. Dust and especially food should also be monitored as they could be important contributors to total intake. Thirdly, dermal exposure is an uptake route which is still not well studied. Two aspects remain to be discovered: 1) Dermal absorption factors considering skin metabolism and 2) the relevance of hand wipe samples to represent total dermal intake, i.e. how they reflect initial dose and intake. A fourth aspect is the kinetic understanding between intake and concentrations of PEs in non-invasive human matrices. This thesis investigates human nail, however, the same could be conducted for other matrices e.g. hair. Currently, it is unknown what the dominant uptake pathway is and what exposure sources are responsible for it. Future studies could determine the relative importance of uptake via dust or PCP either by mathematical modelling or experimental studies. Also, the following alternative internal uptake pathway could be investigated: Transfer of PEs and/or their metabolites occurs from blood into the nail matrix, which consists of viable, growing cells which later develop into the nail plate and nail bed. This means that internal uptake can be hypothesized to occur before nail plate cells are developed, after which they only act as a "trap" for chemicals.

Regarding OPEs, many scientific gaps still exist. Most importantly, there is a need for the determination of accurate elimination, transformation and excretion kinetics for OPEs and their metabolites in humans. Precise dosing experiments as done for some PEs are not available and currently, the most reliable information comes from *in vitro*

studies using human hepatocytes or liver microsomes. In particular, more (animal) *in vivo* studies or quantitative *in vitro* studies using human cell lines should be performed to reduce uncertainties in human metabolism of OPEs. Of high interested is the determination of human excretion factors for exposure assessment. Although formation fractions could be estimated experimentally in *in vitro* studies by quantifying the fraction of a metabolite that is formed from its parent compound, excretion fractions on the other hand have to either be extrapolated from animal *in vivo* studies or estimated using modelling methods. Furthermore, current biomarkers for TPHP and TNBP were found not to be very specific. There are potentially 2 ways to solve the problem: 1) increase the knowledge in exposure of DPHP and DNBP directly as well as the metabolism yield of other parent OPEs in order to accurately back-calculate the contribution of DPHP and DNBP alone, 2) improve analytical methods in order to identify more specific biomarkers for TPHP and TNBP.

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