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CHARACTERIZING CHEMICAL EXPOSURE – FOCUS ON CHILDREN'S ENVIRONMENT

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ABSTRACT

Children are constantly exposed to chemicals in food, water, dust, air and consumer products. Compared to adults, children often have a higher exposure to chemicals due to physical and behavioural factors. Because of their unique exposure patterns, exposure assessments in adults are not directly transferrable to children. Therefore, there is a need for exposure assessments performed for children, with focus on the environments were children spend a large part of their time.

The overall objectives of this thesis were to find an approach to overview existing exposure information and to generate new knowledge about chemical exposures in children. In addition, the thesis aims to identify and evaluate the importance of different exposure sources, such as foods, personal care products and indoor environments, for children's chemical exposure.

In **study I,** we developed an automatic classifier with the ability to retrieve and categorize published exposure information, based on data presented in scientific abstracts. In this study, a taxonomy for exposure information was created and nearly 3700 abstracts relevant for chemical exposure were manually annotated. Based on this annotated corpus, Natural Language Processing (NLP) techniques were used to extract semantic and syntactic features relevant for scientific texts on chemical exposure. Using these features, a supervised machine learning algorithm was trained to automatically classify abstracts according to the structure of the exposure taxonomy. The performance of the developed classifier was generally good and its applicability was demonstrated in several case studies. In conclusion, this automatic classifier has potential to constitute the foundation for a text mining tool to extract relevant exposure information from large amounts of text.

In **study II,** we used a harmonized protocol to study the exposure to phthalates, BPA, parabens and triclosan in 98 Swedish mothers and their children (6-11 years old). Urine samples were collected and the mothers answered a questionnaire about their residential environment, sociodemographic factors, and the mother and child's dietary habits and use of personal care products. Different foods were the main exposure determinants for most phthalates and BPA, whereas use of personal care products and cosmetics were the major determinants for the exposure of parabens and diethyl phthalate (DEP). Children had higher internal levels of most phthalates and BPA, than their mothers, reflecting their higher exposure to chemicals originating from foods and the indoor environment. The mothers had higher levels of parabens and DEP compared to the children. However, the levels were significantly correlated between the mothers and their children, indicating common exposure sources in the home environment.

In **study III** and **IV,** we measured phthalates, non-phthalate plasticizers, bisphenols, brominated flame retardants (BFRs) and organophosphate esters (OPEs) in dust from 100 preschools. In addition, phthalate metabolites, bisphenols and one OPE were measured in urine from 113 children attending these preschools and BFRs and OPEs were measured in

hand wipes from 100 children. The estimated intakes of individual chemicals via preschool dust were below available health based reference values. However, for some of these chemicals, reference values are either lacking or are uncertain, due to insufficient toxicity data. The levels of currently strictly regulated chemicals in dust were higher in older preschools, whereas the levels of chemicals now substituting these old ones were higher in newer preschools. Furthermore, the presence of certain products in the preschools was shown to have impact on the levels of chemicals in dust. For five out of eleven BFRs and OPEs significant correlations were found between preschool dust and children's hand wipes. In addition, the levels of an OPE in urine and dust were significantly correlated. These results indicate that preschool dust may be an important source to children's exposure of these compounds. Levels of phthalates and BPA in preschool dust were not significantly correlated to respective metabolites in urine and the relative contribution from dust to the total exposure of these compounds was low or moderate, indicating that other sources are more important.

SAMMANFATTNING

Barn exponeras ständigt för kemikalier i mat, vatten, damm, luft och konsumentprodukter. Barn har ofta en mer omfattande exponering än vuxna till följd av fysiologiska faktorer och beteende. På grund av sitt unika exponeringsmönster är exponeringsbedömningar för vuxna inte direkt tillämpbara för att bedöma barns exponering. Därför finns behov av exponeringsbedömningar genomförda specifikt för barn och med avseende på de miljöer där barnen spenderar mest tid.

Det övergripande syftet med avhandlingen är dels att utveckla en metod för att överblicka publicerad information om kemikalieexponering och dels att generera ny kunskap om barns exponering för olika kemikalier. Dessutom var målsättningen att identifiera och utvärdera betydelsen av olika exponeringskällor, så som mat, hygienprodukter och inomhusmiljö, för barns kemikalieexponering.

I **studie I** utvecklade vi ett automatiskt klassificeringsverktyg med möjlighet att identifiera och klassificera publicerad information om kemikalieexponering. I studien annoterades nära 3700 vetenskapliga sammanfattningar (abstracts) manuellt, enligt en taxonomi för kemikalieexponering. Baserat på den annoterade textmassan tränades en algoritm för att automatiskt kunna klassificera publicerad exponeringsinformation. Utvärderingen av klassificeringsverktyget visade generellt goda resultat. I ett antal fallstudier demonstrerades användarmöjligheterna, vilka inkluderar underlättad litteratursökning, framtagande av kemikaliespecifika exponeringsprofiler och identifiering av kunskapsluckor.

I **studie II** användes ett harmoniserat studieprotokoll för att studera exponering för ftalater, bisfenol A (BPA), parabener och triklosan. Urinprov från 98 mammor och deras barn (6-11 år) samlades in och analyserades för exponeringsbiomarkörer, samtidigt som deltagarna besvarade ett frågeformulär om hemmiljön, socioekonomi, matvanor och användning av kosmetik och hygienprodukter. Halter av ftalater och BPA i urin var främst korrelerade till intag av olika livsmedel, medan urinhalter av paraberner och dietylftalat (DEP) främst var korrelerade till användning av smink och hygienprodukter. Halterna av de flesta ftalater och BPA var högre hos barnen än hos mammorna, vilket återspeglar deras högre exponering via mat och inomhusmiljön. Halterna av parabener och DEP var högre hos mammorna på grund av deras mer omfattande kosmetikaanvändning. Det var god korrelation mellan mammors och respektive barns exponering, vilket talar för att det finns gemensamma exponeringskällor för individer som bor i samma hushåll.

I **studie III** och **IV** analyserades ftalater, icke-ftalat mjukgörare, bisfenoler, bromerade flamskyddsmedel (BFRer) och fosforbaserade ämnen (OPEer) i damm från 100 förskolor. Dessutom mättes ftalatmetaboliter, bisfenoler och en OPE i urin från 113 barn, medan BFRer och OPEer mättes i handavstrykningsprover från 100 barn. Beräknat intag av dessa kemikalier via förskoledamm bland fyraåriga barn låg under tillgängliga hälsobaserade referensvärden. För vissa av dessa ämnen saknas dock referensvärden, medan vissa andra referensvärden är mycket osäkra på grund av bristande toxikologisk information. Halterna av

tidigare välanvända kemikalier var högre i damm från äldre förskolor medan halterna av ämnen som nu substituerar dessa var högre i nyare förskolor. Vidare tyder resultaten på att förekomsten av vissa produkter och material i förskolemiljön, så som madrasser, elektronik och PVC-golv, påverkar halterna av vissa kemikalier i damm. Halter av fem utav elva BFRer och OPEer i damm var signifikant korrelerade till halterna av samma ämnen i hand-avstrykningsproverna. Dessutom var halterna av en OPE i damm och urin signifikant korrelerade. Detta talar för att förskoledamm bidrar till barns exponering för dessa ämnen. För ftalater och BPA utgjorde det beräknade relativa bidraget från förskoledamm 2-27% av den totala exponeringen och det fanns inga signifikanta korrelationer mellan halterna av dessa ämnen i damm och urin, vilket talar för att andra exponeringskällor är viktigare än damm.

LIST OF SCIENTIFIC PAPERS

I. **Larsson** K, Baker S, Silins I, Guo Y, Stenius U, Korhonen A, Berglund M. Text mining for improved exposure assessment. PLoS One 12(3):e0173132 (2017).

II. **Larsson K**, Ljung Björklund K, Palm B, Wennberg M, Kaj L, Lindh CH, Jönsson BA, Berglund M. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. Environment International 73:323-33 (2014).

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SELECTED RELATED PUBLICATIONS

Berglund M, **Larsson K**, Grandér M, Casteleyn L, Kolossa-Gehring M, Schwedler G, Castaño A, Esteban M, Angerer J, Koch HM, Schindler BK, Schoeters G, Smolders R, Exley K, Sepai O, Blumen L, Horvat M, Knudsen LE, Mørck TA, Joas A, Joas R, Biot P, Aerts D, De Cremer K, Van Overmeire I, Katsonouri A, Hadjipanayis A, Cerna M, Krskova A, Nielsen JK, Jensen JF, Rudnai P, Kozepesy S, Griffin C, Nesbitt I, Gutleb AC, Fischer ME, Ligocka D, Jakubowski M, Reis MF, Namorado S, Lupsa IR, Gurzau AE, Halzlova K, Jajcaj M, Mazej D, Tratnik JS, Lopez A, Cañas A, Lehmann A, Crettaz P, Den Hond E, Govarts E. Exposure determinants of cadmium in European mothers and their children. Environmental Research 141:69-76 (2015).

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Covaci A, Den Hond E, Geens T, Govarts E, Koppen G, Frederiksen H, Knudsen LE, Mørck TA, Gutleb AC, Guignard C, Cocco E, Horvat M, Heath E, Kosjek T, Mazej D, Tratnik JS, Castaño A, Esteban M, Cutanda F, Ramos JJ, Berglund M, **Larsson K**, Jönsson BA, Biot P, Casteleyn L, Joas R, Joas A, Bloemen L, Sepai O, Exley K, Schoeters G, Angerer J, Kolossa-Gehring M, Fiddicke U, Aerts D, Koch HM. Urinary BPA measurements in children and mothers from six European member states: Overall results and determinants of exposure. Environmental Research 141:77-85 (2015).

Becker K, Seiwert M, Casteleyn L, Joas R, Joas A, Biot P, Aerts D, Castaño A, Esteban M, Angerer J, Koch HM, Schoeters G, Den Hond E, Sepai O, Exley K, Knudsen LE, Horvat M, Bloemen L, Kolossa-Gehring M; DEMOCOPHES consortium (Aerts D, Biot P, Katsonouri A, Hadjipanayis A, Cerna M, Krskova A, Knudsen LE, Nielsen JK, Kolossa-Gehring M, Becker K, Rudnai P, Középesy S, Mulcahy M, Burns D, Gutleb A, Fischer M, Ligocka D, Jakubowski M, Reis MF, Namorado S, Gurzau ES, Lupsa IR, Halzlova K, Jajcaj M, Horvat M, Mazej D, Castano A, Esteban M, Berglund M, **Larsson K**, Crettaz P, Sepai O, Lehmann A, Exley K). A systematic approach for designing a HBM pilot study for Europe. International journal of hygiene and environmental health 217(2-3):312-22 (2014).

In addition, co-authorship of 6 publications on study design and results from the DEMOCOPHES project included in the special issue of Environmental Research 141 (2015).

LIST OF CONTENTS

LIST OF ABBREVIATIONS

ATBC	Tributyl O-acetylcitrate
BBzP	Butylbenzyl phthalate
BEH-TEBP	Bis(2-ethylhexyl)tetrabromophthalate
BenP	Benzylparaben
BFR	Brominated flame retardant
BPA	4,4'-(propane-2,2-diyl)diphenol
BPAF	4,4′-(hexafluoroisopropylidene)diphenol
BPF	4,4′-methylenediphenol
BPS	4,4'-sulfonyldiphenol
ButP	Butylparaben
COPHES	Consortium to Perform Human Biomonitoring on a European Scale
DBDPE	Decabromodiphenyl ethane
DBE-DBCH	1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane
DED	Daily exposure dose
DEHA	Bis(2-ethylhexyl) adipate
DEHP	Di-(2-ethylhexyl) phthalate
DEHT	Bis(2-ethylhexyl) terephthalate
DEMOCOPHES	DEMOnstration of a study to Coordinate and Perform Human biomonitoring on a European Scale
DEP	Diethyl phthalate
DiBP	Diisobutyl phthtalate
DiDP	Diisodecyl phthalate
DiNCH	Diisononylcyclohexane-1,2-dicarboxylate
DiNP	Di-iso-nonyl phthalate
DMP	Dimethyl phthalate
DnBP (DBP)	Di-n-butyl phthalate
DNEL	Derived No Effect Level
DPHP	Di(2-propyl heptyl) phthalate
DPhP	Diphenyl phosphate
EH-TBB	2-ethylhexyl-2,3,4,5-tetrabromobenzoate
EthP	Ethylparaben
FFQ	Food frequency questionnaire
HBCDD	Hexabromocyclododecane

HBM	Human biomonitoring
MBzP	Monobenzyl phthalate
MCiNP	Monocarboxyisononyl phthalate
MCiOP (cx-MiNP)	Mono(carboxyisooctyl) phthalate
MCMHP	Mono[2-(carboxymethyl)hexyl] phthalate
MECPP (5-cx-MEPP)	Mono-(2-ethyl-5-carboxypentyl) phthalate
MEHHP (5-OH-MEHP)	Mono-(2-ethyl-5-hydroxylhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
MEOHP (5-oxo-MEHP)	Mono-(2-ethyl-5-oxohexyl) phthalate
MEP	Monoethyl phthalate
MetP	Methylparaben
MHiDP	Monohydroxyisodecyl phthalate
MHiNP (OH-MiNP)	Mono(hydroxyisononyl) phthalate
MnBP	Monobutyl phthalate
MOiNCH	2–4-methyl-7-oxyooctyl-oxycarbonyl-cyclohexane carboxylic acid
MOiNP (oxo-MiNP)	Mono(oxoisononyl) phthalate
OPE	Organophosphate ester
PBDE	Polybrominated diphenyl ether
ProP	Propylparaben
REACH	Registration, Evaluation, Authorisation and restriction of Chemicals
RfD	Reference dose
TBBPA	Tetrabromobisphenol A
TBOEP	Tris(2-butoxyethyl) phosphate
TCEP	Tris(2-chloroethyl) phosphate
TCIPP	Tris(2-chloroisopropyl) phosphate
TDCIPP	Tris(1,3-dichloroisopropyl) phosphate
TDI	Tolerable daily intake
TPHP	Triphenyl phosphate

1. INTRODUCTION

1.1 CHEMICAL EXPOSURE IN CHILDREN

Children are constantly exposed to chemicals in food, water, dust, air and consumer products. Compared to adults, children generally have a higher exposure to chemicals due to physiological factors, such as their relatively higher breathing rate, food consumption and their larger skin surface area. In addition, children's exposure can be higher due to behavioural factors, such as their proximity to the floor or ground and pronounced hand-to-mouth and object-to-mouth behaviour. Children are often more susceptible to toxic effects of chemicals as some organ systems, such as the immune-, nervous-, hormone- and reproductive systems, are continuously developing during the childhood period. Children's metabolism also differs from adults. For example, children form relatively more oxidized metabolites in relation to non-oxidized monoester metabolites after uptake of di-(2-ethylhexyl) phthalate (DEHP) [1].

Furthermore, children should not be seen as a homogenous group, because exposure patterns and physiological characteristics rapidly change as children grow older (Figure 1). Thus, exposure assessments should ideally be performed separately for different age groups.

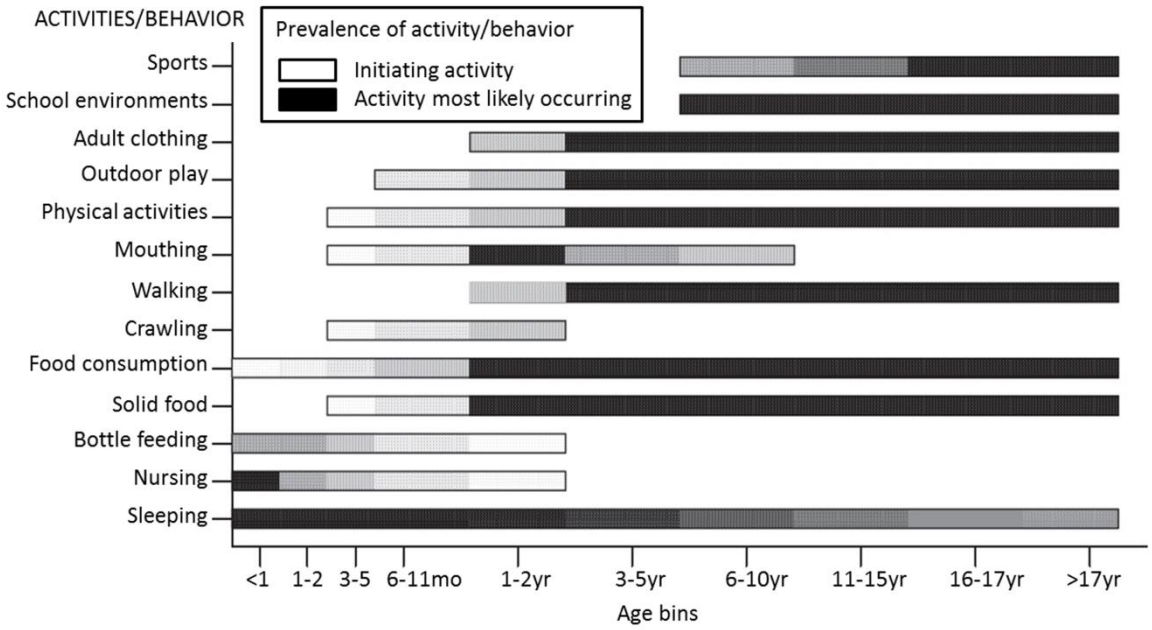


***Figure 1**. Children's activity patterns that influence exposure, from birth to 18 years of age, adapted from IPCS 2006 [2].*

Exposure and risk of chemicals are often studied in adult populations. However, data from adults are not necessarily transferrable to children due to the aforementioned reasons. Therefore, there is a need for exposure and risk assessments specifically performed for children, with focus on the environments were children spend a large part of their time.

1.1.1 Indoor environments

Children spend the majority of their time in indoor environments, such as homes, preschools, schools and sport halls. Chemicals present in building materials and consumer products, such as furnishing, electronic devices and textiles, can be released into these indoor environments [3], where children are exposed via dust and air. Children's higher intake of dust and air makes them particularly vulnerable for these exposures.

1.1.1.1 Preschool indoor environment

Young children spend up to one third of their weekdays in the preschool. Therefore, a considerable part of children's total exposure originates from this environment.

The Swedish Chemicals Agency's action plan for achieving the Environmental Quality Objective (miljömål) for a "non-toxic environment", defined by the Swedish government, puts emphasis on children's environmental health [4,5]. As a result, recommendations for interventions that preschools can perform to reduce potential chemical exposures have been developed (Table 1) [6,7]. However, there is limited research on the effectiveness of such interventions (see section 1.5.1.4*).*

Table 1*. Selected recommendations for reducing chemical exposure in preschool environments [6,7].*

- Remove unsuitable toys (e.g. soft plastic toys produced before 2007)
- Remove non-toys used as toys (electronics, construction materials, etc)
- Remove old foam/upholstered furniture
- Remove old mattresses with foam and/or plastic covers
- Consider replacing old PVC floorings and/or wall coverings
- Wash hands regulaly to remove chemicals
- Maintain good cleaning routines

1.1.2 Diet

In the general population, food is the main exposure source for many chemicals. Short lived chemicals, such as phthalates and bisphenols, mainly contaminate foods as a result of processing and packaging processes [8], whereas persistent chemicals, such as brominated flame retardants (BFRs), accumulate in lipid rich tissues of living organisms and are therefore particularly abundant in fatty fish and meat [9].

In comparison with adults, children have a higher exposure to chemicals in the diet as they consume a larger amount of food relative to their body weight. The consumption patterns may also differ depending on age. For example, nursing children are exposed to persistent chemicals via breast milk [10,11].

Different approaches are used to assess exposure via the diet, such as food frequency questionnaires (FFQs), 24- or 48-hour diet recalls and double portion methods. All approaches have advantages and limitations. For example, FFQs and food recalls can be distributed to a large number of participants but will not give as accurate exposure estimations as double portion methods, which, on the other hand, only can be applied for a limited number of participants and during a short time period. Furthermore, food recall approaches may be more appropriate for short lived chemicals, whereas FFQs may be better for assessing exposure to chemicals with long biological half-lives.

1.1.3 Personal care products

Humans are exposed to chemicals in cosmetics and personal care products mainly via dermal absorption. Children are especially vulnerable as a result of their relatively higher skin area to body weight ratio, which results in higher internal levels. The skin permeability is higher in new-borns and infants, whereas the skin barrier of children older than 2 years of age is believed to be the same as in adults [12].

Certain phthalates, parabens, triclosan and organophosphate esters are used in personal care products. In addition, phthalates and 4,4'-(propane-2,2-diyl)diphenol (BPA) may migrate to these products from storage containers. Exposure to the aforementioned chemicals from personal care products and cosmetics has been demonstrated in several studies that combined questionnaires with biomonitoring data [13,14,15,16,17,18,19].

1.1.4 Socioeconomic factors

Socioeconomic factors (e.g. education, income, race/ethnicity) have been shown to be both positively and negatively associated with body burdens of several chemicals studied in this thesis [20,21,22]. These observed differences can be due to different dietary habits, product use and housing characteristics in different socioeconomic groups. Therefore, variations between socioeconomic groups should be taken into consideration when evaluating chemical exposure in a population.

1.2 METHODS FOR ASSESSING CHEMICAL EXPOSURE

An exposure assessment is defined as the estimation or measurement of the magnitude, duration, frequency and distribution of exposure on the individual, sub-population or population level. It should preferably describe the sources, pathways and routes of the exposure [23].

The exposure assessment is a cornerstone in the risk assessment process (Figure 2) and plays an important role in risk management of chemicals, status and trend analyses and epidemiological studies [24].

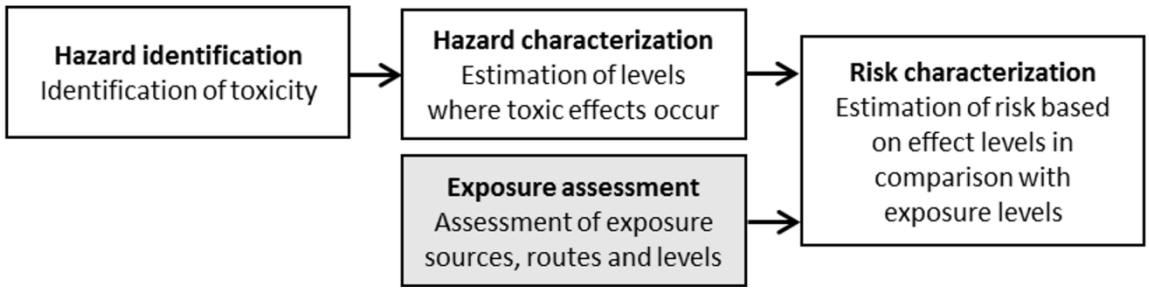


***Figure 2**. The components of a chemical risk assessment [25,26].*

Exposure assessment methods include direct and indirect approaches. The direct methods ("point-of-contact") evaluate the exposure at the interface between the exposure medium and the human during a specified time period. These methods include personal measurements, such as breathing zone air, duplicate portions and dermal patches [24,27]. In addition, human biomonitoring (HBM; see 1.2.1) is regarded as a direct exposure assessment approach. Indirect methods are based on exposure scenarios for a population, combining environmental measurements with e.g. modelling, questionnaires, time-activity diaries and other exposure factor information (Figure 3). Direct approaches have the advantage of generally being more precise for estimating an individual's exposure during a specific time period, whereas exposure scenarios based on indirect measurements are less precise as they rely on assumptions about the exposure in a population. On the other hand, direct methods have the disadvantages of often being expensive and not representing the entire population.

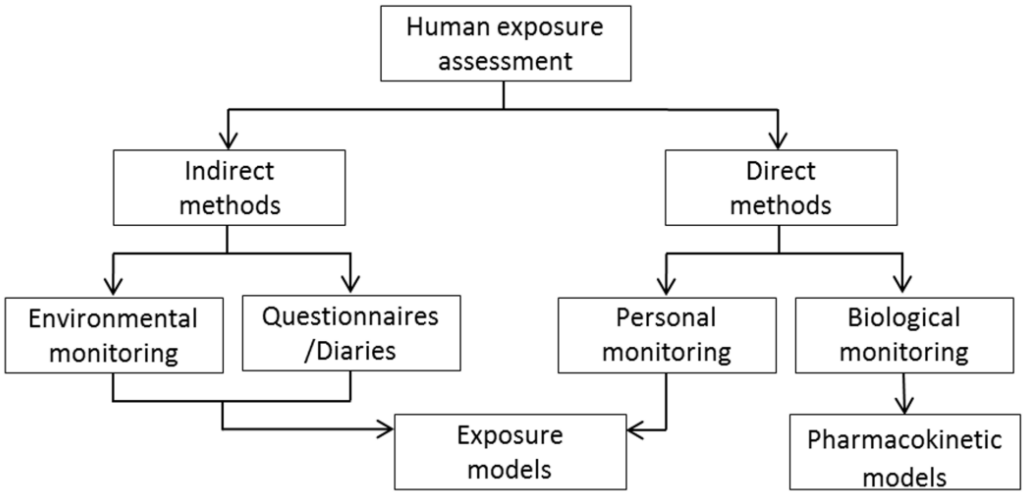


***Figure 3.** Indirect and direct methods for human exposure assessment. Adapted from NRC 1991 [28].*

1.2.1 Human biomonitoring

HBM is the measurement of biomarkers in human fluids or tissues, such as blood, urine, breast milk and hair. The HBM approach describes the internal dose of a chemical or metabolite and represents the total exposure from all sources and routes [29]. If HBM data is combined with information from e.g. questionnaires or time-activity-diaries, conclusions can be drawn about routes and sources of the exposure. HBM approaches are used to assess

exposure in different populations (such as workers, elderly and children), to recognize spatial or temporal trends and to identify highly exposed or susceptible populations.

In contrast to "bottom-up" exposure modelling based on environmental measurements, biomonitoring data can be used to calculate the exposure using "top-down" modelling. Top-down calculations use biological measurements (e.g. urinary metabolite levels) to assess the total intake of a chemical, while incorporating information about metabolism and excretion [30].

Human biomonitoring has been practiced since the 1930s, but the data collected over the years is often not comparable, due to methodological differences [29]. Aiming to overcome these issues and achieve a harmonized approach for biomonitoring across Europe, the Consortium to Perform Human Biomonitoring on a European Scale (COPHES) was initiated in 2009. As a first step towards harmonization of HBM in Europe, a standardized methodology was developed and tested in a pilot study (DEMOCOPHES) performed by 17 EU countries in 2011-2012 [31]. As a continuation and extension of this work, the currently ongoing HBM4EU project will coordinate and drive advances in HBM within Europe between 2017 and 2021 [32].

Large national biomonitoring initiatives of repeated measurements, such as the US National Health and Nutrition Examination Survey (NHANES) and German Environmental Survey (GerEs), are continuously performed to achieve comparable HBM data over time [33,34]. In Sweden, no national representative HBM program exists, instead the health related environmental monitoring (hälsorelaterad miljöövervakning) program supports several continuous HBM studies in specific subpopulations [35].

1.3 TEXT MINING FOR EXPOSURE ASSESSMENT INFORMATION

Exposure assessment methods include various direct and indirect approaches as mentioned above. The large mass of publically available exposure information is definitely a great asset for characterizing exposure of chemicals. However, biomedical literature available from web-based databases (such as PubMed) is currently growing with double-exponential rate, making it increasingly difficult to find the relevant literature and overview the available information [36].

The growing challenges of finding and overviewing published information in general have urged in the development of text mining techniques for automatic retrieval and classification of data. Text mining draws on different computational technologies to refine information by analysing correlations and statistical patterns in unstructured text. In addition to retrieving relevant information, text mining techniques can be used to extract new knowledge hidden in large bodies of text, identify research gaps and create new research ideas. Text mining techniques have been used for several biomedical fields, such as cancer research [37,38], chemical cancer risk assessment [39,40], toxicogenomics [41] and drug effects/safety [42,43].

To the best of our knowledge, the Comparative Toxicogenomics Database, in which exposure is included as one of several modules, is the only database for chemical exposure literature [44]. However, this database is not based on text mining techniques, but time consuming manual curation of all publications. Thus, no text mining based tool for exposure information currently exists.

1.4 STUDIED CHEMICALS

This thesis focuses on chemicals within the groups of phthalates and non-phthalate plasticizers, phenols, parabens, brominated flame retardants (BFRs) and organophosphate esters (OPEs). These chemical groups represent compounds that are short-lived (e.g. phthalates and bisphenols) and more persistent (e.g. BFRs), which is an important factor to take into consideration when assessing exposure. Other important aspects are the current and historical production and use of these compounds. This thesis covers both chemicals that have been used for a long time period but are now subjected to bans or strict legislations, as well as chemicals that are now substituting these compounds.

1.4.1 Phthalates

Phthalates are used for a wide range of applications and are currently the most commonly used plasticizers in the world. Phthalates are mainly (>90%) used for production of PVC plastics which are found in consumer products, such as toys, wrapping materials, food containers and synthetic leather as well as in building materials, such as floorings, wall coverings and roofing membranes. Phthalates are also used to lesser extent for non-PVC applications, such as glues, paints and cosmetics [30,45,46]. Phthalates are not bound to the plastic polymer matrix and have been shown to migrate from PVC plastics [47,48,49]. Humans are consequently exposed via food, air, dust and direct contact with consumer products [50,51,52].

Animal studies have shown that DEHP, di-n-butyl phthalate (DnBP), butylbenzyl phthalate (BBzP) and diisobutyl phthtalate (DiBP) have anti-androgenic properties [53,54,55]. In humans, these phthalates are suggested to cause testicular dysgenesis syndrome, including altered testosterone levels, decreased sperm quality and deformed male genitals after in utero exposure [56,57,58,59,60]. In addition, there is suspicion for weak anti-androgenic effects of di-iso-nonyl phthalate (DiNP) [61,62]. Furthermore, phthalates have been suggested to play a role in the aetiology of asthma and other allergy related diseases [63].

The most toxic phthalates have successively been phased out in the EU by applying gradually stricter regulations. In 2007, DEHP, DnBP and BBzP were banned in toys and childcare articles and DiNP and diisodecyl phthalate (DiDP) were banned in toys intended for mouthing [64]. In 2008, the use of several phthalates in plastic materials that come in contact with food was restricted [65]. In addition, due to legislations or voluntary phase-out of most phthalates, diethyl phthalate (DEP) is the only phthalate currently used in cosmetics [66,67]. Finally, after 2015, DEHP, DnBP, BBzP and DiBP, which are classified as reproduction

toxic category 1B within REACH, cannot be used for any application within the EU without permission [68].

As an effect of these regulations, di(2-propyl heptyl) phthalate (DPHP), DiNP and DiDP are currently the most commonly used phthalates in the EU. However, DEHP still dominates the global market [46]. Although the four most toxic phthalates are not used without permission in EU today, they are still abundant in products and materials that are in use, and will be so for a long time to come.

1.4.2 Non-phthalate plasticizers

As previously commonly used phthalates have been subjected to stricter regulations, non-phthalate plasticizers are becoming more widely used [69,70]. This thesis includes measurements of diisononylcyclohexane-1,2-dicarboxylate (DiNCH), which was introduced in the EU in 2002 and constituted approximately 70% of the alternative plasticizer market in Sweden by 2012 [69], and bis(2-ethylhexyl) terephthalate (DEHT), which was introduced in the 1980s and is currently used in high volumes [71]. In this thesis, we have also measured bis(2-ethylhexyl) adipate (DEHA), which is the most used adipate plasticizer in Sweden [69], and tributyl O-acetylcitrate (ATBC). These alternative plasticizers are used in plastic products, such as toys, childcare articles, vinyl flooring, food wrapping and packaging, cables and gloves [46,72,73]. Some plasticizers are also used in non-plastic products, such as glues, paints and cosmetics. In 2014, the registered use in Sweden of DiNCH, DEHA, DEHT and ATBC were 11 000, 810, 600 and 8 tonnes per year, respectively [74].

These plasticizers do not fulfil the criteria for being persistent, bioaccumulative or toxic [69,75] and are therefore generally considered to be safe alternatives for phthalates. However, exposure monitoring of these compounds is currently insufficient, not the least in young children [69].

1.4.3 Brominated flame retardants

BFRs are used to prevent fires in a variety of products, such as electronic devices and upholstered furniture. Polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCDD) and tetrabromobisphenol A (TBBPA) are historically the most used BFRs. PBDEs and HBCDD are known to be both persistent and bioaccumulative. In addition, they have been shown to disturb the thyroid hormone homeostasis, and to have reprotoxic and neurotoxic effects [76,77,78]. TBBPA is less persistent and bioaccumulative, but has been associated with effects on the thyroid hormone homeostasis [79].

Since 2004, the use of pentaBDE (containing primarily BDE-47, -99, -100) and octaBDE (containing primarily BDE-183) has been restricted to 0.1% by mass in preparations and articles put on the European market [80]. After 2019, this restriction will also be applied to the use of decaBDE (containing primarily BDE-209) [81]. HBCDD is listed in Annex XIV of REACH and is thereby only allowed for authorized use within the EU [68]. Furthermore, penta- and octaBDE, HBCDD and decaBDE have been included in the Stockholm

Convention on Persistent Organic Pollutants since 2009, 2013 and 2017, respectively [82,83,84]. TBBPA is still manufactured and/or imported in large amounts (1000-10 000 tonnes/year) in the EU [85].

PBDEs and HBCDD are used as additive flame retardants, which are not chemically bound to the material. Therefore, they can leach from old products to the environment, even though they are no longer produced. In contrast, TBBPA is mainly used as a reactive flame retardant that is covalently bound to the material. Only up to 10% of TBBPA is used as an additive flame retardant in some hard plastics [86].

The bans of historically used BFRs have urged the introduction of alternative BFRs. For example, decabromodiphenyl ethane (DBDPE) is replacing decaBDE in electronics, 2-ethylhexyl-2,3,4,5-tetrabromobenzoate (EH-TBB) and bis(2-ethylhexyl)tetrabromophthalate (BEH-TEBP) are used instead of pentaBDE in polyurethane foam and PVC, and 1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane (DBE-DBCH) substitutes HBCDD in polystyrene insulation [87].

However, these new BFRs have similar physiochemical properties as old BFRs and for many of these compounds, sufficient exposure and toxicity data are lacking, which prevents comprehensive risk assessments [9,88,89]. A few studies have found indications of endocrine disrupting properties of some emerging BFRs [90,91].

1.4.4 Organophosphate esters

The banned BFRs and phthalates can, to a certain extent, be substituted by OPEs, which are used as flame retardants and plasticizers. Halogenated OPEs, i.e. tris(1,3-dichloroisopropyl) phosphate (TDCIPP), tris(2-chloroethyl) phosphate (TCEP) and tris(2-chloroisopropyl) phosphate (TCIPP) are mainly used as flame retardants in e.g. textiles and polyurethane foam, whereas non-halogenated OPEs, i.e. triphenyl phosphate (TPHP) and tris(2-butoxyethyl) phosphate (TBOEP) are also used as e.g. plasticizers and lubricants [92].

The halogenated OPEs are suspected to be carcinogenic [93,94,95]. Other health effects, such as neurotoxicity and/or reprotoxicity have also been suggested for several OPEs [92,95,96]. Due to the aforementioned toxicity, TCEP has been phased out since the 1980s [95]. In addition, TCEP, TCIPP and TDCIPP are not allowed in the production of toys in the EU [97]. The annual quantities manufactured and/or imported in the EU is 1000-10 000 tonnes each for TDCIPP and TBOEP, and 100-1000 tonnes for TPHP [73]. TCIPP has not been registered in REACH, but the registered use in Sweden was approximately 200 tonnes in 2014 [74].

1.4.5 Bisphenols

BPA is widely used globally for the production of polycarbonate plastics, epoxy resins and thermal paper. The estrogenic properties of BPA have been known since the 1930s. In addition, animal studies of BPA have shown effects on the development and function of the reproductive organs as well as the nervous system and behaviour [98]. However, potential

low-dose effects in humans are debated [99]. To reduce the exposure, the use of BPA in baby bottles and cosmetics is not allowed within the EU and BPA is also banned from baby food containers in Sweden [67,100,101].

The scientific and public concern about potential human health effects of BPA has urged the industry to develop BPA substitutes. Some of the chemicals now used as substitutes are BPA structural analogues, such as 4,4'-sulfonyldiphenol (BPS) and 4,4′-methylenediphenol (BPF). These substitutes are not necessarily better alternatives since animal and in vitro studies have shown that BPF and BPS have endocrine disrupting properties in the same order of magnitude as BPA [102,103].

1.4.6 Parabens

Parabens have been used since the 1920s as antimicrobial preservatives in personal care products, cosmetics and pharmaceuticals. Some parabens are also permitted as food preservatives in confectionaries and dried meat [104]. In vivo and in vitro studies have shown that parabens have weak estrogenic activity, which seems to increase with the length of the alkyl chain, making long-chain parabens (e.g. propyl- and butylparaben) most potent [105,106,107].

Restrictions of the maximal permitted levels of all parabens in cosmetics have been applied in Sweden since 1994. In 2014, the EU legislation for propyl- and butylparaben was updated, further restricting the use of these parabens in personal care products and banning the use in products intended for the diaper region in small children [108,109]. Parabens with shorter alkyl chain (i.e. methyl- and ethylparaben) were not covered by these updated regulations.

1.4.7 Triclosan

Triclosan is an antimicrobial agent which has been used in personal care products, cleaning products, plastics and toys [110]. Triclosan has been shown to have endocrine disrupting effects in animal studies, especially on the thyroid hormone homeostasis [111,112,113,114]. Furthermore, triclosan is toxic to aquatic organisms and is suspected to be bioaccumulative and persistent in the environment [112].

The use of triclosan as a preservative in personal care products and cosmetics in the EU is restricted to 0.3% of the product [67]. Furthermore, triclosan is no longer permitted to be used as a biocide in any products, including personal care products (e.g. antibacterial hand soap and disinfectants) [115], food containers, shoes and sport clothes [116].

1.5 STUDIED CHEMICALS IN DIFFERENT MEDIA

1.5.1 Dust

Humans are exposed to chemicals in dust via ingestion, inhalation and dermal uptake. Children are known to be more exposed than adults due to their proximity to the floor and frequent hand-to-mouth and object-to-mouth activities [117]. Measurements of chemicals in

dust can be used for indirect exposure assessments, which estimate the intake of chemicals from dust in different populations and microenvironments, such as residents, preschools, schools, cars and workplaces.

Using dust sampling for exposure assessments presents several challenges. For example, the representativeness of one single dust sample for the entire microenvironment as well as the influence of different factors (such as ventilation and cleaning) on levels of chemicals in dust are not fully understood. In addition, differences in dust sampling methods, including various vacuuming approaches, wiping, brushing and sedimentation approaches, as well as lack of standardized procedures when using either of these methods complicates the comparability between studies [24,117].

Despite these drawbacks, sampling and analysis of dust are necessary to be able to estimate the chemical exposure from the indoor environment, and the approach has several advantages. For example, dust measurements can be used to identify exposure sources of chemicals in indoor environments and dust has also been used as a proxy for chemical exposure in epidemiological studies [118,119,120]. Dust represents the average exposure over a long time period [121] and may therefore be a more representative measure, than e.g. spot urine samples, for continuous exposure of chemicals with short biological half-lives.

1.5.1.1 Concentrations in dust

Over the last 15 years, BFRs and/or OPEs have been measured in European preschool dust in six individual studies [122,123,124,125,126,127,128,129,130]. Phthalates and non-phthalate plasticizers have been measured in European preschools in four [124,129,131,132] and one study [133], respectively. Previous studies of bisphenols in dust from European preschools are lacking. Due to the limited number of chemical analyses in preschool dust and the generally small sample sizes used in these studies, there is a need to further characterize children's exposure of chemicals, especially those emerging, via dust in these environments.

Compared to preschools, measurements of chemicals in home environments have been performed more frequently. Figure 4 summarizes reported levels of phthalates, non-phthalates plasticizers, BPA, BFRs and OPEs in homes, schools and preschools in Europe, North America and Australasia over the last 10 years [134]. This summary shows that the phthalates DEHP and DiNP are the most abundant compounds in dust. In addition, the few studies of non-phthalate plasticizers in dust reported levels that are in the same concentration range as many commonly used phthalates. OPEs are found at moderate levels in dust, whereas legacy and emerging BFRs are found at relatively low levels.

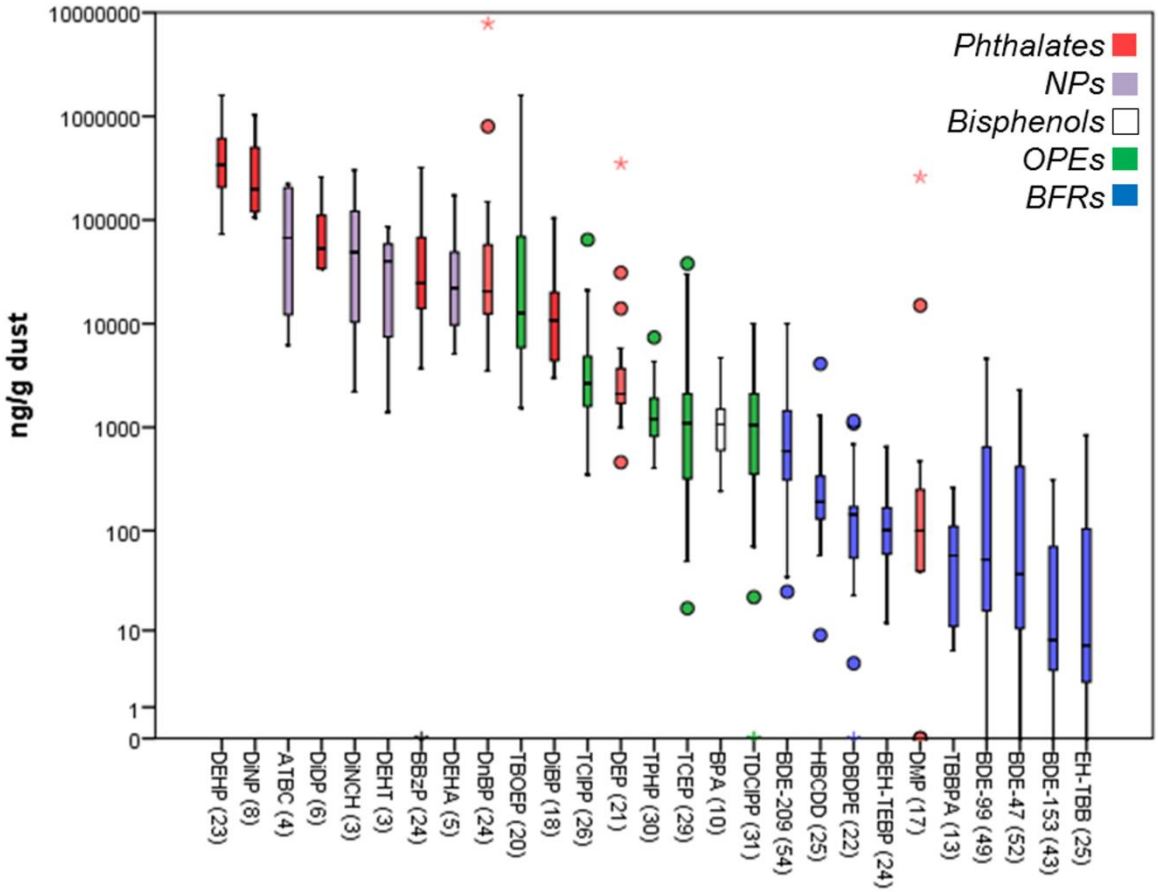


Figure 4. *Reported concentrations of chemicals in dust from homes, schools and preschools in Europe, North America and Australasia in 2005-2017. The number of measurements included in each bar is presented within parenthesis after respective compound. (NPs, Non-phthalate plasticizers).*

1.5.1.2 Correlations between dust and biological samples

Few studies have investigated the association between chemicals in dust from the preschool environment and the total exposure measured in urine or blood from children attending these preschools. In a German study, significant correlations between levels of phthalates (BBzP, DnBP and DEHP) in preschools dust and corresponding metabolites in urine were found, however these correlations did not reach significance after controlling for indoor air concentrations [132]. In the same study, significant correlations were observed between preschool dust levels of the non-phthalate plasticizer DiNCH and corresponding metabolites in urine [133]. In addition, a Danish study showed significant correlations between phthalate (DEP, DnBP, DiBP and BBzP) levels in indoor dust from preschools and homes and corresponding urinary metabolites in children [135]. A German study that exclusively studied exposure to DEHP in dust from homes did not observe any significant correlations between DEHP in house dust and corresponding metabolites in children's urine [136].

There are no studies of BFRs in preschool dust in relation to children's internal doses. However, several studies of household dust have shown significant correlations between levels of PentaBDEs in dust and in blood from adults [137,138,139,140] and children [141], umbilical cords [139], human hair [142] and breast milk [143,144,145]. On the contrary,

other studies have not found any correlations between levels of pentaBDEs in household dust and levels in blood from adults or children [146,147,148,149,150].

There are a few studies relating levels of OFRs in house dust to the corresponding metabolites in urine from residents. Two studies have found significant correlations between the concentrations of TDCIPP in dust and the corresponding metabolite in urine from adults and children [151,152]. Furthermore, one study has found a significant correlation between TPHP in dust and the corresponding metabolite in urine from children [151], whereas no significant correlations could be found in studies of adults [151,152,153].

In conclusion, these results imply that the exposure from dust can have a significant impact on the total exposure of some of the studied chemicals.

1.5.1.3 Relative contribution from dust to the total intake

To explore the importance of dust as an exposure source in relation to other exposure sources, the estimated intake via dust can be compared with the total intake.The relative contribution from dust to the total intake of phthalates in the US has been assessed by Guo and Kannan [154]. They concluded that the exposure via dust contributed with 10-58% of total DEHP, 3-21% of total BBzP, 1-16% of total DiBP and <1% of total DEP. The relative contribution from dust was highest in toddlers followed by infants, children, teenagers and adults. In addition, Bekö et al. estimated that the relative contribution of phthalates from dust in Danish homes and preschools, to the total exposure in 3-6 year old children, was 8% for DEHP, 2% for BBzP and <1% for DnBP, DiBP and DEP. [155]. For BPA, the relative contribution from dust to the total exposure has been estimated to be less than 5% [156,157,158].

The relative contribution from dust to the total exposure of BFRs has been assessed in several studies [9,10,149,159,160,161]. Taken together, dust can be an important exposure source of PBDEs, TBBPA and HBCDD, especially for small children and for populations living in areas where the environmental concentrations of these compounds are high (e.g. North America), whereas diet is the dominant exposure source in other parts of the world. It is noteworthy that the relative contribution from dust to the total intake of BDE-209 generally is higher than for other BDEs.

Few studies have estimated the relative contribution from dust to the total exposure of OPEs. Poma et al. estimated that the intake of OPEs from dust in Swedish adults were in the same order of magnitude as the intake via the diet [162]. However, the relative contribution for different OPEs varied. This study did not evaluate the relative contribution from dust to the total exposure of OPEs in children, which is expected to be higher than for adults.

1.5.1.4 Sources of chemicals in dust

Dust measurements can be used to elucidate which products, furnishing and other indoor characteristics that are important for the exposure of chemicals in preschools or other microenvironments.

PVC floorings have been suggested to be an important source of phthalates present in indoor dust. Studies of Swedish homes have reported that PVC floorings and wall materials were correlated with the levels of DEHP and BBzP in indoor dust [163] and that infants living in houses with PVC flooring had higher levels of a BBzP metabolite in urine [164]. On the contrary, two other smaller studies of preschool environments found no significant associations between PVC floorings and concentrations of phthalates in dust [132,165].

Old foam or upholstered furniture may contain phased out PBDEs. In studies where the presence of BFRs in furniture has been confirmed, significant correlations to respective compounds in dust have been found [166,167]. In concordance, studies have found significant correlations between pentaBDE in dust and the presence of foam or upholstered furniture (with unknown content of bromide) [168,169] as well as foam mattresses [168]. In contrast, other studies have not been able to find significant correlations between foam or upholstered furniture and levels of PBDEs in dust [145,170,171].

Old electronics can contain old PBDEs, especially BDE-209, which has been widely used in these products. Allen et al. found significant correlations between electronic devices with confirmed content of bromide and levels of decaBDE in dust [167]. In concordance, another study reported higher levels of BDE-153 and decaBDE in dust from rooms with a higher number of electronics (with unconfirmed bromide levels) [168]. On the other hand, other studies have not found associations between electronic devices in the indoor environment and PBDE concentrations in dust [145,169,170].

Sources of OPEs in indoor dust have been poorly studies. Foam mattresses have been correlated to higher levels of TDCIPP and TCEP in dust [169]. In addition, higher levels of TPHP have been found in dust collected on electronics in comparison with dust collected around electronics [172].

In conclusion, there is limited research about the impact of different sources and other factors in the indoor environment for levels of chemicals in dust. Furthermore, most of these studies included a fairly low number of dust samples, which decreases the statistical power.

1.5.2 Urine

The elimination half-lives of the urinary metabolites measured in this thesis are generally short (Table 2). Therefore, the internal doses of these chemicals may fluctuate over time depending on the current exposure. Consequently, the representativeness of one spot urine sample for exposure assessment can be questioned. However, assuming frequent consumption of foods and other products containing the studied compounds, recurrent exposure over time is likely to occur. Thus, one urine sample is believed to reasonably represent an individual’s ongoing exposure [173,174,175,176]. On the contrary to the other compounds, the representativeness of one spot urine sample for long term BPA exposure is quite low, which limits the possibility to assess long term exposure based on single urinary BPA measurements [177,178].

Table 2. *Elimination half-lives in urine.*

Compound	Route	Species	Elimination half-lives in urine	ref
DEHP	oral	human	5 hours (MEHP), 10 hours (MEHHP & MEOHP), 12-15 hours (MECPP), 24 hours (MCMHP)	[179]
DnBP	oral	human	3-7 hours	[180]
DiBP	oral	human	4 hours	[180]
DiDP	oral	rat	14 hours	[181]
DPHP	oral	human	6-8 hours	[182]
DiNP	oral	human	3-8 hours	[183,184]
DiNCH	oral	human	10-18 hours	[185]
BPA	oral	human	4-5 hours	[186,187]
TPHP	-	in vitro	Several hours	[152]
Triclosan	oral	human	10-20 hours	[188]
	dermal	human	1.4 days	
Parabens	oral	rat	1 hour (propylparaben)	[189]
	dermal	human	7 hours (butylparaben)	

The biological half-lives differ depending on the route of administration. For example, the half-life can be longer after dermal exposure than oral exposure. Therefore, when using urinary biomarkers for assessing exposure from food versus personal care products, different exposure intervals may apply.

1.5.2.1 Time trends of urinary metabolites

The shift of chemicals used by industry, as a consequence of stricter legislations and resulting substitutions, has impact on human exposure. However, the exposure to currently banned chemicals will continue for a long time as they are still released from old products. Biomonitoring studies can be an efficient tool for following and evaluating time trends of human exposure to chemicals. Whereas most trend studies have been performed in the adult population, there are few time trend studies in children.

Time trend studies have been used to detect decreasing trends of DEHP metabolites and other "old" phthalates in urine from German men [190], Swedish men [191], Swedish women [192] and the US population [193]. At the same time, increasing time trends have been found for the still widely used phthalates DiDP and DPHP [192,193,194]. The time trend for DiNP has been reported to be increasing in Swedish adults [191] and in the US population [193], but decreasing in German men [190]. Time trend studies of DiNCH in Swedish, German and US adults have shown that the urinary levels of DiNCH metabolites were below the detection limits prior to 2006 and then rapidly increased over recent years [192,195,196]. For example, urinary DiNCH metabolites in Swedish women increased by 200% between 2007 and 2010 [192].

Exposure to BPA, assessed by urinary measurements, has decreased in US children [197,198] and adults [199], and in Swedish women [200]. The few existing time trend studies of BPA analogues in urine have found increasing levels of BPS in US adults [199] and increasing levels of BPF in Swedish women [200]. Furthermore, the urinary levels of triclosan seem to be decreasing [200,201]. We could not find any time trend studies of parabens in urine.

Time trends based on continuous measurements of OPEs are lacking. However, a time trend analysis of several US epidemiological studies performed between 2002 and 2015 showed a strong increase of a TDCIPP metabolite and a moderate increase of a TPHP metabolite in urine [202].

Taken together, these studies show clear temporal trends in human exposure to different chemicals and urge the continuation of repeated biological measurements, not the least in children and of chemicals used as substitutes for regulated or banned compounds.

1.5.3 Hand wipes

Hand wipe samples describe the chemical loads on an individual's hands and can be used to assess exposure via the hand-to-mouth pathway. As hand wipe sampling is a direct personal exposure assessment approach, which account both for chemicals in indoor dust and the individual's activity pattern, this is probably a more biologically relevant measure of children's indoor exposure than dust samples *per se*. The relevance of hand wipes for exposure assessment has been supported in studies showing that, in comparison to dust measurements, hand wipe measurements is better correlated with children's urine and blood levels of flame retardants [202,203,204].

2. AIMS

The overall objectives of this thesis were to develop a method to overview existing exposure information and to generate new knowledge about chemical exposures in children. In addition, the thesis aims to identify and evaluate the importance of different exposure sources, such as foods, personal care products and indoor environments, for children's chemical exposure.

The specific aims of the studies were to…

…develop an automatic classifier capable of retrieving and categorizing published information about chemical exposure and to evaluate the capability and usefulness of a text mining based tool for the exposure research area (**study I**).

…identify exposure sources and other factors in the home environment important for the internal levels of short lived endocrine disrupting chemicals in mother-child pairs, using a harmonized methodology for biomonitoring (**study II**).

…identify products and other factors in the preschool environment important for concentrations of chemicals in dust (**study III** and **IV**).

…estimate and evaluate children's exposure to chemicals via preschool dust in relation to the total exposure and to health risks (**study III** and **IV**).

3. SUBJECTS AND METHODS

This section serves as an overview of the study populations and methods used in this thesis. In addition, some methodological considerations are discussed. Detailed descriptions of the techniques and methods can be found in the associated publications.

3.1 TEXT MINING (STUDY I)

The vast amount of published exposure data is a great asset to the scientific community. However, manual literature gathering is an extremely time consuming task and overviewing the information is almost impossible. In **study I**, we addressed these issues by developing an automatic classifier, based on text mining techniques, for retrieval and categorization of exposure information. This transdisciplinary research project was a collaboration between exposure scientists at Karolinska Institutet, Sweden and computational linguists at the University of Cambridge, UK.

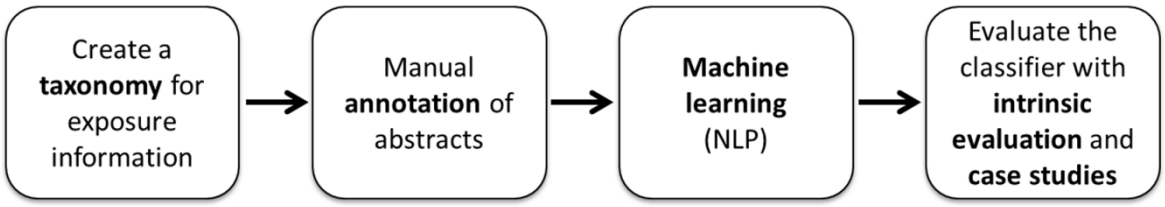


Figure 5. *Brief overview of the work flow for developing and evaluating the automatic classifier. (NLP, Natural Language Processing).*

Here, we present a very brief overview of the procedure for developing and evaluating the automatic classifier, as illustrated in Figure 5. As a first step, a taxonomy relevant for exposure information was created. To the best of our knowledge, the Exposure Science Ontology (ExO), used for manual curation in the Comparative Toxicogenomics Database, is the only existing ontology for exposure data [205]. This structure and focus were not considered suitable for our classifier. Therefore, a new and more concise taxonomy was created, consisting of 32 nodes under two main branches *biomonitoring* and *exposure routes* (see Figure 7 in section 4.1). The structure of the taxonomy was developed for human exposure data only. Therefore, in vitro and animal data as well as environmental monitoring without human exposure assessment were generally not classifiable.

In the next step, 7762 potentially relevant scientific abstracts from the PubMed database were retrieved and manually reviewed. Out of these, 3686 abstracts were considered relevant for exposure assessment. These abstracts were subsequently manually annotated according to the structure of the exposure taxonomy.

Based on Natural Language Processing (NLP) techniques, a supervised machine learning algorithm was trained on the annotated corpus to automatically categorize abstracts according to the taxonomy. In the next step, the performance of the classifier was tested by intrinsic

evaluation, using 3-fold cross validation where the classifier was trained on three quarters of the annotated data and tested on the last quarter, in a rotating manner.

The standard measurements (precision, recall, accuracy and F-score) used in the intrinsic evaluation are specified below.

$$\text{precision} = \frac{true\ postives}{true\ postives + false\ postives}$$

$$\text{recall} = \frac{true\ postives}{true\ postives + false\ negatives}$$

$$\text{accuracy} = \frac{true\ postives + true\ negatives}{total}$$

$$\text{F score} = 2\frac{precision \times recall}{precision + recall}$$

Finally, different case studies were performed to further evaluate the function and usability of the automatic classifier. In these case studies, the automatic classifier based the selection of abstracts on the entire PubMed database, currently containing more than 28 million publications.

3.2 STUDY POPULATION AND PERSONAL SAMPLING (STUDY II)

3.2.1 Recruitment and study participants

Study II was based on the Swedish data from the pilot study DEMOCOPHES (DEMOnstration of a study to Coordinate and Perform Human biomonitoring on a European Scale), which was performed in 17 European countries, with the aim to harmonize biomonitoring in Europe [31]. All components of the study, including recruitment, sampling, questionnaire information gathering and chemical analyses were performed according to the harmonized approach developed within the DEMOCOPHES/COPHES consortium.

Mothers and children (6-11 years old) were recruited via inhabitant registers. The participants lived either in the urban area of Uppsala or in a rural area in Västerbotten county, Northern Sweden. Mother-child pairs were eligible to participate in the study if the mother was younger than 45 years of age, had lived in the area for more than three years, lived at the same address as the child more than half of the time and if the mother and child had no chronic kidney or liver disease.

In total, 98 mother-child pairs participated in the study. After exclusion of urine samples with creatinine levels below 30 mg/dL or above 300 mg/dL [206] and one sample that was not first morning urine, 95 mothers and 97 children (50 girls and 47 boys) were included in the analyses. Among the children, 47 were living in urban area and 50 children were living in the rural area. The response rate was only 22%, but the non-responder analysis showed no significant differences between participating and non-participating mothers regarding smoking, education, civil status and working status.

3.2.2 Urine sampling

The mothers and children collected first morning urine at home. The samples were collected in paper cups and transferred to polypropylene tubes, according to written instructions. The tubes were stored in −20 °C until analysis.

3.2.3 Questionnaires

To obtain information about factors potentially relevant for chemical exposure, the mothers answered a questionnaire about the mother and child's dietary habits and use of personal care products, the residential environment and sociodemographic factors. The questions about foods and personal care products were based on the frequency of use (i.e. how many times a week/month do you eat/use…).It can be speculated that food consumption and use of products reported during the last 24/48 hours before sampling might be more suitable for source identification of short lived chemicals, than the frequency questionnaire used in this study. However, the questionnaire used in this study was designed to concurrently capture exposure to other chemicals (i.e. cadmium and mercury) with longer biological half-lives, for which frequency questions may be more suitable.

An additional questionnaire was answered at the time of the urine sampling to obtain information about the sampling procedure and intake of certain foods (e.g. fast food and frozen food in plastic container) within 24 hours before the sampling.

3.3 STUDY POPULATION AND PERSONAL SAMPLING (STUDY III AND IV)

3.3.1 Recruitment and study participants

In **study III** and **IV**, children between 3.5 and 4.5 years of age attending any of 30 selected preschools were invited to participate in the study via a written invitation. In a few preschools, parents were also invited at parent-teacher meetings via an oral presentation of the study. The parents signed an informed consent before the samples were collected. Urine and hand wipe samples were collected between March and May 2015, within a month from when the dust sample had been collected at respective preschool.

Urine samples were collected from 113 children attending any of 28 preschools. The number of participating children from each preschool ranged from 1 to 13 children, with an average number of three children per preschool. Among these children, the percentage of boys and girls were 59% and 41%, respectively, and the average age was 50 months (range 40-58 months). The children had started preschool at an average age of 18 months (range 12-48 months) and spent between 24 and 45 hours per week at the preschool, with a mean of 36 hours per week.

Hand wipe samples were collected from 100 of the children who provided urine samples. Hand wipe sampling was performed at 27 preschools, where the number of participants ranged between 1 and 7 children per preschool, with an average number of 3 children per preschool.

3.3.2 Urine sampling

To assess the total exposure, including at least two days at the preschool, urine samples were collected on Thursday mornings. To study the variation in urinary metabolite levels over the week, a urine sample was also collected on a Monday morning from 24 of the children. The parents collected the child's first morning urine in a paper cup and transferred the sample to a polypropylene tube (Sarstedt, Numbrecht, Germany), according to written instructions. The samples were delivered to respective preschool in the morning where they were stored in cooling boxes, until they were transported to the research facility. The samples were stored at -20°C.

3.3.3 Historical urine samples

To study differences in children's exposure to phthalates and bisphenols over time, we analysed urine samples collected fifteen years earlier, within the ongoing prospective longitudinal cohort BAMSE [207]. These urine samples had been collected in 1998-2000 from 50 girls and 50 boys of an average age of 49 months (45-55 months) at the time. These urine samples had been stored at -80°C until analysis. Even though the samples had been

stored for more than 15 years, the degradation of phthalate metabolites during this time is believed to be small [208].

3.3.4 Hand wipe sampling

To obtain a personal exposure measure of BFRs and OPEs, which could not be analysed in the urine samples, hand wipe samples from preschool children were collected. The samples were collected at the preschool generally at mid-day or afternoon. Prior to sampling, the children had been engaged in indoor activities and the personnel had been asked not to wash the children's hands for at least 30 minutes. The type of activity before sampling (e.g. eating, resting, reading, playing) and the time between hand wash and sampling were not standardized. Therefore, the measured amounts of chemicals in children's hand wipes may be affected by these confounding factors.

A sterile 5x5 cm gauze compress soaked in 3 mL >99.5% isopropanol (Sigma-Aldrich) was used to wipe the palm, back of the hand and between the fingers on both hands of the child. The compress was enclosed in a glass jar, which had been heated at 300°C for 12 hours and washed with acetone prior to sampling. The samples were stored at -20°C until analysis. Field blank samples were collected from one third of the preschools by soaking a gauze compress in isopropanol and placing it directly into a glass jar.

The analysis of the field blank samples showed contamination of TCEP, TCIPP and TDCIPP. The source of this is unknown. To correct for contamination, the amount of chemicals detected in the hand wipes were corrected for the mean amount of respective chemical in the blanks. This correction resulted in a low detection frequency, which prevented full statistical analysis of these compounds.

3.3.5 Questionnaires

The parents answered a questionnaire with information about the child (age, weight, time spent at preschool, etc.), residential environment (type of housing, floor and wall coverings, products in the home environment, etc.) and parent's education.

In addition, questionnaires about the urine sampling and hand wipe sampling were answered by parents and field workers, respectively.

3.4 PRESCHOOL DUST SAMPLING (STUDY III AND IV)

3.4.1 Selected preschools

In the pilot phase of **study III** and **IV**, 30 preschools were recruited for dust sampling via email or phone invitation and the participation was voluntary. In the second stage of the study, including 70 preschools, the dust samples were collected by personnel working at the Stockholm City Environmental Management (Miljöförvaltningen) as part of their routine inspections. Therefore, participation was not voluntary in the second sampling round.

Dust samples were collected from 100 preschools in February-April or September-November 2015. The preschools were located in six areas of Stockholm municipality. The preschools were built between 1890 and 2015, with the majority built in the 1970s and 1980s. The percentage of communal preschools were higher in this study (71%) than in Stockholm in general (57%), whereas the percentage of private preschools (26%), parent's cooperatives (2%) and staff cooperatives (1%) were lower in this study compared to Stockholm in general.

Six of the preschools were Waldorf preschools (based on the Steiner education philosophy), which avoid plastic materials and electronics in the indoor environment. In addition, children in these preschools sleep on sheep skin instead of mattresses. None of the Waldorf preschools in the study had PVC-flooring. The percentage of Waldorf preschools were higher in this study (6%) compared to Stockholm in general (2%).

The preschool selection in our study does not directly represent Stockholm preschools, due to the deviations from the general distribution of organization forms, preschool types and locations. Nevertheless, it can be assumed that the results based on this preschool selection reasonably reflect chemical contamination in Stockholm preschools.

3.4.2 Dust sampling

From each participating preschool, one settled dust sample was collected in a play room where 4 year old children usually played. The dust sample was collected on a cellulose filter fixed in a styrene-acrylonitrile holder (Krim.Teknisk Materiel AB, Bålsta, Sweden; Figure 6), which was inserted in a nozzle made of polypropylene (Krim.Teknisk Materiel AB, Bålsta, Sweden) and mounted on the intake nozzle of a vacuum cleaner. A sieve was used for collecting dust samples for analysis of BFRs and OPEs (Figure 6). Settled dust was collected from elevated horizontal surfaces. After sampling, the filter holder lid was replaced, the holder was wrapped in aluminium foil and then sealed in a polyethylene plastic bag. The samples were stored at -20°C until analysis. Field blank samples were collected in one third of the preschools.

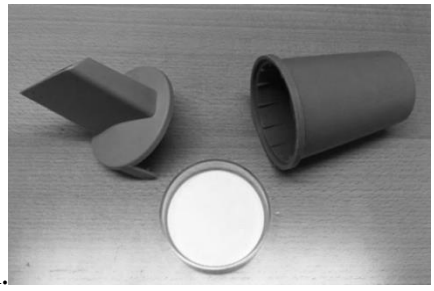
A.  B. 

Figure 6. *Sampling material used for dust collection. A) Filter holder and two-pieced nozzle. B) Filter holder with mounted sieve for collection of dust for BFR and OPE analysis.*

The analysis of the field blank samples showed contamination of TCEP and TCIPP originating from the filter holders. To correct for contamination, the dust sample concentrations were corrected for the mean concentration of respective chemical in the blank

samples, which resulted in a low detection frequency of these compounds, which prevented full statistical analysis of these compounds.

3.4.3 Preschool inspections

At the time of the dust sampling, the field workers performed an inspection of the preschool environment to obtain information about the preschool building, cleaning routines and details about floorings, furniture and other products present in the room and/or in the department. To distinguish between older and newer materials, the preschool personnel were asked to estimate the age of certain products and furnishing. The floor type was distinguished visually.

In the pilot study of 30 preschools, an extensive inspection questionnaire was used. After the pilot study, the data was evaluated and questions that showed little variability between preschools and questions that were too time consuming to answer were removed from the questionnaire. Shortening of the questionnaire was crucial as there were time restrictions in the later sampling campaign. Discrepancies between the questionnaires posed few difficulties in the final analyses of the data, which were generally solved by redefining or dropping variables.

3.5 CHEMICAL ANALYSIS

A summary of the chemicals and metabolites analysed in dust, hand wipes and urine is presented in Table 3.

3.5.1 Urine samples

The urine samples collected in **study II, III** and **IV** were analysed at the Division of Occupational and Environmental Medicine, Lund University. This laboratory was a reference laboratory for analyses of phthalates and BPA in the DEMOCOPHES project [209] and participates in Erlangen inter-laboratory comparison program for compounds where this is possible. The samples were analysed for phthalate and DiNCH metabolites, bisphenols and diphenyl phosphate (DPhP) using LC-MS/MS according to modified methods described in previous studies [61,186,210,211]. In addition, creatinine was analysed with the Jaffe method [212] and urine density was determined using a hand refractometer.

The urine samples collected in **study II** were also analysed for parabens and triclosan at the Swedish Environmental Research Institute (IVL) using HPLC-MS/MS according to a modified method described in Ye et al. 2006 [213].

3.5.2 Dust samples and hand wipes

In **study III**, dust samples were analysed for phthalates, non-phthalate plasticizers and bisphenols at IVL using GC-MS/MS according to a modified method described in Bergh et al. 2012 [214].

Table 3. *Chemicals and metabolites analysed in dust, hand wipes and urine samples in respective study.*

	Dust (study III & IV)	**Hand wipes (study IV)**	**Urine metabolites (study II)**	**Urine metabolites (study III & IV)**
Phthalates	DEHP		MEHP 5-OH-MEHP/MEHHP 5-oxo-MEHP/MEOHP 5-cx-MEPP/MECPP	MEHP 5-OH-MEHP/MEHHP 5-oxo-MEHP/MEOHP 5-cx-MEPP/MECPP MCMHP
	BBzP		MBzP	MBzP
	DnBP		MnBP	MnBP
	DiBP			
	DEP		MEP	MEP
	DMP			
	DiNP		OH-MiNP/MHiNP oxo-MiNP/MOiNP cx-MiNP/MCiOP	OH-MiNP/MHiNP oxo-MiNP/MOiNP cx-MiNP/MCiOP
	DPHP DiDP			MHiDP[a] MCiNP[a]
NPs	DEHT			
	DEHA			
	ATBC			
	DiNCH			MOiNCH
BPs	BPA		BPA	BPA
	BPS			BPS
	BPF			BPF
	BPAF			
BFRs	BDE-47, -99, -100, -153 and -209	BDE-47, -99, -100, -153 and -209		
	DBDPE	DBDPE		
	α- and β-DBE-DBCH	α-DBE-DBCH		
	EH-TBB	EH-TBB		
	BEH-TEBP	BEH-TEBP		
	α-, β- and γ-HBCDD	α-, β- and γ-HBCDD		
	TBBPA	TBBPA		
OPEs	TCEP	TCEP		
	TCIPP	TCIPP		
	TDCIPP	TDCIPP		
	TPHP	TPHP		DPhP
	TBOEP	TBOEP		
Ps			MetP , EthP, ProP, ButP, BenP	
			Triclosan	

NPs; Non phthalate plasticizers. BPs; Bisphenols. Ps; parabens. [a] *Metabolite of DPHP and DiDP*.

In **study IV**, dust samples and hand wipes were analysed for BFRs and OPEs at the Department of Environmental Science and Analytical Chemistry, Stockholm University. For the first 30 samples, fractionation and clean up was performed according to Ionas and Covaci 2013 [215]. Unexpectedly, this method resulted in loss of BEH-TEBP and HBCDD in some samples. Consequently, the extraction and clean-up of the last 70 samples was performed according to a method described in Sahlström et al. 2012 [216]. TBBPA and HBCDD were analysed with UPLC-MS/MS with electrospray ionization (ESI), whereas other BFRs were analysed with GC-MS with electron capture negative ionization (ECNI). OPEs were analysed with GC-MS with electron impact ionization (EI).

3.6 EXPOSURE CALCULATIONS AND RISK ASSESSMENT

In **study III** and **IV**, we calculated the daily intake of chemicals from dust in four year old children. The intakes of chemicals via ingestion of dust were calculated for all studied compounds. Exposure via dermal absorption was only calculated for BFRs and OPEs. For the exposure assessment, we used a normal and a high exposure scenario, based on the geometric mean and the 95th percentile concentration in dust, respectively.

3.6.1 Ingestion of dust

The daily oral exposures doses (DED_{oral}) from preschool dust were calculated using the following equation [160]:

$$DED_{oral} = \frac{C_{dust} * I_{dust}}{BW}$$

C_{dust} is the concentration of the chemical in preschool dust. I_{dust} is the daily intake of dust from the preschool environment (30 mg), assuming that the total daily dust intake during the waking hours is 60 mg and that children spend half of that time in the preschool [217]. *BW* is the mean body weight of the children in our study. We assumed the bioavailability to be 100%, which will result in an overestimation of the exposure [218].

3.6.2 Dermal absorption of dust

The daily intake of BFRs and OPEs in preschool dust via dermal absorption was calculated using the following equation [160]:

$$DED_{dermal} = \frac{C_{dust} * BSA * DA * AF * TF}{BW * 1000}$$

BSA is the exposed body surface area (hands, arms, legs) of children. *DA* is the amount of dust adhered to the skin. *AF* is the absorption factor and *TF* is the fraction of the day spent in the preschool. In contrast to the oral intake estimation, the equation for dermal exposure includes absorption factors. These factors have higher impact on the dermal exposure as the dermal absorption generally is lower than the oral absorption.

Except for the measured concentrations in dust, the exposure assessment is obviously highly dependent on the other exposure factors used in the equation. Various exposure factors are used in different studies, which introduce a question about the accuracy of these estimations. Furthermore, due to the use of different assumptions, the results cannot be directly compared between studies. However, these calculations are considered sufficient to estimate the magnitude of the exposure in relation to other exposure routes and to health based reference values, especially for chemicals with large margins between exposure and risk.

3.6.3 Total exposure

In **study III**, we estimated the relative contribution of DEHP, DnBP, BBzP, DiNP and BPA via dust ingestion to children's total exposure of these compounds. The total exposures were

estimated by volume based back-calculation from urinary metabolite levels [132], according to the following equation:

$$DED_{total} = \frac{\Sigma \left[\frac{C_u}{MW_m}\right] * MW_p * V_{excr}}{F_{UE}}$$

C_u is the concentration of respective metabolite in urine (µg/L). MW_m and MW_p are the molecular weights of the metabolite and parent phthalate, respectively. V_{excr} is the urinary volume excreted per day for children. F_{UE} is the molar fraction value, which explains the molar fraction of the monoester excreted in urine in relation to the intake of the parent compound.

There are several limitations when using this exposure estimation. First, the F_{UE} values were estimated using adult study participants, although the metabolism may be different in children. For example, children oxidize monoester metabolites of DEHP more readily than adults [1]. In addition, the equation does not account for the absorption rate over the gastrointestinal tract, which introduces a bias when the total intake is compared to the calculated intake via dust ingestion and to the health based reference values. Furthermore, the comparison between the estimated total exposures and the health based reference values may be biased because the back-calculated exposures regard all exposure routes, whereas the health based reference values only consider oral intake.

3.6.4 Health based reference values

In **study III** and **IV**, health based reference values were used to relate the intake of chemicals via dust to health risks.

If available, we used:

- Tolerable daily intake (TDI) established by the European Food Safety Authority (EFSA) or the Scientific Committee on foods (SCF) or the Scientific Committee on Health and Environmental Risks (SCHER) under the European Commission.
- Reference Doses (RfD) established by the US Environmental Protection Agency (US EPA) or the US National Research Council (NRC).
- Derived No Effect Levels (DNEL) established by the European Chemicals Agency's (ECHA) risk assessment committee.

For chemicals without consolidated reference values, we used DNELs reported by importers or manufacturers who have performed risk assessment under the European Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). The evidence base for deriving these DNELs is often not fully transparent. These reference values should therefore be interpreted with caution. Furthermore, there were no available health based reference values for some of the studied chemicals.

3.7 STATISTICAL METHODS

SPSS 20 and 22 (IBM Inc.) and STATA 13 (Statacorp TX, USA) were used for the statistical analyses.

In **study II**, the data was ln-transformed to allow for the use of parametric tests. We used ANOVA and multiple regression analysis, which were recommended by the DEMOCOPHES guidelines for statistical analysis.

In **study III** and **IV**, the data was not normally distributed even after ln-transformation. Therefore, we used non-parametric tests. Non-parametric tests have the advantage of being more robust against outliers and imputed values below the LOD.

3.7.1 Adjusting urinary concentrations

To compare chemical concentrations in spot urine samples within a population, the urine samples should be adjusted for the degree of dilution. This can be done either by correcting for creatinine or density (or specific gravity). In addition to increasing the comparability between individuals in a homogenous study population, dilution adjustment also has the advantage of correcting for the relatively higher urine excretion in relation to body-weight in children compared to adults [219]. However, density adjustments may introduce bias due to differences in e.g. gender, muscle mass and meat consumption [220,221]. The issue of dilution especially affects the comparison between mothers and children in **study II**, whereas the comparisons within the quite homogenous groups of children in **study II, III** and **IV** are less likely to be influenced.

In **study II**, the urinary concentrations of chemical metabolites in mothers and children were adjusted for creatinine as decided by the DEMOHOPHES consortium. In **study III** and **IV**, we chose to adjust the concentrations for density.

3.7.2 ANOVA

One-way analysis of variance (ANOVA) is used to compare the means of a continuous outcome, divided into two or more groups of an independent variable (e.g. gender), by testing the null hypothesis that the variance *between* the groups is equal to the variance between the individuals *within* the groups. In **study II**, one-way ANOVA was used to identify significant exposure determinants for internal levels of phthalates, BPA and parabens.

3.7.3 Multiple regression analysis

Multiple regression was used in **study II**, to further identify the most important exposure determinants for internal levels of the studied compounds, while accounting for the effect of other independent variables.

Multiple regression models were created separately for mothers and children and for each compound independently. Age and creatinine were forced into each model, as suggested by the statistical analysis plan for DEMOCOPHES. Other variables that were significantly

correlated to the biomarker in the one-way ANOVA analysis at a significance level of <0.25 were included in stepwise multiple regression analysis. After the stepwise selection, the final models included the variables that were correlated to the biomarker at a significance level of <0.05.

3.7.4 Pearson's chi-squared test

Pearson's chi-squared test explores the difference between two sets of categorical data. In **study II**, we used this test in the non-responder analysis to assess potential differences between the 98 participating mothers and 65 mothers who declined participation. The analysis included questions about smoking, civil status, education and work status.

3.7.5 Mann Whitney U test

Mann Whitney U test (Wilcoxon rank sum test) is the non-parametric equivalent to the independent samples t-test. In contrast to the t-test, which compares the means of different groups, the Mann Whitney U test compares the medians. In **study III** and **IV**, we used this test to identify predictors for chemicals in preschool dust, to find exposure determinants for metabolites in children's urine and to compare metabolite levels in urine from 1998-2000 and 2015, respectively.

3.7.6 Multivariable median regression

Multivariable median regression (quantile regression) is a non-parametric test that compares the medians of the dependent variable in different groups of the independent variables. In **study III** and **IV**, we used stepwise backward multivariable median regression to further identify the most important factors for the levels of chemicals in preschool dust.

We chose to apply bootstrapping in the analysis because it increases the robustness when the data is comprised of a limited number of observations. In this procedure, the observations in the existing data set are picked randomly in a repeated fashion until a new distribution, based on the original data, is formed. Every time this procedure is performed, new multivariable models will be created, which will be slightly different due to the variations in the hypothetical distributions. Finally, variables significantly correlated with the dependent variable at a certain cut-off (e.g. 50%) will be included in the final model.

3.7.7 Spearman's rank correlation test

Spearman's rank correlation test is a non-parametric analysis describing the correlation between two numerical variables, using the ranks of the observations.

Spearman's rank correlation test was used to study the correlations between 1) urinary levels in mothers and children in **study II**, 2) metabolite concentrations within urine samples in **study II** and **III**, 3) chemical concentrations within hand wipes and dust samples, respectively, in **study III** and **IV**, 3) factors in the preschool environment and levels of chemicals in dust in **study III** and **IV**, and 4) metabolite/chemical concentrations between

urine, hand wipes and dust samples in **study III** and **IV**. In the latter analysis, we accounted for non-independence and for the varying numbers of participating children per preschool by correlating the concentrations in dust from the preschools with the median levels in urine or hand wipes from the children attending respective preschool.

3.7.8 Wilcoxon's matched pairs test

In **study III**, we used Wilcoxon's matched pairs test (signed-rank test) to compare the levels of metabolites in urine samples collected on Mondays and Thursdays, respectively. This test, which is the non-parametric counterpart to the paired t-test, ranks the differences between paired observations under the null hypothesis that the median of the differences in the study population is equal to zero.

3.8 ETHICAL ASPECTS AND PERMITS

When children are studied, non-invasive samples should preferably be used to avoid discomfort for the participants. **Study II, III** and **IV** are biomonitoring studies using non-invasive methods to collect personal (urine, hand wipe) and environmental (dust) samples for exposure assessments.

The urine samples were collected by the parents, which makes the sampling process less frightening for the child. The hand wipe samples were collected at the preschools by the PhD student. If a child was unwilling to give a hand wipe sample, the child's wish was respected and the sample was not taken. Informed consent was signed by the parents before the samples were collected and the participants were informed that they could discontinue their participation at any time.

All ethical permits were granted by the regional ethical review board in Stockholm with the following grant numbers:

- Study II - Dnr 2011/1024-31/1
- Study III and IV - Dnr 2015/128-31/1
- Study III (analysis of urine samples from the BAMSE cohort) - Dnr 2014/448-32/1

4. RESULTS AND DISCUSSION

In this section, the most important results are presented and discussed. Detailed results and in-depth discussions are found in the associated papers.

4.1 TEXT MINING

In **study I**, we developed an automatic classifier for retrieval and categorization of exposure information available in published abstracts. To the best of our knowledge, this is the first time text mining techniques have been used for chemical exposure information. The intrinsic evaluation of the classifier showed generally good performance in the three top node levels of the taxonomy (Figure 7). The performances of the more specific nodes in the effect biomarker branch were lower, which is probably due to the large variety of effect biomarkers mentioned in abstracts.

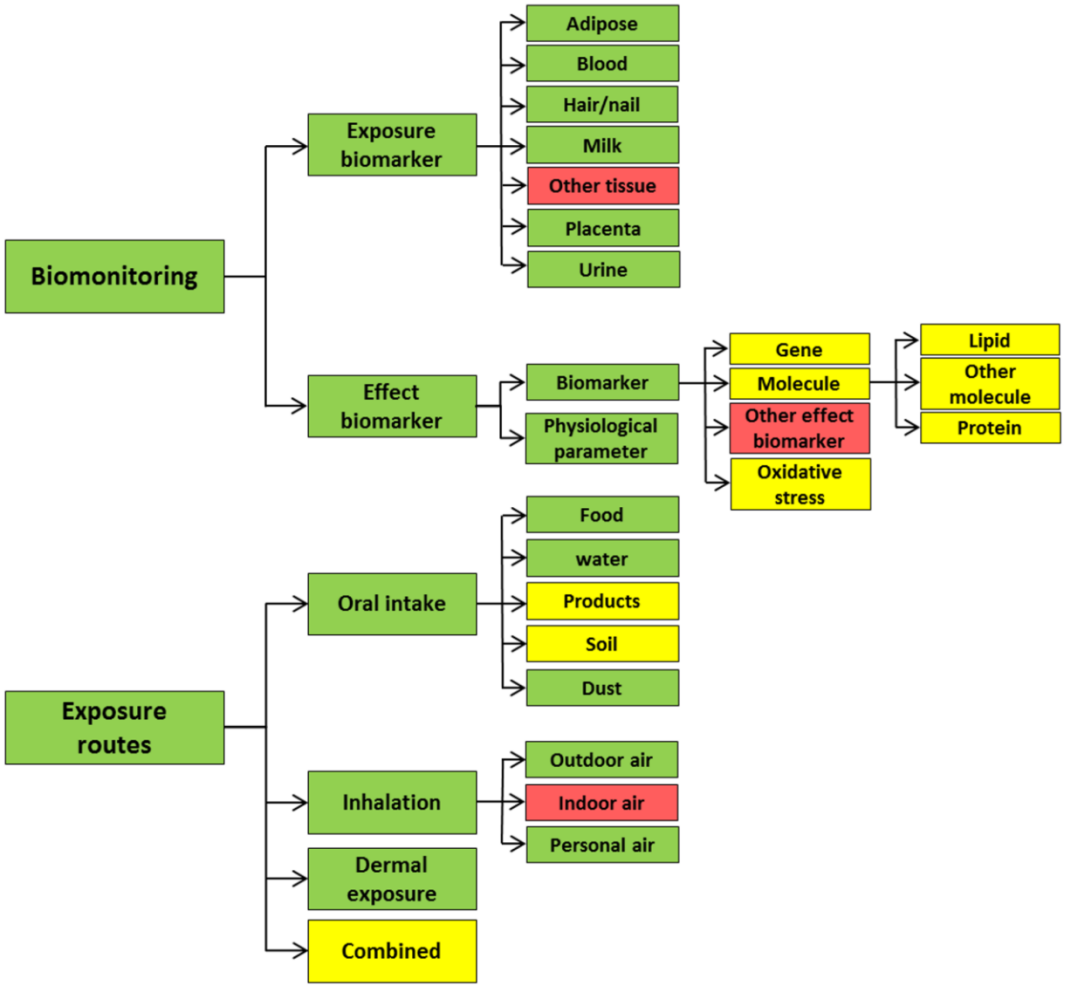


Figure 7. *Results of the intrinsic evaluation with colour coding based on F-scores; green = >75% (good), yellow = 50-75% (moderate), red = <50% (poor).*

Initially, the branches for exposure biomarkers and exposure routes included an additional node level categorizing studies of potentially susceptible or highly exposed populations (i.e. children, pregnant women or workers). Due to the low number of annotated abstracts in these sub-nodes, generally low or moderate F-scores were achieved. These findings reflect the need

for more exposure studies specifically studying children and other susceptible populations. Due to the low F-scores, we did not include these population specific sub-nodes in the further examination of the classifier.

Case studies were performed to further evaluate the function and usability of the automatic classifier. In the first case study, we compared manual gathering of literature about persistent organic pollutants in blood and breast milk, with automatic retrieval and categorization of such literature. This comparison showed that the automatic classifier identified almost all of the publications that were found in the manual search. In other words, we found that the classifier can be used in the first selection of publications when preparing for e.g. reports or reviews.

In a second case study, we hypothesized that the automatic classification could create chemical specific exposure profiles, which should reflect the current knowledge about the exposure of these chemicals. The evaluation of automatically generated exposure profiles for lead, hexachlorobenzene and 4-nonylphenol confirmed our hypothesis. This shows that exposure profiles can be used to compare the knowledge base for different compounds and to identify data gaps.

In the third case study, we evaluated the amount and the distribution of publications about different phthalates. In line with the results from the second case study, the exposure profiles for different phthalates reflected the patterns expected based on current knowledge (Figure 8). Interestingly, the evaluation showed that there were substantially more exposure information about the phthalates which are now being phased out in the EU (DEHP, DnBP and BBzP), compared to information about phthalates which are still in use (DiNP and DiDP). This exemplifies how the classifier can be used to overview and compare exposure information about different chemicals within a chemical group and how it can be useful to identify knowledge gaps for individual chemicals.

In the fourth case study, we evaluated the performance of our automatic classifier in relation to ordinary PubMed searches. We demonstrated that our classifier retrieved a higher amount of abstracts in specific sub-nodes compared to when specific search strings in PubMed were used. Furthermore, we showed that the publications retrieved by the automatic classifier had a higher precision (i.e. less false positives) than if PubMed search strings were used.

In the evaluation of the classifier, we identified a number of challenges for further development and optimization of the classifier. Nonetheless, the automatic classifier created in this study has a great potential to constitute the foundation of a publically available text mining tool for exposure assessment.

Lastly, these results highlight the need for exposure studies in children and of compounds, which now substitute strictly regulated or banned chemicals. These aspects are further addressed in **study II**, **III** and **IV.**

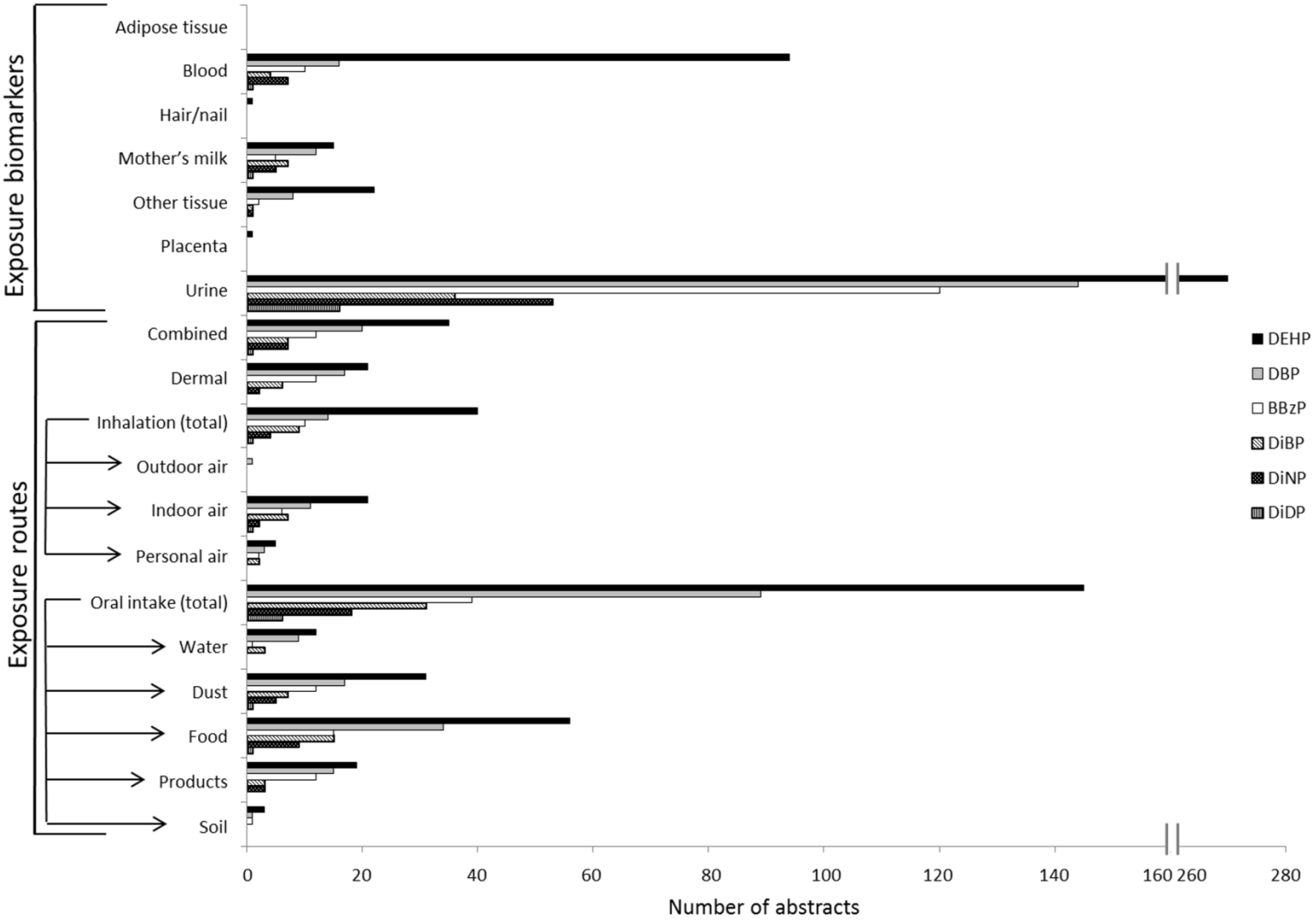


Figure 8. *Publication profiles of exposure biomarkers and exposure routes for different phthalate esters.*

4.2 URINARY LEVELS OF CHEMICALS IN CHILDREN

Children's urinary levels of phthalates and BPA were measured in **study II** (6-11 year olds) and **study III** (4 year olds). Metabolites of all phthalates and BPA were detected in 100% of the samples, reflecting a population wide exposure to these compounds. Parabens and triclosan, measured in **study II**, had a lower detection frequency of 0-86% for different parabens of 37% for triclosan.

In **study II**, younger children (6-8 years) had significantly higher levels of several compounds than older children (9-11 years). Age-dependent exposures in children have also been shown in a German study [222]. In **study III**, there were no differences between older and younger children, which can be due to the narrow age span (18 months) in this study population. None of the studies showed significant differences in urinary metabolite levels between boys and girls.

None of the children in **study II** or **III** exceeded the health related human biomonitoring values (HBMI) for DEHP (300 µg/L) or BPA (1500 µg/L) [223,224]. In other words, the urinary concentrations were in a range where no health effects are expected, according to current knowledge. In concordance, the estimated total intakes of DEHP, BBzP and BPA calculated from urinary levels in **study III,** were below the health based reference values in all children. However, the estimated total intakes of DiNP and DnBP exceeded the health based reference values in one and two children, respectively, out of the 113 children in the study.

One objective of the DEMOCOPHES study was to generate comparable biomonitoring data between the 17 European countries participating in the study (**study II**). In this comparison, urinary metabolite levels of DEHP and DEP in Swedish mothers and children were close to the European average, whereas the levels of DnBP and BBzP metabolites were higher in Sweden than in the other countries [225]. Furthermore, Swedish children had the lowest concentrations among the six countries that measured urinary BPA within DEMOCOPHES [226].

Parabens and triclosan were not included in the DEMOCOPHES study, but comparisons to other studies showed that the levels of parabens and triclosan in Swedish children were generally lower than reported levels in children from Spain, Norway, Denmark and the US [177,227,228,229].

In **study III**, we compared urinary levels of phthalates and bisphenols in preschool children in 2015 and a similar group of children who provided urine samples in 1998-2000. The levels of DEHP, DnBP, BBzP and DEP metabolites and BPA were significantly higher in 1998-2000, whereas the levels of DiNP metabolites were higher in 2015. These results reflect the phase out of certain phthalates and BPA, at the same time as other phthalates have become more common. Similar results have been shown in other time trend series [190,193,200,230].

4.2.1 Exposure in children vs mothers

Study II included measurements of phthalates, BPA, parabens and triclosan in both children and their mothers. Compared to the mothers, children had significantly higher urinary metabolite levels of phthalates and BPA present in food and the indoor environment, which is in concordance with children's relatively higher exposure via food, dust and air. The mothers had higher levels of parabens and a phthalate that is used in personal care products and cosmetics, which reflects the higher use of these products in adult women. These patterns have also been shown in previous studies of children and adults [177,228,229,231,232,233]

The levels of the studied compounds were generally significantly correlated between the mothers and their children, indicating that individuals of the same household share common exposure sources, such as food, personal care products and indoor environment.

4.3 EXPOSURE DETERMINANTS IN THE HOME ENVIRONMENT

Exposure to the high molecular weight phthalates (DEHP and DiNP) is believed to primarily come from foods, whereas other exposure sources, such as dust and cosmetics, contribute more to the exposure of low molecular weight phthalates. In **study II**, children who reported frequent ice cream consumption and mothers who reported frequent chocolate consumption had higher urinary levels of DiNP and DEHP metabolites, respectively (Table 4). These particular foods may serve as proxy for convenience foods, which are normally processed and packaged.

The univariate analysis of **study II** showed that mothers and children living in houses with PVC floorings or wall coverings had significantly higher levels of a BBzP metabolite in urine, and these children had also higher levels of a metabolite of DnBP. Interestingly, significantly higher levels of BBzP and DnBP metabolites in children living in homes with PVC floorings were also observed in **study III**. In concordance, these correlations were observed in the analysis of all countries participating in the DEMOCOPHES study (including 1773 mother-child pairs) [225]. Also a previous study by Bornehag et al. reported higher levels of a BBzP metabolite in infants living in homes with PVC floorings [164].

The results from **study II** showed higher levels of DnBP and BBzP metabolites in children of parents who had a low level of education and who were living in the rural area. This might be a result of the higher prevalence of PVC floorings in these families.

In **study II**, we observed higher levels of parabens and a DEP metabolite in mothers and children using certain personal care products and cosmetics. The types of products that were significantly correlated with these compounds in urine were generally leave-on products that are applied to a large area of the skin, such as lotion and skin make-up, whereas products covering a small areas and/or are rinsed off, such as shampoo, hair styling products, deodorant and nail polish, were not associated with internal levels of these compounds. In line with our results, other studies have reported significant correlations between DEP

metabolites and parabens in urine and use of personal care products and cosmetics in adults and children [13,14,15,16,17,18].

In conclusion, the levels of phthalates and BPA in **study II** were significantly correlated with different food items, whereas the levels of parabens and MEP were significantly correlated with the use of personal care products and cosmetics (table 4). This overall pattern of identified exposure sources is in concordance with the current knowledge about the most important exposures sources for these compounds. This shows that the harmonized questionnaire used in this study was suitable for identifying the overall exposure determinants in the home environment, even when the study population was small. However, the precision for identifying specific foods and personal care products is probably limited and these results should therefore be interpreted with caution.

Finally, the evaluation of the pan-European DEMOCHOPES study showed that it is possible to obtain comparable data on a European level, when using stringent quality control for the data collection, chemical analysis and data processing [225].

Table 4. *Overview of significant correlations in the univariate analysis of determinants for exposure to phthalates, BPA and parabens in mothers and children (study II). Correlations that were significant in the multiple regression analysis are indicated with bold script.*

	CHILDREN				**MOTHERS**		
	Phthalates and BPA		Parabens		Phthalates and BPA		Parabens
Age *<37 years*[a] *6-8 years*[b]	**↑DEHP***** **↑MnBP**** **↑DiNP**** ↑BPA*		↑MetP*		↑MBzP*	**↓BPA***	
Area *Urban*[c]		**↓MBzP***** **↓MnBP***** ↓MEP**	**↑MetP**** **↑ProP****			**↓MBzP***** **↓MnBP***** **↓MEP***	
Education *<High school/ college*[d]	↑MEP** ↑MBzP** ↑MnBP*				↑MBzP**		**↑EthP***
PVC floor/wall	↑MBzP** ↑MnBP*				**↑MBzP*****		
Meat						**↓BPA**** **↓DiNP***	
Fish					↑BPA*		
Fast food	↑DiNP*				↑BPA*		
Chocolate	**↑BPA***				**↑DEHP****		
Cheese	↑MBzP*						
Chewing gum							↑MetP* ↑ProP*
Ice cream	**↑DiNP*** ↑DEHP*						
Canteen food				↓ProP*		**↓MBzP****	
Well water[e]	↑MBzP* ↑MnBP*		**↑MetP***		↑MnBP*		
Rubber gloves							**↑MetP*** **↑ProP***
Lotion			**↑MetP**** **↑ProP****				**↑MetP***** ↑ProP**
Eye make-up	**↑MEP****	↓DiNP*	**↑ProP***			↓MBzP* ↓DEHP*	↑ProP **
Skin Make-up						↓MBzP*	**↑MetP***** **↑ProP*****
Fragrance		↓MnBP*			**↑DiNP***		
Sun screen					**↑MEP****		**↑EthP***
Mouth wash						↓MBzP*	↑MetP* ↑ProP*
Number of PCPs							↑MetP** ↑ProP**

*p<0.05, **p<0.01, ***p<0.001. PCPs; personal care products.
a) vs. >41 years, b) vs. 9-11 years, c) vs. rural, d) vs. Universtiy/PhD, e) vs. public water supply.

4.4 PRESCHOOL ENVIRONMENT

In **study III** and **IV** we assessed the exposure to phthalates, non-phthalate plasticizers, bisphenols, BFRs and OPEs via preschool dust and identified factors in the preschool environment important for the levels of these chemicals in dust.

4.4.1 Concentrations in dust

Phthalates, especially DiNP and DEHP, were generally the most abundant chemicals in preschool dust (Figure 9). Interestingly, non-phthalate plasticizers where found in the same concentration range as other well used phthalates. In addition, TBOEP was abundant in dust. Concentrations of BFRs in dust were considerably lower than the other compounds.

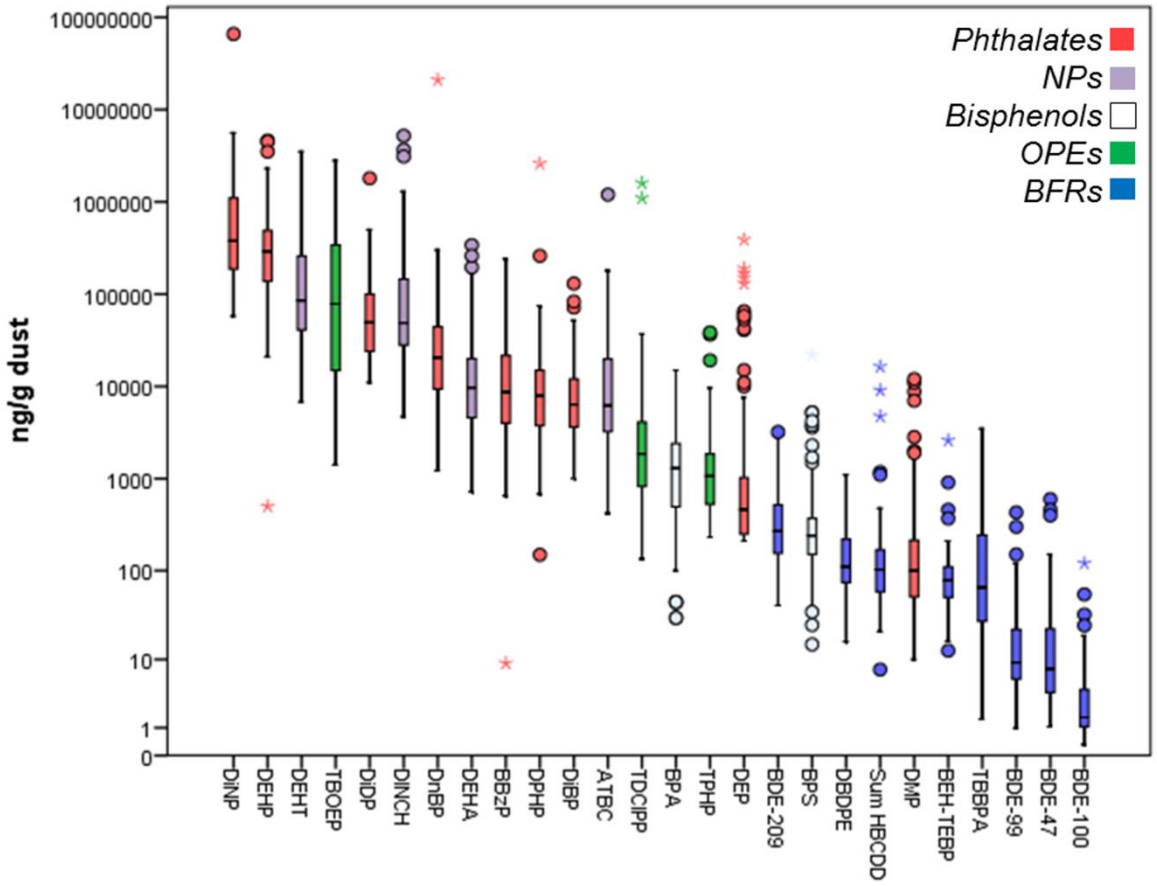


Figure 9. *Concentrations of chemicals in preschool dust. (NPs, non-phthalate plasticizers).*

In our study, concentrations of the phthalates and BFRs that are being phased out were generally lower in comparison with previous studies of European preschools [124,126,129,130,131,132]. Furthermore, the levels of TDCIPP and TPHP were similar to previously reported levels in preschool, whereas the levels of TBOEP were somewhat lower [122,123,124,125,128,129].

Our study contributed with valuable exposure information about emerging BFRs, non-phthalate plasticizers and certain phthalates, which are currently used unrestrictedly, as there are few previous studies reporting concentrations of these compounds in preschool dust

[124,127,132,133]. Due to the limited number of previous measurements, we could not compare the levels of these compounds in Swedish preschools to other studies.

4.4.2 Important factors for chemical concentrations in preschool dust

In **study III** and **IV**, we identified factors in the preschool environment important for the levels of chemicals in dust. One major aim of this evaluation was to see whether the individual interventions that preschools are recommended to perform could have an impact on the levels of chemicals in dust and consequently, if these interventions should be prioritized.

4.4.2.1 Age of the preschool building

The age of the preschool building was found to be an important determinant for some of the studied compounds in dust. Preschools built before 1999 had generally higher levels of DnBP, pentaBDEs and TBOEP in dust, whereas the levels of DPHP, DiDP, DEHT, ATBC, DiNCH, BPA and DBDPE were higher in newer preschools (Table 5). These results clearly reflect the decreased use of chemicals subjected to strict regulations, whereas the use of compounds now substituting these chemicals are increasing. The unexpected drop in TBOEP concentrations in recently built preschools is probably due to that new preschools have not yet used floor maintenance products, which may contain this compound.

Few studies have investigated the presence of chemicals in indoor dust in relation to the age of the building. A Swedish study found higher levels of DEHP in buildings constructed before 1960 compared to newer buildings [163] and an Italian study reported that the levels of phthalates (sum of DEHP, DnBP, BBzP, DnOP, DEP, DMP) were higher in older homes compared to newer [234]. On the contrary to our results, previous studies have not found significant correlations between the building age and levels of PBDEs or other flame retardants in dust [148,168,235,236,237]. However, most of these studies were based on smaller sample sizes.

In our study, the levels of old BFRs were significantly correlated with the age of the building as well as to the year that the preschool activities were initiated. In contrast, the year that the preschool activities started was generally not a significant predictor for phthalates in dust, even though the levels were significantly correlated to the building age. This finding implies that phthalates partially originates from the building materials, whereas the BFRs are more dependent on products present in the indoor environment, which are indroduced during the renovation when a new preschool is established.

4.4.2.2 Furnishing, floorings and products

Aiming to reduce children's exposure to hazardous chemicals, preschools are advised to discard or replace certain products, such as old foam mattresses and old plastic toys (see section 1.1.1.1). Therefore, we wanted to elucidate whether the presence of these particular products affects the levels of the studied chemicals in dust.

Table 5*. Overview of significant correlations in the univariate analysis of chemical levels in dust and factors in the preschool environment. Correlations that were significant in the multivariable median regression analysis are indicated with bold script.*

	Phthalates and BPA		BFRs and OPEs	
Preschool building year *<1999*[a]	**↑ DnBP****	**↓ DPHP*** ↓ DiDP* ↓ DEHT* ↓ ATBC* ↓ DiNCH** ↓ BPA**	**↑ BDE-47*** **↑ BDE-99*** ↑ BDE-100*** ↑ TBOEP*	**↓ DBDPE****
Preschool funding year[b] *<1999*[a]	↑ DnBP***	↓ DiNCH*	↑ BDE-47*** ↑ BDE-99*** ↑ BDE-100*** ↑ TBOEP*	↓ DBDPE*
Waldorf *Yes*		↓ DiNP**		↓ TDCIPP*** ↓ TPHP**
Cleaning frequency *<4 times/week*	↑ DMP* ↑ DEHT**		↑ TBOEP*	
Spring cleaning frequency[c] *<1 time/year*			↑ BDE-209* ↑ α-HBCDD*	
Polish/wax on floor *Yes*	NA	NA	**↑ TBOEP*** **↑ TPHP**** ↑ BDE-47* ↑ BDE-99*	
Room area *<32 m^2*		↓ ATBC**	↑ TDCIPP*	↓ β-HBCDD*
Foam mattresses *Yes*	**↑ DiNP**** ↑ DiDP* ↑ DEHA*		↑ TDCIPP**	↓ DBDPE*
Electronic devices *Yes*	↑ DiNP*** ↑ ATBC*		**↑ TDCIPP**** ↑ TPHP*	
Foam/upholstered furniture >10 yrs[d] *Yes*	NA	NA	↑ BDE-47* ↑ BDE-99* ↑ BDE-100* ↑ TBOEP*	
Upholstered furniture >30 yrs[e] *Yes*	NA	NA	↑ BDE-47* ↑ BDE-99*	
Old soft plastic toys *Yes*	↑ ATBC*		NA	NA
Amount of any plastic toys *>2 crates*	↑ ATBC**		NA	NA
PVC floor *Yes*	**↑ DiNP*****	↓ DMP*	NA	NA
PVC floor year *<1999*[a]	↑ DEHP*	↓ DiNCH*	NA	NA
Recent wall paint *Yes*	↑ DnBP*		NA	NA

*p<0.05, **p<0.01, ***p<0.001. NA; Not assessed. [a] Compared to >2000. [b] The year the preschool activities started. [c] How often the preschool is thoroughly cleaned. [d] In the sampling room. [e] In the preschool.

In our study, we found higher levels of DiNP, ATBC, TDCIPP and TPHP in dust from rooms where electronic devices were present. Furthermore, rooms with foam mattresses had higher levels of DiNP, DiDP, DEHA and TDCIPP in dust. In line with our results, previous studies have shown significant correlations between TPHP in dust and presence of electronics [172] and between TDCIPP in dust and foam mattresses [169]. To the best of our knowledge, studies investigating the influence of electronic devices or mattresses on concentrations of plasticizers in dust are lacking.

The levels of pentaBDEs in dust were higher in preschools with old upholstered or foam furniture. A couple of previous studies have also reported this finding [168,169], whereas other studies have not found this association [145,170,171].

Rooms with PVC floors had significantly higher levels of DiNP in dust. When stratifying for the age of the floors, the levels of DEHP in dust were higher in rooms with older floors, whereas the levels of DiNCH were higher in rooms with newer floors. This is consistent with the gradual substitution of DEHP by non-phthalate plasticizers, such as DiNCH. In an extension of our study (not part of this thesis), performed by the Stockholm City Environmental Management, levels of DiNP and DiNCH in PVC floor samples from a subset of these preschools were significantly correlated with the concentrations of respective compound in dust [238]. In line with our results, another study of Swedish residences performed in 2001 found significantly higher levels of DEHP and BBzP in dust from homes with PVC floorings or wall coverings [163]. In contrast, two previous studies of preschools did not find significant correlations between PVC floorings and phthalates in dust [132,165].

4.4.2.3 Cleaning

Higher levels of TBOEP in preschools and schools compared to home environments have been reported in several studies [122,125,129,239]. It has been suggested that this is due to the use of floor polish in these public environments. In our study, we found significantly higher levels of TBOEP and TPHP in preschools reporting that polish or wax had been used for floor maintenance.

Preschools with a lower cleaning frequency had higher levels of dimethyl phthalate (DMP), DEHT and TBOEP in dust and preschools with infrequent spring cleanings had higher levels of BDE-209 and α-HBCDD. Lower levels of flame retardants in dust from homes with more frequent vacuum cleaning routines have also been reported in a previous study [236]. It can be speculated that the composition of chemicals in the dust may differ between newly deposited dust and dust that has been deposited over a longer time period.

4.4.2.4 Waldorf preschools

Waldorf preschools have essentially no plastics, electronics, foam mattresses or PVC floorings in the indoor environment. Consequently, we hypothesized that the levels of chemicals present in these products should be lower in these preschools. In our study, the concentrations of most chemicals in dust from Waldorf preschools were generally in the low end of the concentration range. Furthermore, we found significantly lower levels of DiNP, TDCIPP and TPHP in Waldorf preschools compared to other preschools. The lack of significant results for the other chemicals may be due to low statistical power as a result of the low number of Waldorf preschools in our study. Nevertheless, these results show that there are other sources of the studied chemicals in preschool dust, in addition to visible plastics, electronics, PVC floors and mattresses.

4.4.3 Is dust a relevant source for children's total exposure?

The relative contribution from preschool dust to children's total exposure was 27%, 19%, 5%, 2% and 6% for DiNP, DEHP, BBzP, DnBP and BPA, respectively. In other words, the total exposure of DiNP and DEHP can to some extent be affected by dust ingested at the preschool. In line with our findings, previous studies have found that DEHP is the phthalate with the highest relative contribution from dust, compared to other phthalates (DiNP has not yet been studied) [154,155]. This is contradictive to previous studies showing that high molecular weight phthalates, such as DEHP and DiNP, mainly originate from the diet, whereas other phthalates are more dependent on other exposure sources, such as dust [30,240,241].

There were no significant correlations between phthalates, DiNCH or BPA in preschool dust and the corresponding metabolites in children's urine. In contrast to these results, previous studies have found significant correlations between preschool and/or household dust and urinary levels of some phthalate metabolites [132,133,135]. The lack of correlations in our study may be due to the low number of participating children per preschool or that morning urine samples reflect the exposure to these short-lived compounds from the home environment rather than the preschool environment. In concordance with the lack of associations between dust and urine, children's urinary levels of plasticizers were not seemingly affected by different variables in the preschool environment.

Significant correlations between levels in hand wipes and dust were found for BDE-47 and γ-HBCDD, TBBPA, TBOEP and TPHP, but not for the other six studied compounds. Significant correlations between PBDEs in dust and children's hand wipes have also been shown in previous studies [141,203]. These results indicate that chemicals in dust end up on children's hands, where they can be ingested via hand-to-mouth exposure. Another possibility is that chemicals present in dust and hand wipes, respectively, share common exposure sources in the indoor environment. In addition, levels of a metabolite of TPHP in urine were significantly correlated with TPHP in dust and hand wipe samples, which is in concordance with a previous study of children [151]. This result indicates that indoor dust may be a relevant exposure source for OPEs in children.

4.4.4 Is chemical exposure in the preschool a threat to children's health?

Hazard Quotients (HQ) were used to quantify the relation between estimated intakes from preschool dust and health based reference values. The highest HQs (i.e. smallest margins between exposure and risk level) were found for DEHP and DiNP, for which the estimated exposure via preschool dust were approximately 1% and 10% of the reference values using the geometric mean and 95th percentile concentration in dust, respectively. For other plasticizers, BFRs and OPEs, there were large margins between the exposure from dust and respective reference value.

Given these results, one can ask the question: If chemical exposures from preschool dust are lower than the levels where health effects may occur, is chemical exposure in the preschool environment still of concern for children's health or can we stop caring about this issue?

First of all, we have only assessed the intake of the chemicals from preschool dust. However, there are other exposure sources in the preschool environment, such as ingestion of food, inhalation of air and direct contact or mouthing of objects, which contribute to children's total exposure. In line with the precautionary principle, the presence of products or materials containing the most hazardous chemicals (such as DEHP and PBDEs) should be kept at a minimum in environments where children spend a considerable part of their time.

Furthermore, the recommended interventions do obviously not target chemicals that are currently used without restrictions. On the contrary, substitution of old materials may increase the levels of these chemicals in preschool dust. According to current risk assessments, these chemicals are generally considered safe to use and to be better alternatives to the chemicals that are being phased out. However, lacking or uncertain risk assessments of these compounds, due to insufficient exposure and toxicity data, calls for continuous monitoring of these compounds in children's close environments.

5. CONCLUSIONS

There is a general lack of exposure information for many chemicals used in the society, and especially for children. In this thesis, we have developed an automatic classifier for overviewing published exposure information and generated more knowledge about exposure to historically widely used as well as emerging chemicals in children, with focus on the home and preschool environment.

The most important conclusions from the thesis are:

- The automatic classifier for exposure information has potential to constitute the foundation for a text mining tool, which could be used by researchers to facilitate information gathering and classification. The evaluation showed that the classifier can be used to support literature collection, overview exposure information for individual or groups of chemicals and identify knowledge gaps (study I).
- The main exposure determinants for most phthalates and BPA were different food items, whereas use of personal care products and cosmetics were the major determinants for internal levels of parabens and MEP. These results showed that the questionnaire developed within the harmonized biomonitoring project DEMOCOPHES was suitable for overall source identification (study II).
- Children were more highly exposed to chemicals present in food and in the indoor environment, compared to the mothers, whereas the mothers had a higher exposure to chemicals used in cosmetics and personal care products. However, there were significant correlations between the mother-child pairs, indicating common exposure sources in the home environment (study II).
- The age of the preschool building as well as the presence of certain materials and products in the preschool environment had impact on the levels of chemicals in dust. Therefore, by discarding certain old products, such as mattresses, electronics and PVC floors, the levels of hazardous chemicals in the preschool can, to some extent, be decreased (study III and IV).
- Levels of five out of eleven BFRs and OPEs were significantly correlated between preschool dust and children's hand wipes. Furthermore, the levels of an OPE in urine and dust were significantly correlated. These results indicate that preschool dust contributes to children's total exposure. Phthalates and BPA in preschool dust were not significanly correlated to respective metabolite in urine and the estimated relative contributions of these compounds from dust were low to moderate, indicating that other exposure sources are more relevant for these compounds.
- Intakes of phthalates, bisphenols, BFRs and OPEs via preschool dust were below available health based reference values. However, for some of the studied compounds, reference values are uncertain or lacking (study III and IV).

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