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Daily intake of phthalates, MEHP, and DINCH by ingestion and inhalation

Jana M. Weiss [a, b], Åsa Gustafsson [c, d], Per Gerde [d, e], Åke Bergman [d], Christian H. Lindh [f], Annette M. Krais [d, f, *]

[a] Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences, Box 7050, 75007, Uppsala, Sweden
[b] Department of Environmental Science and Analytical Chemistry, Stockholm University, Svante Arrheniusväg 12, 10691, Stockholm, Sweden
[c] Department of Chemistry, Umeå University, SE-901 87, Umeå, Sweden
[d] Swetox, Karolinska Institute, Unit of Toxicology Sciences, Forskargatan 20, 151 36, Södertälje, Sweden
[e] Institute of Environmental Medicine (IMM), Karolinska Institute, Box 287, SE-17177, Stockholm, Sweden
[f] Division of Occupational and Environmental Medicine, Institution of Laboratory Medicine, Lund University, SE-221 85, Lund, Sweden

HIGHLIGHTS

- Five phthalate esters and one monoester (MEHP) could be quantified in all dust samples.
- The EDI of DEHP and MEHP via ingestion of dust for a 21-month old is 727 and 277 ng/kg bw respectively.
- Our modelling data suggest that inhalation is a minor pathway of exposure compared to ingestion.
- The EDI of phthalate esters for adults are 2–12 times lower than for 21-months old.
- Dust is a direct exposure pathway for the transformation product MEHP and should be considered in health risk assessments.

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ABSTRACT

Phthalate esters, suspected endocrine disrupting chemicals, are used in a wide range of applications. Because phthalate esters are not covalently bound, they can easily leach into the indoor environment and associate to dust particles. Thus, exposure may occur through inhalation, ingestion, or contact with the skin. However, it is unclear to what degree indoor dust contributes to the daily intake of phthalate esters.

This study investigates household dust as an exposure pathway for seven phthalate esters, the monoester MEHP, and the plasticizer DINCH. Household dust collected from children's sleeping rooms and from living rooms were analysed using gas and liquid chromatography tandem mass spectrometry. To compare two exposure pathways, different dust particle sizes were generated: a respirable fraction (<5 μm) and an ingested particle fraction in the anticipated size range of skin adherence (<75 μm). Modelling of dust inhalation and ingestion showed that the daily intake of dust-bound phthalate esters was likely to be 2 times (inhalation) to 12 times (ingestion) higher for 21-month-old children than for adults. These children's daily uptake of phthalate esters was 40–140 times higher through ingestion than inhalation. Furthermore, dust may be an exposure pathway for phthalate esters as well as for MEHP. Therefore, phthalate monoesters could be environmental contaminants of their own and need to be considered in health risk assessments.

Abbreviations: Diethyl phthalate, DEP; Di-iso-butyl phthalate, DiBP; Di-n-butyl phthalate, DnBP; Benzylbutyl phthalate, BBzP; Bis(2-ethylhexyl) phthalate, DEHP; Di-iso-nonyl phthalate, DiNP; Di-iso-decyl phthalate, DiDP; Di(2-propyl heptyl) phthalate, DPHP; Di-iso-nonyl cyclohexane-1,2-dicarboxylate, Hexamoll® DINCH®; Mono(2-ethylhexyl) phthalate, MEHP; Mass median aerodynamic diameter, MMAD; Geometric standard deviation, GSD; Brunauer-Emmett-Teller, (BET) method; Coefficient of variation, CV; Limit of detection, LOD; Limit of quantification, LOQ; Tolerable daily intake, TDI; Scanning electron microscopy, SEM.

* Corresponding author. Division of Occupational and Environmental Medicine, Department of Laboratory Medicine, Lund University, 221 85, Lund, Sweden.
E-mail address: annette.krais@med.lu.se (A.M. Krais).

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1. Introduction

Although many studies have investigated the impact of outdoor pollution on human health [IARC, 2013], few studies have investigated the impact of indoor pollution on the human health. Because people spend most of their time indoors, it is crucial to understand how indoor pollutants, including household dust, impact human health. Indoor pollution is largely influenced by outdoor sources, but indoor activities (e.g., cooking, cleaning, and the use of consumer products and building materials) are also sources of indoor pollution [Weschler and Nazaroff, 2008; Schettler, 2006].

As semivolatile organic compounds (SVOC), many indoor pollutants are either present in the gas phase or adsorbed to surfaces or household dust [Weschler and Nazaroff, 2008]. Phthalate esters are SVOCs that are found in a wide range of applications, such as food packaging, building materials, furniture, paints, plastics, cleaning products, cosmetics, and children's toys [Bekö et al., 2013; Dodson et al., 2012; Bornehag et al., 2005]. Because phthalate esters are not covalently bound to the product matrix, they can easily leach into the air [Bergh et al., 2012], food and water [Shi et al., 2012; Gao and Wen, 2016], and they adhere to dust [Bornehag et al., 2005].

Phthalate esters are suspected endocrine disruptors and the phthalate esters bis(2-ethylhexyl) phthalate (DEHP), benzyl butyl phthalate (BBzP), di-n-butyl phthalate (DnBP), and di-iso-butyl phthalate (DiBP) have been recently added to the REACH Candidate List as Substances of Very High Concern (SVHC) [https://echa.europa.eu/candidate-list-table, June 2017].) Several animal studies have linked phthalate esters to asthma [Oie et al., 1997; Hsu et al., 2012; Jaakkola and Knight, 2008; Bornehag et al., 2004], allergic reactions [Bekö et al., 2015; Kolarik et al., 2008; Bornehag and Nanberg, 2010], and birth defects of the male reproductive system [Jeng, 2014]. Furthermore, phthalate esters may be involved in carcinogenesis, cardiotoxicity, hepatotoxicity, and nephrotoxicity [Singh and Shoei-Lung Li, 2011; Wittassek and Angerer, 2008; Ventrice et al., 2013].

Due to the widespread use of phthalate esters, humans are constantly exposed to phthalates through ingestion, inhalation, and skin absorption of indoor dust or contaminated food [Weschler and Nazaroff, 2008; Bekö et al., 2013; Koch et al., 2013]. Phthalate metabolism and type of exposure may differ between children and adults [Wittassek and Angerer, 2008]. Typically, children ingest DEHP via mouthing plastics and inhale or dermally absorb diethyl phthalate (DEP) and BBzP [Koch et al., 2013]. Consequently, robust bio-monitoring reveals phthalate metabolites in blood [Wan et al., 2013], urine [Langer et al., 2014] and breast milk [Fromme et al., 2011]. However, cleavage of the carbon chain of phthalate esters can also occur in the air and in dust by abiotic processes [Heudorf et al., 2007] or by bacteria and fungi [Liang et al., 2008]. Therefore, phthalate monoesters, such as MEHP, could be considered environmental contaminants of their own.

The role of indoor dust particles on the daily intake of phthalates diesters or their monoesters remains unclear and its impact on the development of diseases needs to be investigated, especially in children. As such, this study has the following aims: (i) to study seven phthalate esters, the monoester MEHP, and the alternative plasticizer DINCH in household dust of different particle size fractions, representing hand-to-mouth exposure and inhalation; (ii) to model the exposure of phthalate esters, MEHP, and DINCH via ingestion or inhalation of household dust in small children and adults; and (iii) to analyse and quantify levels of phthalate esters, MEHP, and DINCH in household dust collected in Sweden.

2. Materials and methods

2.1. Chemicals and reagents

All phthalate ester standards, their corresponding D_4-labelled internal standards, as well as phthalate metabolites and their D_4-labelled corresponding internal standards were purchased from TRC Chemicals (Toronto, Canada). Hexamoll® DINCH, here referred to as DINCH, was kindly provided by BASF, Ludwigshafen, Germany. Toluene and Acetonitrile (LC–MS grade) were purchased from Merck (Darmstadt, Germany) and formic acid from Sigma-Aldrich (St Louis, MO, USA). β-Glucuronidase (*Escherichia coli*) was obtained from Roche Diagnostics (Mannheim, Germany). Water was produced by Milli-Q Integral 5 system, Millipore (Billerica, MA, USA).

2.2. Samples

2.2.1. Pooled household dust

Dust samples were collected in schools at three locations in Sweden. Scholars from Skellefteå (n = 16), Örnsköldsvik (n = 13), and Stockholm area (n = 32) provided us with vacuum cleaner bags used to clean their homes. No instructions were given to the people who collected the vacuum cleaner bags. The dust from the three locations were pooled separately for the subsequent sieving process. Briefly, the household dust was separated to a respirable fraction by sieving through six stages of plane woven steel meshes, followed by passage of a cyclone, after which the dust was collected in a filter bag. A final sieving process was further performed using twilled woven steel, yielding the respirable fraction. The whole process was performed under constant air flow and mechanical deagglomeration [Gustafsson et al., 2018].

The method for determining size distribution of the respirable household dust has been previously described [Selg et al., 2010; Selg et al., 2013; Gustafsson et al., 2018]. Briefly, the dust was aerosolized using the PreciseInhale system (Inhalation Sciences Sweden AB, Stockholm, Sweden) and the impaction of dust was performed using a cascade impactor (Marple Andersen, EnVirREC AB, Sweden), following suction of 2 L/min through the aerosol generator system. The mass of dust deposited on the nine stages in the impactor was used to calculate the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD).

Household dust was characterized for size, morphology, and tendency to agglomerate using field-emission scanning electron microscopy (SEM; Carl Zeiss Merlin) equipped with a backscatter electron detector at different values of accelerating voltage (kV) and probe current (pA). The specific surface area was determined using Brunauer-Emmett-Teller (BET) [Gustafsson et al., 2018].

2.2.2. Individual household dust

Phthalate esters in individual household samples were analysed in dust samples from the MiSSE project (FORMAS 210-2012-131, Mixture Assessment of Endocrine Disrupting Compounds [EDCs]). MiSSE investigates the effects of mixtures of EDCs on thyroid function, using cats as a model for human indoor exposure. Dust was sampled from 17 families living in the Stockholm and Uppsala region. Samples were vacuumed from the living room, adult's bedroom, and the child's room using a dust collector (Dustream™, Indoor Biotechnologies Ltd., Wiltshire, UK) fitted with a disposable filter (mesh size 40 μm) attached to a household vacuum cleaner tube. The samples were sieved (1 mm) to isolate the estimated ingestion fraction (0.04–1.0 mm) for cats licking their fur. These dust samples have been analysed for an array of organohalogene compounds [Norrgran Engdahl et al., 2017; Dahlberg and Weiss, 2016]. Here, a small set of samples was selected to demonstrate

the presence and congener profile of phthalate esters in households with children (i.e., 10 living rooms and 5 children's rooms connected to the living rooms). In addition, a questionnaire was used to obtain details on the household, such as type of house, age, flooring, and the type and age of furniture. These methods were designed to investigate possible associations between the chemicals adhered to dust and house and living conditions.

2.3. Chemical analysis

2.3.1. GC-MS/MS analysis

2.3.1.1. Sample preparation. Dust (10 mg) was weighed into a 10 mL glass vial and 1 mL of toluene containing 50 μg of internal standard was added. Samples were sonicated for 30 min at maximal amplitude, centrifuged for 10 min at 3000 r/min, and the supernatants were transferred to a HPLC glass vial (Agilent, Waldbronn, Germany). All glass vials and glass pipettes were heated overnight before use.

2.3.1.2. GC-MS/MS instrumentation and conditions. GC-MS analysis method was adapted from Zou et al. [Zou and Cai, 2013]. Analysis was performed on an Agilent 7890 gas chromatograph coupled to an Agilent 7000B triple quadrupole mass spectrometer (Agilent, Waldbronn, Germany). Samples (1 μL) were injected using an Agilent autosampler unit. The capillary column used was a HP-5MS-UI (15 m × 0.25 mm, 0.25 μm, Agilent, Waldbronn, Germany). Nitrogen was the carrier gas at a flow rate of 1.5 mL/min and helium was used as quenching gas at 2.25 mL/min. The temperature program was as follows: initial temperature 60 °C for 1.5 min; ramp at 20 °C/min to 220 °C and held for 1 min; ramp at 5 °C/min to 280 °C and held for 4 min; injection at oven temperature at 280 °C; and transfer line at 280 °C. Sample injection volume was 1 μL and splitless injection mode was used. Electron impact ionization was performed at 70 eV energy and at a 280 °C ion source temperature. The quadrupole temperature was 280 °C. The MS was operated in selected reaction mode (SRM). Supplementary Table 1 shows the quantifier ions and qualifier ions as well as collision energies for all investigated compounds.

2.3.1.3. Quality assurance/quality control. For quality control, plain silica particles (Ovolin Färg & Byggnadsvård, Örebro, Sweden) were extracted and analysed for background contamination. The silica particles (n = 3 per size fraction) were sieved as described for the dust samples to <75 μm and <5 μm to evaluate possible contamination steps during sieving. NIST house dust material (SRM 2585) samples (n = 3) were analysed for accuracy. Average background levels of clean solvent samples (n = 10) were subtracted from all quantified values. All samples (individual dust samples as well as pooled dust particle fractions) were analysed during the same analytical run.

The instrumental performance using this method was determined by analyses of 10 toluene samples spiked with 50, 100, or 500 ng/mL phthalate esters each. The coefficient of variation (CV) at the three concentration levels of the analysed compounds was below 22%, with the exception of the volatile DEP (CV up to 41%). The CV values as well as mean quantified values at the three concentration levels (50, 100, and 500 ng/mL) are shown in Supplementary Table 2.

Excellent linearity was seen for the calibration standards ranging from 50 to 1000 ng/mL in toluene. The correlation coefficient (r^2) observed for all eight phthalate esters and DINCH was above 0.998. The analytical performance was determined by analysis of 10 different blank toluene samples spiked with internal standard. The limit of detection (LOD) was calculated as three times the standard deviation of the ratio between the peak area at the analyte retention time and the peak area of internal standard, divided by the slope of the calibration line. The limit of quantification (LOQ) was similarly determined as 10 times the standard deviation of the ratios. The determined LOD for all analysed plasticizers ranged from 0.2 to 12 ng/mL and LOQ values were determined to be between 0.5 and 41 ng/mL (Supplementary Table 3).

2.3.2. LC-MS/MS analysis of MEHP

2.3.2.1. Sample preparation. Dust (10 mg) was weighed into a 10 mL glass vial and 1 mL of acetonitrile was added. Samples were sonicated for 30 min at maximal amplitude and centrifuged for 10 min at 3000 r/min and 0.2 mL of supernatants were transferred to a glass insert (Nr 08091081, Teknolab Sorbent, Göteborg, Sweden) of a 96-well Rittner plate (Nr 08050894, Teknolab Sorbent, Göteborg, Sweden). Beta-glucuronidase was used to hydrolyse possible glucuronide conjugates of DEHP metabolites. Therefore, 0.1 mL of ammonium acetate (pH 6.5) and 0.01 mL glucoronidase (Escherichia coli) was added and the solution was incubated at 37 °C for 30 min [Bornehag et al., 2015]. After adding 0.025 mL of a 50:50 (vol:vol) water/acetonitrile and 0.025 mL of D_4 labelled MEHP (internal standard), the plates were centrifuged for 10 min at 3000 rpm before injection.

2.3.2.2. LC-MS/MS instrumentation and conditions. Samples were analysed for five DEHP metabolites: MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), mono-(2-ethyl-5-oxohexyl)phthalate (5-oxo-MEHP), mono-(2-ethyl-5-carboxypentyl)phthalate (5-cx-MEPP), and mono-[2-(carboxymethyl), hexyl]phthalate (2-cx-MMHP). These analyses were performed according to a method previously developed in our lab [Bornehag et al., 2015]. A C18 column (2.1 mm i.d. × 50 mm; Genesis Lightn; Grace, Deerfield, IL, USA) was used before the injector to reduce the interference of contaminants during the mobile phase. A C18 column (1.5 μm, 2.0 mm i.d. × 30 mm VisionHT; Grace) was used for analysis and the mobile phases were water and acetonitrile with 0.1% formic acid. The samples were analysed on a Shimadzu UFLC system (Shimadzu Corporation, Kyoto, Japan) coupled to a QTRAP5500 (triple quadrupole linear ion trap mass spectrometer) equipped with a TurboIon Spray source (AB Sciex, Foster City, CA, USA). All samples were analysed in duplicates.

2.4. Daily intake modelling

2.4.1. Hand-to-mouth exposure

The daily intake of each phthalate and DINCH from the size fraction <75 μm was calculated with the estimated intake of 40 mg dust/day and 20 mg dust/day for children and adults, respectively, taken from the Child Specific Exposure Factors Handbook [US EPA, 2017]. The estimated bodyweights of 12 kg, 15 kg, and 75 kg were used for 21-month-old children, three-year-old children, and adults, respectively. The daily intake of chemicals by hand-to-mouth behaviour followed by a gastrointestinal exposure was calculated according to equation (1) [Bekö et al., 2015]:

$$DIgi = \left(\frac{Pgi}{1000}\right) Cgi/bw, \quad (1)$$

where *DIgi* is the daily intake of the chemical compound (μg/day) following gastrointestinal (gi) exposure, *Pgi* is the mass (mg) of Particles that is ingested each day, *Cgi* is the concentration of the chemical on the dust, and *bw* is the bodyweight (kg).

2.4.2. Inhalation exposure

The deposition fraction of household dust in the respiratory tract was estimated using the multiple-path particle dosimetry

model (MPPD v 2.1, 2016: http://www.ara.com/products/mppd.htm) by providing the input parameters for the airborne size distribution as mass median aerodynamic diameter and geometric standard deviation for each of the respirable dust samples from Stockholm, Skellefteå, and Örnsköldsvik. In "particle properties", the default setting for density was applied to 1 g/cm^3: "number of particles calculated = single" and "inhalability = no". The total deposition (the head, trachea-bronchial, and pulmonary regions) was calculated with the default setting "airway morphometry" for humans by applying "age-specific symmetric" for the 21-month-olds, three-year-olds, and adults. Respiratory frequency was set at 28, 24, and 14 per min and tidal volume was set at 0.08, 0.12, and 0.48 L for 21-month-olds, three-year-olds, and adults, respectively. The bodyweights used to measure the daily intake following inhalation were 12 kg (21-month-olds), 15 kg (three-year-olds), and 75 kg (adults). The exposure scenario was fixed to oronasal-mouth breather and the exposure conditions were calculated based on a worse-case scenario with regard to a constant exposure and deposition only (i.e., no clearance included in the calculations). Particle concentrations for low exposure and high exposure scenarios were taken from earlier studies using particle concentrations of 0.01 mg/m^3 with a particulate matter ($PM_{2.5}$) [Morawska et al., 2013] and 0.105 mg/m^3 (PM_4), respectively [Weschler and Salthammer, 2008]. The calculations for the mass of particles inhaled per 24 h is shown in equation (2):

$$Pinh = \left(\frac{RR\ TV}{1000}\right)\ t\ Cp\ DFtot, \quad (2)$$

where *Pinh* is the mass (mg) of particles inhaled and deposited during the chosen study interval (24 h), *RR* is the Respiratory Rate (min), *TV* is the Tidal Volume (Litre), *t* is the 24 h exposure duration of the study interval (minutes), *Cp* is the particle concentration (mg/m^3), and *DFtot* is the total Deposition Fraction (i.e., tracheobronchial + alveolar + head). The daily intake of the phthalate esters, MEHP, and DINCH following inhalation exposure of dust particles was calculated according to equation (3):

$$DIinh = \left(\frac{Pinh}{1000}\right) Cinh/bw, \quad (3)$$

where *DIinh* is the daily intake of the chemical compound (μg/24 h) following inhalation exposure (inh), *Pinh* is the mass of dust particles inhaled (see equation (2)), *Cinh* is the concentration of the chemical compound on the dust (μg/mg dust), and *bw* is bodyweight (kg).

The inhaled particle mass for 24 h was calculated by multiplying the volume of air inhaled by the air concentration of dust. The total mass of deposited dust was assessed using the size-weighted deposition fraction of inhaled dust as calculated from the MPPD model multiplied by the mass of particles inhaled per 24 h.

3. Results & discussion

In this study, we compared the daily intake – gastrointestinal versus inhalation – of phthalate esters, MEHP, and DINCH via household dust. Consequently, a large quantity of household dust was collected from vacuum cleaning bags from resident homes to produce two dust particle fractions: one fraction with an average diameter <75 μm (cut off) and one fraction with a diameter <5 μm. These fraction sizes correlate to hand-to-mouth and inhalation exposure, respectively. Particles with a diameter smaller than 75 μm are likely to adhere to skin [Choate et al., 2006; Yamamoto et al., 2006], and particles with a diameter smaller than 5 μm are likely to be inhaled [Oberdörster et al., 2005].

3.1. Particle size distribution and physical characterization of pooled dust samples form three locations in Sweden

The size, morphology, size of distribution, and surface area were determined for household dust collected from three Swedish regions. Fig. 1 A–C shows representative SEM pictures that reveal the heterogeneous composition of the individual dust samples.

The larger size fractions (<75 μm) consisted of flakes, spherical particles, and fibres of different size ranges, whereas dust particles in the respirable size mainly consisted of spherical particles that were agglomerated. Cao et al. produced similar SEM pictures where smaller particles adhered to larger particle surfaces as well as different shapes such as fibres, flakes, and particles [Cao et al., 2013]. A previous study from our lab showed that the respirable fraction from the Stockholm area contained a heterogeneous mixture of silicon dioxide (quartz), calcium carbonate (calcite), and organic matter, consisting mainly of bacteria and fungi as well as skin fragments [Gustafsson et al., 2018].

Particle characteristics are shown in Supplementary Table 5. The MMAD of the respirable fraction from Stockholm, Skellefteå, and Örnsköldsvik was determined to be 3.7 ± 0.15 μm (GSD, 2.3 ± 0.03 μm), 1.5 ± 0.36 μm (GSD, 2.2 ± 0.17 μm), and 2.4 ± 0.34 μm (GSD, 2.2 ± 0.21 μm), respectively. The average specific surface areas from the BET measurement of the particles in fraction <75 μm were measured as 0.15 m^2/g (Stockholm), 0.74 m^2/g (Skellefteå), and 0.61 m^2/g (Örnsköldsvik). The smaller respirable fractions were found to have surface areas of 2.5 m^2/g, 4.5 m^2/g, and 4.2 m^2/g for Stockholm, Skellefteå, and Örnsköldsvik, respectively. These results support previous findings that report a larger surface-to-volume ratio for smaller particles compared to larger sized particles [Mudunkotuwa and Grassian, 2011].

3.2. Chemical analysis of phthalate esters, MEHP, and DINCH on indoor dust

As phthalate esters are abundant indoor air contaminants, quality controls were included to quantify laboratory background levels. Silica particle samples in the two comparative size ranges of the analysed dust particles (n = 3 per size range) and reference dust material (NIST SRM 2585, n = 3) were analysed. No phthalate esters could be detected on the larger (75 μm) silica particles, whereas the silica particles in the respirable size (<5 μm) contained 12 μg/g dust (37 nmol/g) BzBP, 250 μg/g dust (640 nmol/g) DEHP, 5.2 μg/g dust (12 nmol/g) DiNP, 12 μg/g dust (36 nmol/g) DPHP, as well as 31 μg/g dust (93 nmol/g) of the monoester MEHP (Fig. 2 and Supplementary Table 3). Reported levels below three times the analytical blanks are indicated with an asterisk in Supplementary Table 3 and should be considered below LOD.

The phthalate levels in the NIST household dust material (SRM 2585) agreed with earlier studies – i.e., 72% (DnBP), 82% (BzBP), and 75% (DEHP) – compared to the average of the reported values (Supplementary Table 3) [Bergh et al., 2012, Mercier et al., 2014; Luongo and Östman, 2016; Larsson et al., 2017]. Due to high background contamination, the levels for DEP, DiBP, DnBP, DiNP, and DiDP were below detection limits but were determined in the other reports [Bergh et al., 2012, Mercier et al., 2014; Luongo and Östman, 2016; Larsson et al., 2017]. The sample amount used in this study was low (10 mg) compared to the other studies, analysing between 75 mg [Luongo and Östman, 2016] up to 200 mg [Mercier et al., 2014] of reference dust. This limitation affects the LOD/LOQ as well as the accuracy of the reported values. Also, the extraction method (pressurized liquid extraction, microwave-assisted extraction, or repeated sonication), extraction solvent (acetone, hexane, dichloromethane, or toluene), and the use of clean-up or not (SPE florisil) differs between the studies reporting phthalate

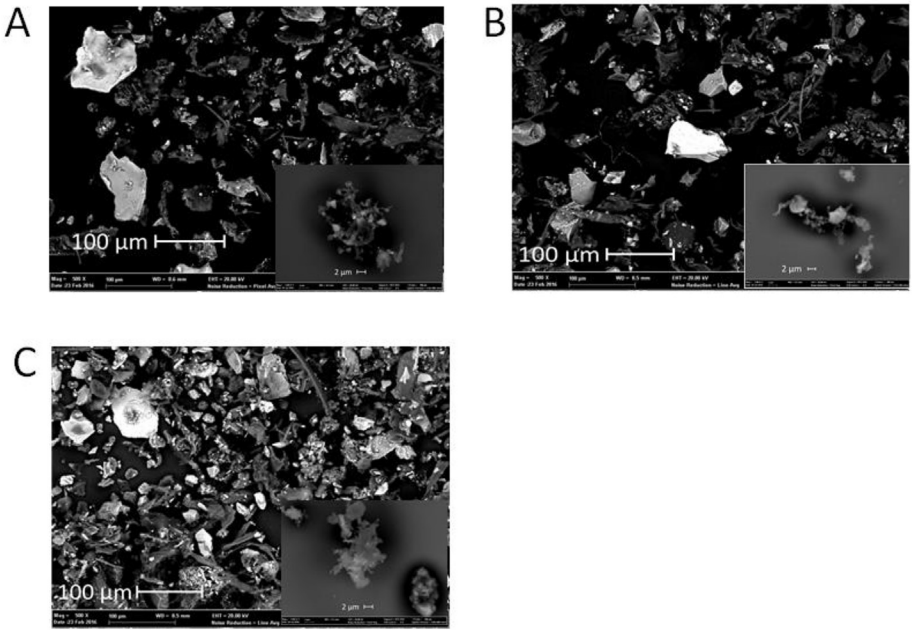

Fig. 1. Visual characterization of dust using scanning electron microscopy (SEM): Stockholm (A), Skellefteå (B), and Örsnköldsvik (C).

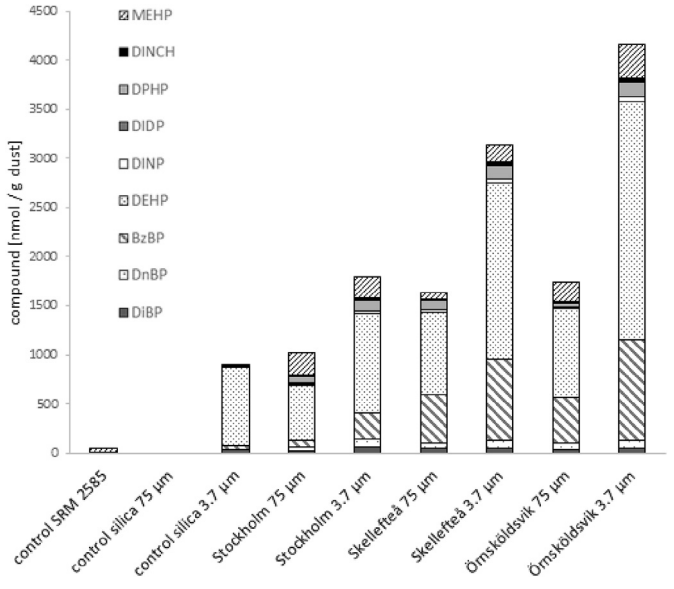

Fig. 2. Levels of phthalate esters, MEHP, and DINCH [in nmol/g dust] pooled dust particles with diameter of 75 µm and 3.7 µm as well as matching controls. Values are given as average of three consecutive analytical runs per sample.

ester analysis of the NIST house dust material (SRM 2585). Despite the variance, the analysis of phthalate esters in dust is rather straightforward. The levels are high enough to allow for a simple extraction. Moreover, as no pre-concentration or clean-up step is needed, our study avoided another source of contamination.

3.3. Regional differences of levels of phthalate esters, MEHP and DINCH on indoor dust

The phthalate esters DiBP, BzBP, DEHP, DINP, and DPHP as well as the monoester MEHP could be quantified in all dust samples: DnBP (73%), DIDP (80%), and DINCH (73%) in the majority of the samples. DEP was below detection limit in all samples.

DEHP was found in the highest levels in dust from all regions (Fig. 2). DEHP concentrations ranged from 218 µg/g dust (556 nmol/g) for Stockholm to 328 µg/g dust (840 nmol/g) for Skellefteå to 355 µg/g dust (909 nmol/g) for Örnsköldsvik in the larger dust particle size (75 µm diameter) (Fig. 2 and Supplementary Table 3). Although these DEHP concentrations were comparable to dust analyses from other studies, values were mostly calculated as median values, whereas the data of this study is represented as mean values of pooled samples. A study from California reported DEHP in concentrations of 386 µg/g dust (100 µm dust particles, median, n = 11) [Hwang et al., 2008], while a study from Canada found DEHP levels of 347 µg/g dust (80 µm dust particles, median, n = 38) [Kubwabo et al., 2013]. Dust particles from Germany (63 µm diameter particles) showed slightly higher DEHP values, with 515 µg/g dust (median, n = 252) [Becker et al., 2004] and 604 µg/g dust (median, n = 30) [Abb et al., 2009].

On the dust particles in the respirable size fraction, we found DEHP in concentrations of 396 µg/g dust (1015 nmol/g) for Stockholm, 700 µg/g dust (1791 nmol/g) for Skellefteå and 949 µg/g dust (2429 nmol/g) for Örnsköldsvik (Fig. 2 and Supplementary Table 3). Those DEHP levels were similar to other studies from Sweden where settled dust was collected from residential homes, with DEHP concentrations of 770 µg/g dust (median, n = 346) [Bornehag et al., 2005] and 680 µg/g dust (median, n = 10) [Bergh et al., 2011]. The second most abundant phthalate ester to be found in dust from all regions was BzBP, ranging from 23 µg/g dust (73 nmol/g) in the larger size fraction from Stockholm to 318 µg/g dust (1019 nmol/g) in the respirable size fraction from Örnsköldsvik. These levels are slightly higher than BzBP concentrations from other studies: 135 µg/g dust (median, n = 346) [Bornehag et al., 2005], 17 µg/g dust (median, n = 10) [Bergh et al., 2011], 25.8 µg/g dust (France, size of 100 µm dust, median, n = 7) [Mercier et al., 2014], 15.2 µg/g dust (median, n = 30) [Abb et al., 2009], and 49.6 µg/g (median, n = 38) [Hwang et al., 2008]. The levels of DiDP ranged from 0.1 to 0.6 µg/g dust, which is low compared to other studies that detected levels of 45 µg/g dust [Bornehag et al., 2005] and 4 µg/g dust [Bergh et al., 2011].

In general, smaller particles showed a higher content of phthalate esters than larger particles on a molecular basis. This difference is likely to be explained by the higher ratio of surface/mass of the smaller particles [Mudunkotuwa and Grassian, 2011]. When comparing the levels of phthalates between cities, Örnsköldsvik followed by Skellefteå showed higher phthalate levels of the "older" phthalate esters DnBP, DiBP, BzBP, and DEHP compared to dust particles isolated from the Stockholm region. This difference was observed for both particle size fractions. No such trend was visible for the more recently introduced phthalate esters DiNP, DiDP, and the alternative plasticizer DINCH. DIDP levels were close to the detection limit in all samples.

Phthalate diesters can degrade to monoesters in the environment by abiotic processes [Heudorf et al., 2007] or by bacteria and fungi under aerobic, anoxic, and anaerobic conditions [Liang et al., 2008]. In the dust samples analysed, MEHP, but none of the other main DEHP metabolites [Koch et al., 2006] – i.e., 5OH-MEHP, 5oxo-MEHP, 5cx-MEPP or 2cx-MMHP – could be detected. Fig. 2 shows that MEHP levels were found in all dust particle samples in levels ranging from 97 nmol/g dust (Stockholm, 75 μm particles) to 461 nmol/g dust (Örnsköldsvik, respirable fraction) (Supplementary Table 3).

With the exception of dust particles collected from the Stockholm area, where MEHP levels were similar in the smaller and larger particle ranges, MEHP was usually found to be 3- to 8-fold (on a molar basis) lower compared to the corresponding parent compound DEHP. Similar to our findings on phthalate ester distribution (see above), smaller particles showed a higher content of MEHP than larger particles, except in dust from Stockholm.

The presence of MEHP in dust suggests that exposure occurs via metabolism of diesters and that MEHP may be a contaminant of its own. We hypothesized that the transformation of DEHP to its monoester could be caused by microorganisms within the dust, as analysis of the dust from the Stockholm area [Gustafsson et al., 2018] has shown the presence of several bacteria and fungi. Hydrolysis is another reaction that may occur in abiotic environments and could contribute to the formation of monoesters [Wolfe et al., 1980].

MEHP has been shown to induce apoptosis of germ cells [Lambrot et al., 2009] as well as DNA damage in sperm cells [Hauser et al., 2007]. Additionally, MEHP, but not DEHP or other tested phthalate esters, has a weak potency (inhibition concentration 32 μM) to competitively bind to the thyroid hormone transport protein transthyretin (TTR) [Ouyang et al., 2017]. The capability of phthalate esters to disrupt the levels of circulating thyroid hormones have been reported and phthalate monoesters may affect thyroid function [Boas et al., 2012; Meeker and Ferguson, 2011].

3.4. Prediction on daily intake of phthalate esters, MEHP, and DINCH

As we spend most of our time indoors, it is of great importance to investigate how dust exposure influences the ingestion and inhalation of phthalate esters and their monoesters. Small children and fetuses are most vulnerable due to their sensitive developing stages and their high exposure in relation to their bodyweight [Heudorf et al., 2007; Wittassek and Angerer, 2008; Giovanoulis et al., 2016]. Small children are especially prone to ingesting dust due to their hand-to-mouth behaviour, suggesting a constant exposure to various compounds, as has recently been shown with the exposure to PBDEs [Harrad, 2010].

The daily intake of phthalate esters, MEHP, and DINCH deposited in the airways following inhalation was calculated using the MPPD model combined with the measured particle size distribution of MMAD and GSD for each of the respirable fractions from Stockholm, Skellefteå, and Örnsköldsvik (Supplementary Table 5). The MPPD model is a freely available well-established model used to determine the deposited fraction of hydrophobic spherical aerosol particles in airways [National Institute for Public Health and the Environment, 2002]. The advantage of using this model is that the exposure dose of chemicals is based on the actual deposition of particles; however, many studies calculate the chemical exposure based on the total volume inhaled each day. The prediction on daily intake was based on the deposition of the two size fractions and the measured levels of each chemical compound on the particles. The concentration of particles is highly variable and depends on indoor activity [Isaxon et al., 2015]. In this study, we used two particle concentrations representing a high exposure and low exposure scenario [Morawska et al., 2013; Weschler and Salthammer, 2008]. In addition, the ingestion exposure depends on activity patterns and behaviours such as how frequently children put their hands in their mouth or lick their hands, toys, etc. In this study, we used the recommended values for daily dust ingestion (mg/day) taken from the latest publication from US EPA [US EPA, 2017]. Deposition of dust in children was modelled following hand-to-mouth behaviour compared to inhalation, and daily intake from the gastrointestinal tract was estimated with 40 mg of dust (children) and 20 mg of dust (adults) [U.S. EPA, 2017].

The estimated daily intake for a 21-month-old child exposed to dust from Stockholm resulted in highest exposure to DEHP (727 ng/kg bw) by dust ingestion followed by the DEHP metabolite MEHP (277 ng/kg bw), BzBP and DPHP (77 ng/kg bw), DnBP (37 ng/kg bw), DINCH (33 ng/kg bw), DINP (22 ng/kg bw), DiBP (21 ng/kg bw), and DIDP (2 ng/kg bw) (Supplementary Table 6A-C). The corresponding daily intake by ingestion of dust for adults was calculated for DEHP (58 ng/kg bw), MEHP (22 ng/kg bw), BzBP and DPHP (6 ng/kg bw), DnBP and DINCH (3 ng/kg bw), DINP and DiBP (2 ng/kg bw), and DIDP (0.1 ng/kg bw) (Supplementary Table 6A-C). These findings indicate that a 21-month-old child may be exposed to these chemicals via ingestion at an amount that is 12.5-fold higher than an adult.

The estimated daily intake for dust inhalation was calculated based on a worse-case scenario of high particle concentration (0.1 mg/m^3) and actual particle deposition in the lungs. For a 21-month-old child, the estimated deposition in the lungs was found highest for DEHP (8.52 ng/kg bw), followed by BzBP (1.81 ng/kg bw), MEHP (1.76 ng/kg bw), DPHP (0.75 ng/kg bw), DnBP (0.49 ng/kg bw), DiBP (0.34 ng/kg bw), DINCH (0.28 ng/kg bw), DINP (0.22 ng/kg bw), and DIDP (0.01 ng/kg bw). The corresponding dose in adults was 2.2-fold lower compared to a 21-month-old child following inhalation. The comparison of the daily intake of phthalate esters, MEHP, and DINCH resulting from hand-to-mouth compared to inhalation exposure from the Stockholm area is expressed as an x-fold ratio and presented in Fig. 3 A–B and Supplementary Table 6.

Results for dust from the Stockholm region were calculated for high (Fig. 3A) as well as low (Fig. 3B) dose exposure scenarios using particle concentrations of 0.01 mg/m^3 [Morawska et al., 2013] and 0.105 mg/m^3, respectively [Weschler and Salthammer, 2008]. The exposure profile patterns for the three locations are similar; the results from Skellefteå and Örnsköldsvik are presented in Supplementary Table 6. Our calculations revealed that 21-month-old children, compared to three-year-old children, were exposed to more phthalate contaminated dust. In addition, we found that adults were the least affected group. These differences are due to a higher respiratory frequency [Zota et al., 2017] and higher estimated daily intake of dust (mass) for children (40 mg/day) than for adults (20 mg/day) [U.S, EPA, 2017]. These results agree with previous studies that show young children may be at greater risk of exposure to contaminants than adults [Lunder et al., 2010; Mitro

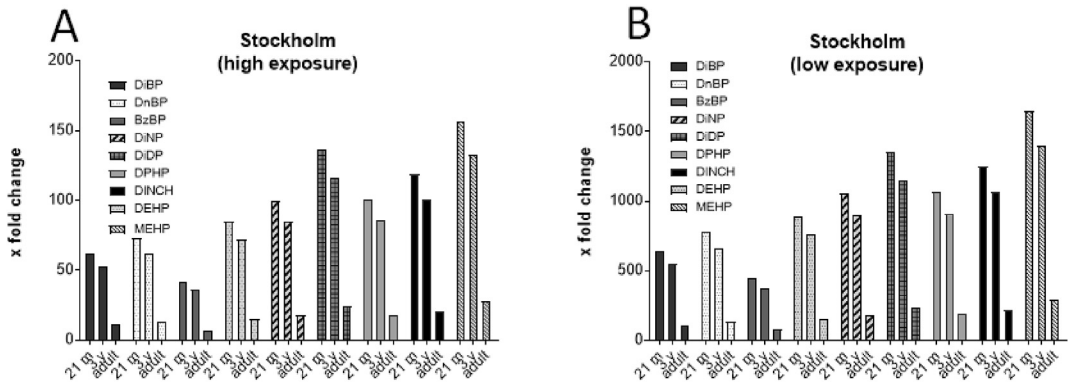

Fig. 3. Multiple-Path Particle Dosimetry (MPPD) model on daily intake of phthalate esters and MEHP: x-fold higher intake of phthalate esters from Stockholm dust, comparing hand-to-mouth with inhalation intake, calculated for the high particle exposure (A) versus low particle exposure scenario (B).

et al., 2016; Stapleton et al., 2012].

The ratio for hand-to-mouth versus deposition by inhalation from Stockholm dust in a 21-month-old child (high exposure scenario, Fig. 3A and Supplementary Fig. 3) was calculated to constitute a 40- to 80-fold increase for phthalate esters with low molecular weight (DiBP, DnBP, BzBP, and DEHP) and a 100- to 140-fold increase for the phthalate esters with higher molecular weight (molecular weight above 418 g/mol, such as DiNP, DiDP, DPHP, and DINCH). The corresponding values for MEHP coated particles was calculated as a 160-fold increase (high exposure scenario, Fig. 3A).

All together the sum of phthalate esters and MEHP that may be ingested and inhaled each day by a 21-month-old child was calculated to be 1.252 μg/kg bw, whereas an adult was estimated to ingest 0.105 μg/kg bw (Supplementary Table 6A, Stockholm dust). The Tolerable Daily Intake (TDI μg/kg bw/day) for phthalates has been established to be 500 μg/kg bw/day (BzBP), 150 μg/kg bw/day (DiNP and DiDP), 50 μg/kg bw/day (DEHP), and 10 μg/kg bw/day (DiBP and DnBP), indicating that the total daily exposure to phthalate esters, MEHP, and DINCH by dust ingestion and dust inhalation may be well below the proposed TDIs [Cheng et al., 2016].

The human lung consists of a large surface area (50–100 m^2) [BéruBé et al., 2009] that is in contact with 3.3 m^3 (21-month-old children), 4.4 m^3 (three-year-old children), and 9.6 m^3 (adult) inhaled air each day (MPPD Default settings). Dust concentration in air has been measured to be 10.6–54 μg/m^3 (particulate matter size 2.5 μm) and 18–140 μg/m^3 (particulate matter size 4 μm) [Morawska et al., 2013; Weschler and Salthammer, 2008], suggesting a large amount of dust is in contact with the lungs each day [Borm et al., 2015; Gerde et al., 2001]. Due to the short distance of the air blood barrier, it is likely that some chemicals desorb from the dust and pass over to the blood system [Gerde et al., 2001; Oberdörster et al., 2005]. Especially small particles, respirable size range <1 μm, are of high concern as they can penetrate deep into the lung, carrying a larger surface area than similar masses of larger-sized materials [Morawska et al., 2013; Butte and Heinzow, 2002]. As the ratio of surface area per mass increases, a greater amount of chemicals could be absorbed to the surface and thus more chemicals could come into contact with the surrounding lung tissue.

Several factors influence the estimation of inhalation uptake, such as the deposition of particles, airborne concentrations, or the total volume of air that is inhaled, ranging from 4.2 m^3/day (this study) to 10.9 m^3/day [Bekö et al., 2013]. We calculated the inhalation exposure based on the measured levels of compounds found in the respirable size fraction of dust that can reach the lower region of the airways. It is important to analyse the particle fraction that is relevant for inhalation exposure [Luo et al., 2014] as larger particles (>10 μm) are deposited in the head and rarely reach the respirable region [Butte and Heinzow, 2002]. Calculating the data without considering the deposition as well as increasing the inhaled volume will lead to overestimation of inhalation exposure.

3.5. Analysis of individual household dust samples

Individual dust samples were analysed to demonstrate the variance of phthalate esters, MEHP, and DINCH concentration in common households with children. A few samples were selected from the MiSSE project, containing dust samples from 10 living rooms and 5 children's room. To investigate possible associations with life style factors or house conditions, a questionnaire provided details about the house, flooring, and furniture. Fig. 4 and Supplementary Table 4 show the amounts of phthalate esters present in dust from children's rooms and living rooms of the investigated houses.

DEHP was found in the highest levels (on a molar basis), followed by DINCH, DnBP, and DPHP. The levels in the individual samples were comparable to the pooled dust sample from the Stockholm region, indicating that concentrations found in common households were similar. Weschler et al. suggested that repeated

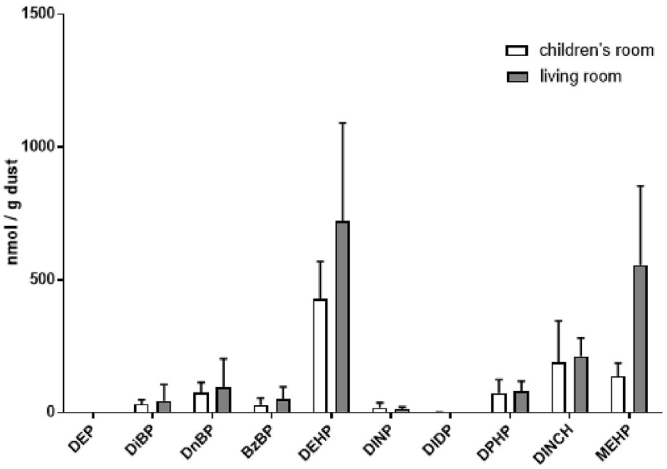

Fig. 4. Levels of phthalate esters and MEHP in individual household dust samples (nmol/g dust), average of all samples. Standard deviation was calculated from dust samples from living rooms (n = 10) and children's rooms (n = 5).

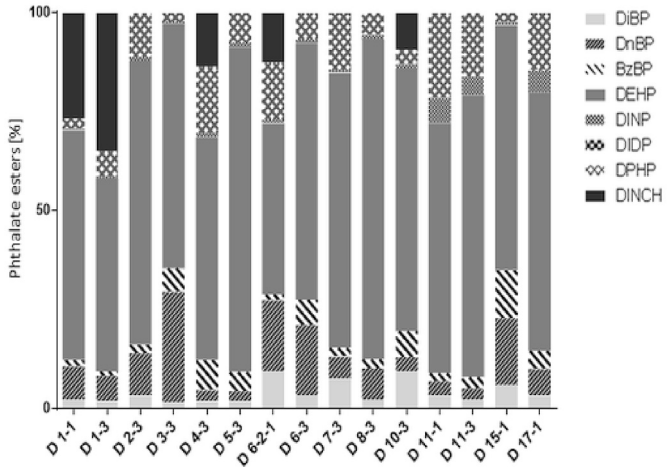

Fig. 5. Distribution of phthalate esters per individual dust sample.

desorption and adsorption cycles of indoor air pollutants may lead to the production of surface films of a mixture of organic chemicals. These films would be similar within the households as many of the organic compounds are derived from the human occupants themselves, from occupant activities, or from materials containing semivolatile compounds [Weschler and Nazaroff, 2017].

In eight of the 15 samples, MEHP could be quantified, with average levels of 556 ± 298 nmol/g dust (n = 5) in living rooms and 138 ± 49 nmol/g dust (n = 3) in children's rooms (Fig. 4 and Supplementary Table 4). MEHP was not detectable in the larger silica control particles (cut off <75 μm), but it was present in the respirable size fraction with 93 nmol MEHP/g dust, probably due to contamination during processing of the dust (see above).

In general, the levels of phthalate esters, MEHP, and DINCH were found to be lower in the children's rooms compared to the living rooms. This observation was not significant for any of the compounds individually, probably due to the small number of samples. Due to EU restrictions, DEHP, DnBP, and BBzP have been replaced by alternative compounds such as DPHP and DINCH [Ventrice et al., 2013]. However, DEHP still dominates the global market; consequently, DEHP was the most abundant phthalate ester measured in this study. The phthalate levels in the individual dust samples analysed ranged between 0.6 nmol/g dust (DIDP, living room) and 1552 nmol/g dust (DEHP, living room).

The patterns between the households did not differ significantly (Fig. 5); DEHP always dominated the profile, with an average share of 58% (children's rooms) and 67% (living rooms). DEHP levels ranged between 43% and 82%, with percentages calculated as levels (nmol/g dust) compared to the total concentration (Fig. 5). BzBP, DnBP, DPHP, and DINCH were also found rather frequently, but the presence of DINCH was sparser (quantified in five of 15 samples). DINCH could constitute up to 35% in some samples, but in the majority of the samples it was below 9.3% of the total phthalate content (Fig. 5).

The wide range of applications of phthalate esters as well as the small sample numbers made any correlation to life style factors or building materials difficult. Previous studies handling larger datasets have established correlations between phthalate ester emissions and toys, plastics, consumer products, and building materials. DnBP and BzBP have been detected in soaps, lipstick, pillow cases, dryer sheets, shaving creams, and cleaning products [Dodson et al., 2012]. BBzP and DEHP levels in household dust could be correlated to the use of PVC in flooring and wall material [Carlstedt et al., 2013; Bornehag et al., 2005; Dodson et al., 2012].

4. Conclusions

In this study, we analysed household dust for seven phthalate esters, the phthalate monoester MEHP, as well as the alternative plasticizer DINCH. Our data show that dust may be a carrier of phthalate esters and their monoesters and this contaminated dust can enter the body via ingestion, inhalation, and skin absorption. Therefore, phthalate monoesters, such as MEHP, could be considered environmental contaminants on their own, and they need to be considered in health risk assessments. Furthermore, this study shows that for 21-month-old children the daily intake of dust-bound phthalate esters is estimated to be between 40- to 140-fold higher via ingestion compared to inhalation (high particle exposure scenario), whereas the intake of MEHP was calculated to be as much as 160 times higher by ingestion. The daily intake in 21-month-old children was about 2times (inhalation) to 12 times (ingestion) higher compared to adults. These data suggest that the inhalation route may constitute just a minor pathway of exposure to dust particles and attached pollutants. The role of indoor dust for the daily intake of phthalate esters or their monoesters remains unclear, and new insights are needed to fully understand the impact of dust on the development of diseases in children.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.chemosphere.2018.05.094.

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