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# Multi-pathway human exposure assessment of phthalate esters and DINCH

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ABSTRACT

Phthalate esters are substances mainly used as plasticizers in various applications. Some have been restricted and phased out due to their adverse health effects and ubiquitous presence, leading to the introduction of alternative plasticizers, such as DINCH. Using a comprehensive dataset from a Norwegian study population, human exposure to DMP, DEP, DnBP, DiBP, BBzP, DEHP, DINP, DIDP, DPHP and DINCH was assessed by measuring their presence in external exposure media, allowing an estimation of the total intake, as well as the relative importance of different uptake pathways. Intake via different uptake routes, in particular inhalation, dermal absorption, and oral uptake was estimated and total intake based on all uptake pathways was compared to the calculated intake from biomonitoring data. Hand wipe results were used to determine dermal uptake and compared to other exposure sources such as air, dust and personal care products. Results showed that the calculated total intakes were similar, but slightly higher than those based on biomonitoring methods by 1.1 to 3 times (median), indicating a good understanding of important uptake pathways. The relative importance of different uptake pathways was comparable to other studies, where inhalation was important for lower molecular weight phthalates, and negligible for the higher molecular weight phthalates and DINCH. Dietary intake was the predominant exposure route for all analyzed substances. Dermal uptake based on hand wipes was much lower (median up to 2000 times) than the total dermal uptake via air, dust and personal care products. Still, dermal uptake is not a well-studied exposure pathway and several research gaps (e.g. absorption fractions) remain. Based on calculated intakes, the exposure for the Norwegian participants to the phthalates and DINCH was lower than health based limit values. Nevertheless, exposure to alternative plasticizers, such as DPHP and DINCH, is expected to increase in the future and continuous monitoring is required.

## 1. Introduction

Plasticizers, such as phthalate esters (PEs), are necessary additives in numerous consumer products due to their ability to make plastic materials flexible and durable. PEs are not covalently bound to the polymeric macromolecules. As a result, they can easily leach out and contaminate the surrounding environment, leading to human exposure with adverse health outcomes (Schug et al., 2011; Wormuth et al., 2006). When PEs enter the human body, they are rapidly metabolized to their respective hydrolytic and/or oxidative monoesters, which are further excreted through urine and feces after partial glucuronidation (Koch and Angerer, 2007; Koch et al., 2005; Koch et al., 2013; Leng et al., 2014; Volkel et al., 2016). Despite their fast metabolization and excretion from the human body, people are continuously exposed to PEs since they are ubiquitous in the indoor environment.

Exposure to PEs from indoor air and house dust may have

*Abbreviations:* PEs, phthalate esters; PCPs, personal care products; DMP, dimethyl phthalate; DEP, diethyl phthalate; DiBP, diisobutyl phthalate; DnBP, di-n-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DINP, diisononyl phthalate; DIDP, diisodecyl phthalate; BBzP, benzyl butyl phthalate; DPHP, di(2-propylheptyl) phthalate; DINCH, cyclohexane-1,2-dicarboxylic acid diisononyl ester; PK, pharmacokinetic; A-TEAM, Advanced Tools for Exposure Assessment and Biomonitoring; RSD, relative standard deviation; LOD, limit of detection; DF, detection frequency; DI, daily intake; BMI, body mass index; BSA, body surface area; MPHP, monopropylheptyl phthalate; MMP, monomethyl phthalate; HQ, hazard quotient; RfD, reference dose; TDI, tolerable daily intake

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significant impacts on human health since most people spend a large part of their time indoors, where concentrations of plasticizers are comparatively high (Bergh et al., 2011; Luongo and Ostman, 2016). Therefore, inhalation of air and the inhalable dust fraction, unintended dust ingestion and dust adhered to the skin have to be considered as important pathways for the assessment of exposure. In the case of toddlers, who often crawl on the floor and have more hand to mouth contact, oral and dermal uptake from dust might be of additional relevance (Wensing et al., 2005). This early-life exposure could cause concern, since non-dietary phthalate exposures, such as daily indoor intakes from dust ingestion, inhalation and dermal absorption, were significant associated with allergic sensitization among children with asthma, rhinoconjunctivitis or atopic dermatitis (Beko et al., 2015).

At the same time, the commercial success of plastics and resins as food packaging materials have indicated that diet could be a potentially important source of plasticizer exposure. Since PEs may migrate from packing materials into food and beverages, the contribution of diet to human plasticizer exposure might be significant (Rudel et al., 2011). Breast milk is another important source of PEs for infants, while the hand to mouth behavior and mouthing of plastic toys might additionally contribute to children's exposure (Wittassek et al., 2011).

The use of cosmetics and personal care products (PCPs) is a contributing pathway of human transdermal exposure, mainly for low molecular weight PEs, such as dimethyl phthalate (DMP), diethyl phthalate (DEP), diisobutyl phthalate (DiBP) and di-n-butyl phthalate (DnBP). Many studies (Guo and Kannan, 2013; Koniecki et al., 2011; Wormuth et al., 2006) have analyzed a variety of consumer products, such as fragrances, hair care products, deodorants, nail polishes and body lotions, finding high levels of DEP, among others. Furthermore, the direct transdermal uptake from air is not routinely considered, and has only recently been included in human exposure assessments (Beko et al., 2013; Gaspar et al., 2014). For DEP and DnBP, dermal absorption directly from air may occur at rates that can be comparable to inhalation intake (Weschler et al., 2015; Weschler and Nazaroff, 2014). The total dermal absorption has been estimated using skin wipes from different body spots (e.g. palm, back-of-hand, arm, and head) by Gong et al. (2014) and Shi et al. (2017), who concluded that this pathway contributes significantly to the uptake of PEs.

High molecular weight PEs, such as di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP) have been restricted due to their reproductive toxicity and endocrine disrupting properties (Hauser et al., 2016; Hauser et al., 2006). Certain PEs, like DiBP, DnBP, benzyl butyl phthalate (BBzP) and DEHP, have been prohibited in toys and childcare articles in the European Union, U.S. and Canada (Canada, 2012; EC, 2005; USA, 2008). Since 2015, these chemicals are included in Annex XIV of REACH Regulation EC No. 1907/2006 (EC, 2006), and special authorization is required for any kind of application. Moreover, there is a proposal to restrict the use in articles on the EU market containing these four PEs, individually or in combination, in a concentration in excess of 0.1% *w*/w of the plasticized material (ECHA, 2016).

Due to these strict regulations and the increasing evidence for adverse health effects on humans, there is a need for alternative plasticizers that have favorable migration and toxicity properties. Currently available toxicological data suggest that di(2-propylheptyl) phthalate (DPHP) and the non-phthalate plasticizer cyclohexane-1,2-dicarboxylic acid diisononyl ester (DINCH) do not induce reproductive toxicity or endocrine disruption (Bhat et al., 2014; EFSA, 2006; Furr et al., 2014). There is an increasing use of DINCH after its market introduction in 2002. However, data based on external DINCH exposure measurements are still limited, and only few studies (Fromme et al., 2016; Larsson et al., 2017) have recently determined concentrations of DINCH in dust and children's urine in daycare centers. Also, people are increasingly exposed to DPHP, nonetheless this exposure is considerably lower than other high molecular weight PEs (Schutze et al., 2015a).

Several studies have determined internal human exposure to PEs and DINCH by using metabolites as biomarkers (Giovanoulis et al., 2016; Gomez Ramos et al., 2016; Larsson et al., 2014; Silva et al., 2013). In addition, pharmacokinetic (PK) models have been introduced to predict metabolite concentrations in urine, serum (Lorber et al., 2010; Lorber and Koch, 2013; Schutze et al., 2015b) and nails (Bui et al., 2017), following oral exposure to plasticizers. Biomonitoring methods do not provide any information about the sources of human exposure. They are prone to physiological variability among the different study populations (Clark et al., 2011), and might lead to underestimation of the actual initial exposure (Das et al., 2014). Therefore, there is a need for multi-pathway exposure assessments based on external concentrations in order to complement the available urinary biomonitoring data (Wormuth et al., 2006).

In this study, we determine the presence of PEs and DINCH in environmental (house dust, personal and indoor air), dietary (food) and personal (hand wipes) samples from a Norwegian cohort of 61 adults and their households in the Oslo area. Human intake rates were estimated for all external exposure pathways. The total external intake was compared to back-calculated intakes from previously published biomonitoring data for the same study population (Giovanoulis et al., 2016) as well as to literature information. The relative importance of external uptake pathways is summarized and discussed in detail. Using these methods and the advantages of a comprehensive dataset, we provide a powerful case study for an accurate identification of exposure sources, and we are able to draw conclusions regarding the links between external and internal concentrations.

## 2. Methods

### 2.1. Sampling campaign

The present study is part of the Advanced Tools for Exposure Assessment and Biomonitoring (A-TEAM) project that aims to increase knowledge of internal and external exposure to selected consumer chemicals. The study population consisted of 61 adults (age: 20–66; gender: 16 males and 45 females) living in the Oslo area (Norway). The sampling campaign was conducted during 2013–2014, and indoor environment, dietary and biological samples were collected from each individual participant and their household, during a 24 h period. Information about the home environment, personal and lifestyle characteristics was collected via questionnaires (Papadopoulou et al., 2016).

Indoor air sampling ($n$ = 61) was performed in each participant's living room for 24 h, with a SKC Leland Legacy pump (SKC Inc., Pennsylvania, U.S.) connected to four ENV + SPE cartridges in parallel (200 mg, 6 mL, Biotage, Uppsala, Sweden). At the same time, personal air samples ($n$ = 33) were taken, using a portable SKC 224-PCMTX4 pump (SKC Inc., Pennsylvania, U.S.) connected to one ENV + SPE cartridge (1 g, 25 mL, Biotage Uppsala, Sweden), which was attached close to the participant's face. The participant was asked to carry the sampling device throughout the entire 24 h sampling event (including sleeping hours). The airflow, for both personal and stationary air collection, was set to 1–1.2 L/min for each cartridge. Floor dust samples ($n$ = 60) from the living room were taken separately from each house using a cellulose paper filter fixed in a styrene acrylonitrile container, which was inserted in a holder made of polypropylene (KTM AB, Bålsta, Sweden) and mounted on the nozzle of a vacuum cleaner. All dust filters were weighed under identical conditions, before and right after the sampling procedure. Dust from vacuum cleaner bags ($n$ = 58) from individual household were also collected. The different types of flooring material, from where the dust was collected, were 71% parquet, 13% wood, 8% laminate, 5% PVC, 2% wall to wall carpet and 1%, which in addition to the age, can influence the levels in floor dust. Food samples ($n$ = 61) were collected using a duplicate diet method, where the duplicate portion of all foods consumed over 24 h was homogenized in the laboratory. Hand wipes ($n$ = 61) were collected from both hands of participants, who were recommended not to wash their hands 60 min