Estimating children's exposure to per- and polyfluoroalkyl substances

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Abstract

Per- and polyfluoroalkyl substances (PFASs) are highly stable, surface active chemicals, which are water- and oil/stain-repellent. Because of their unique properties, PFASs are widely used in consumer products. Their application ranges from personal-care products, food packaging and textiles to interior materials, thus leading to a continuous human exposure to PFASs in every-day life. Possible exposure pathways are the ingestion of food, drinking water and dust; the inhalation of fine dust and air; as well as dermal absorption after contact with the products and dust.

Despite the increasing number of monitoring studies, including measurement of concentrations in human exposure media and blood, childhood exposure is poorly understood.

The state of current knowledge on childhood exposure was investigated in **paper I**, by reviewing existing PFAS literature on exposure media, on daily intakes via different exposure pathways and on levels in blood and serum. Subsequently, recommendations for future research needs were made and implications presented on the regulation and assessment of PFASs. For **paper II, III** and **IV**, a cohort of background-exposed Finnish children was followed throughout childhood. Indoor air and floor dust samples of their bedrooms were taken at the age of 10.5 years in 2014/2015 and analysed for a wide range of PFASs (**paper II** and **III**). The estimated daily intakes (EDIs) via these two media were calculated in **paper III**. The EDIs revealed that dust ingestion and air inhalation are of similar importance for the intake of single perfluoroalkyl acids (PFAA), if the metabolism of PFAA precursors to PFAAs was included. The metabolism of precursors contributed considerably to the total intake of PFAAs via the inhalation of air (e.g. 38 % for perfluorooctanoic acid (PFOA) and 90 % for perfluorooctane sulfonic acid (PFOS)) and to the total intake of PFOS via the ingestion of dust (69 %; median values at the intermediate exposure scenario). In **paper IV**, the internal exposure during childhood was monitored by measuring serum concentrations, which were decreasing with age; and by calculating body burdens at 1, 6 and 10.5 years of age, which were constant or increasing, depending on the respective PFAS. These results demonstrated that it is crucial to account for growth dilution when studying exposure trends and PFAS intakes during childhood.

This thesis contributes to a better understanding of children's exposure to PFASs, especially the internal exposure during childhood and the relative importance of both, indoor exposure pathways, as well as individual PFASs.

Keywords: *PFAS, PFAA, fluorinated, fluorotelomer, FTOH, PAP, early life, child, human, exposure, intake, indoor, bedroom, air, dust, serum.*

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"We live in a society exquisitely dependent on science and technology, in which hardly anyone knows anything about science and technology." – Carl Sagan

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Abstract

Per- and polyfluoroalkyl substances (PFASs) are highly stable, surface active chemicals, which are water- and oil/stain-repellent. Because of their unique properties, PFASs are widely used in consumer products. Their application ranges from personal-care products, food packaging and textiles to interior materials, thus leading to a continuous human exposure to PFASs in everyday life. Possible exposure pathways are the ingestion of food, drinking water and dust; the inhalation of fine dust and air; as well as dermal absorption after contact with the products and dust.

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This thesis contributes to a better understanding of children's exposure to PFASs, especially the internal exposure during childhood and the relative importance of both, indoor exposure pathways, as well as individual PFASs.

Sammanfattning

Högfluorerade ämnen (PFAS) är mycket stabila, ytaktiva substanser som är vatten- och fett/smuts-avvisande. På grund av deras egenskaper, används PFAS i många konsumentprodukter. Användningsområdena sträcker sig från hudvårdsprodukter, matförpackningar och textiler till byggmaterial, vilket leder till att människor utsätts för en kontinuerlig exponering av högfluorerade ämnen i vardagen. Möjliga exponeringsvägar är intag av livsmedel, dricksvatten och damm, inandning av partiklar och luft, samt absorption genom huden efter kontakt med produkter och damm. Trots det ökande antalet studier av koncentrationer i miljön, inklusive mätning av exponeringsmedier för människor och blodkoncentrationer, är kunskaperna om barns exponering bristfälliga.

Det nuvarande kunskapsläget kring exponering under barndomen undersöktes i **artikel I**, genom att sammanfatta och syntetisera existerande PFAS studier om halter i exponeringsmedier, dagligt intag genom olika exponerings vägar samt halter i blod och serum. Därefter utarbetades rekommendationer för framtida forskningsbehov och implikationer för reglering och bedömning av högfluorerade ämnen. En kohort av bakgrundsexponerade finska barn följdes genom barndomen i **artikel II**, **III** och **IV**. Inomhus luft- och golvdammprover i deras sovrum togs när de fyllde 10.5 år under 2014/2015 och analyserades för ett stort antal PFAS ämnen (**artikel II** och **III**). Det uppskattade dagliga intaget (EDI) genom de två medierna beräknades i **artikel III**. EDI:t visade att intaget av damm och luft har en likvärdig relevans för enskilda perfluorerade syror (PFAA), om metabolismen av PFAA prekursorer till PFAA räknas in. Prekursorerna bidrog betydligt till det totala PFAA intaget genom luftinandningen (t.ex. med 38 % för perfluoroktansyra (PFOA) och 90 % för perfluoroktansulfonsyra (PFOS)) och till det totala PFOS intaget genom damm (med 69 %; median för det genomsnittliga exponeringsscenariot).

Den interna exponeringen under barndomen undersöktes i **artikel IV** genom serumkoncentrationsanalyser, som visade en minskning med ålder, och genom att beräkna den totala kroppsbelastningen vid 1, 6 och 10,5 års ålder, som var konstant eller ökade beroende på PFAS. Dessa resultat visade att utspädningen med den ökande kroppsvikten är ytterst viktigt när man studerar exponeringstrender och intag av högfluorerade ämnen under barndomen.

Den här avhandlingen bidrar till en bättre förståelse av barns exponering till PFAS, speciellt för den interna exponeringen under barndomen och den

relativa betydelsen av både inomhus exponeringsvägar och särskilda högfluorerade ämnen.

Zusammenfassung

Per- und Polyfluoroalkyl Substanzen (PFASs) sind hoch stabile, oberflächenaktive Chemikalien, die wasser-, fett/schmutzabweisend sind. Wegen ihrer Eigenschaften sind PFASs in Verbrauchsgütern weit verbreitet. Die Anwendungsgebiete reichen von Körperpflegeprodukten, über Textilien, bis hin zu Verpackungs- und Baumaterialien; was dazu führt, dass Menschen PFASs kontinuierlich in ihrem Alltag ausgesetzt sind. Mögliche Aufnahmewege sind oral über Lebensmittel, Trinkwasser und Staub; über das Einatmen von Feinstaub und Luft, sowie über die Haut nach Kontakt mit Produkten und Staub.

Obwohl die Anzahl der Monitoring Studien, inklusive Messung von menschlichen Aufnahmemedien und Blutkonzentrationen, steigt, ist die Exposition während der Kindheit noch kaum verstanden.

Der gegenwärtige Wissensstand um die Exposition im Laufe der Kindheit wurde in **Artikel I** durch die Synthese von existierenden PFAS Studien zu Expositionsmedien, zur täglichen Aufnahme über verschiedene Expositionswege und zu Blut und Serumkonzentrationen untersucht. Daraus wurden Bereiche mit zukünftigem Forschungsbedarf abgeleitet und deren Rolle in der Gesetzgebung und Bewertung von PFASs erläutert. Für **Artikel II, III** und **IV** wurde eine hintergrundbelastete Gruppe finnischer Kinder während ihrer Kindheit begleitet. Im Alter von 10,5 Jahren (2014/2015) wurden Innenraumluft- und Bodenhausstaubproben in ihren Schlafzimmern genommen und für eine Vielzahl an PFASs analysiert (**Artikel II** und **III**). Die geschätzte tägliche Aufnahme (EDI) über diesen zwei Medien wurde in **Artikel III** berechnet. Die EDIs zeigten, dass die Aufnahme über Staub und Luft eine vergleichbare Relevanz für einzelne Perfluoroalkylsäuren (PFAAs) hat, wenn der Stoffwechsel von Ausgangsstoffen zu PFAAs mit betrachtet wurde. Die Ausgangsstoffe trugen deutlich zur gesamten PFAA Aufnahme über das Einatmen von Luft (z.B. mit 38 % für Perfluoroktansäure (PFOA) und 90 % für Perfluoroktansulfonsäure (PFOS)) und zur gesamten Aufnahme von PFOS über das Schlucken von Staub (mit 69%; Medianwerte für ein durchschnittliches Expositionsszenario) bei. In **Artikel IV** wurde die interne Exposition während der Kindheit durch die Messung von Serumkonzentrationen ermittelt, die mit zunehmenden Alter sanken; und durch die Berechnung der Körperbelastung mit 1, 6 und 10,5 Jahren erfasst, die abhängig von der Substanz konstant war oder stieg. Es zeigte sich, dass es für die PFAS Aufnahme während der Kindheit elementar ist, die mit dem Wachstum einhergehende relative Verdünnung zu berücksichtigen.

Diese Arbeit trägt zum besseren Verständnis der PFAS Exposition von Kindern bei; besonders der internen Exposition im Verlauf der Kindheit, als auch der relativen Wichtigkeit von Aufnahmewegen in Innenräumen und von verschiedenen einzelnen PFAS Substanzen.

Contribution statement of Kerstin Winkens

General

I designed the idea and set-up of the project on children's exposure with the supervisors; established and coordinated the cooperation with the National Institute for Health and Welfare (THL) and the LUKAS2 study; prepared amending documents (water and air sampling protocols and a short questionnaire) for ethical applications with Finnish translational help.

Serum samples were taken within the LUKAS 2 study; dust and air sampling and serum extraction, analysis and peak integration were conducted by cooperation partners at the THL.

Specific papers

Paper I: researched literature; made required calculations and all figures, including the graphical abstract; took the lead in writing the paper, except for topic 4 on pharmacokinetic models.

Paper II: designed the air sampler housings together with the university workshop; produced air samplers (SIPs) with support at Environment and Climate Change Canada; was responsible for the experimental work; developed the GC-MS method after instrumental advice; extracted the air samplers after minor method adjustments; analysed the samples, on LC-MS/MS with instrumental help; processed all sample data; made the figures, graphical abstract and statistical analysis; interpreted the data; took the lead in writing the paper.

Paper III: was responsible for the experimental work; developed the extraction method for dust and extracted the samples, both with assistance; analysed the extracts, on LC-MS/MS after instrumental advice; processed all sample data, including further calculations and statistics; made the figures and graphical abstract; took the lead in data interpretation and writing the manuscript.

Paper IV: conducted parts of the statistics and designed some figures, including the graphical abstract; took the lead in interpreting the data and writing the results, discussion and conclusion parts of the manuscript, revised the introduction and method chapters thoroughly.

List of papers

This doctoral thesis consists of a summary and four papers.

I Winkens K.*, Vestergren R., Berger U., Cousins I.T. (2017): Early life exposure to per- and polyfluoroalkyl substances (PFASs): A critical review. *Emerging Contaminants* 3 (2): 55-68.
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II Winkens K.*, Koponen J., Schuster J., Shoeib M., Vestergren R., Berger U., Karvonen A.M., Pekkanen J., Kiviranta H., Cousins I.T. (2017): Perfluoroalkyl acids and their precursors in indoor air sampled in children's bedrooms. *Environmental Pollution* 222: 423-432.
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III Winkens K.*, Giovanoulis G., Koponen J., Vestergren R., Berger U., Karvonen A.M., Pekkanen J., Kiviranta H. Cousins I.T.: Perfluoroalkyl acids and their precursors in floor dust of children's bedrooms – Implications for indoor exposure. *Submitted manuscript.*

IV Koponen J. * & Winkens K.* (shared first authorship), Airaksinen R., Berger U., Vestergren R., Cousins I.T., Karvonen A.M., Pekkanen J., Kiviranta H.: Longitudinal trends of per- and polyfluoroalkyl substances in children's serum. *Submitted manuscript.*

* corresponding author

Abbreviations

Acronym	Definition
ASE	accelerated solvent extraction
ATSDR	Agency for Toxic Substances and Disease Registry
bw	bodyweight
C_8, C_x	backbone of 8 or x carbon atoms as a chemical structure
C18 column	carbon 18 column for LC-MS
CLP	Classification, Labelling and Packaging (Regulation)
ECF	electrochemical fluorination
ECHA	European Chemicals Agency
EDI	estimated daily intake
EPA	Environmental Protection Agency
EtFOSE	*n*-ethyl-perfluorooctane sulfonamidoethanol
FASA	perfluoroalkane sulfonamide
FASAA	perfluoroalkane sulfonamidoacetic acid
FASE	perfluoroalkane sulfonamidoethanol
FOSA	perfluorooctane sulfonamide
FOSAA	perfluorooctane sulfonamidoacetic acid
FOSE	perfluorooctane sulfonamidoethanol
FT(M)AC	fluorotelomer (meth)acrylate
FTOH	fluorotelomer alcohol
FTSA	fluorotelomer sulfonic acid
GC-(PCI-)MS	gas chromatograph (positive chemical ionisation) (coupled to) mass spectrometer
ID	inner diameter
l-	linear-

LC-(ESI-)MS/MS	liquid chromatograph (electrospray ionisation) (coupled to) mass spectrometer/mass spectrometer
log K_{oa}	octanol-water partition coefficient
M2PFOA	PFOA with 2 mass-labelled carbons
M8PFOS/PFOA	PFOS/PFOA with 8 mass-labelled carbons
MeFOSE	*n*-methyl-perfluorooctane sulfonamidoethanol
NOAEL	no-observed-adverse-effect level
PAP	polyfluoroalkyl phosphoric acid ester
PBT	persistent, bioaccumulative and toxic
PFAA	perfluoroalkyl acid
PFAS	per- and polyfluoroalkyl substance
PFCA	perfluoroalkyl carboxylic acid
PFDA	perfluorodecanoic acid
PFDoDA	perfluorododecanoic acid
PFHxA	perflurohexanoic acid
PFHxS	perfluorohexane sulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonic acid
PFSA	perfluoroalkane sulfonic acid
POP	persistent organic pollutant
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (European chemical legislation)
SIP	sorbent impregnated polyurethane
SRM 2585	standard reference material 2585 (dust)
SVHC	substance of very high concern
TDI	tolerable daily intake
UPLC	ultra-performance liquid chromatography
vPvB	very persistent and very bioaccumulative

1 Background

1.1 Per- and polyfluoroalkyl substances (PFASs)

Per- and polyfluoroalkyl substances (PFASs) is a collective term for chemicals, of which more than 3000 are commercially available (KEMI 2015) and which are produced in industrial processes (Buck et al. 2011). All PFASs have a fully (per-) or partly (poly-) fluorinated carbon chain, which is attached to different functional groups (Figure 1). The perfluoroalkyl chains can be bound to acids (perfluoroalkyl acids, PFAAs), such as carboxylic acids, resulting in perfluoroalkyl carboxylic acids (PFCAs), or sulfonic acids, i.e. perfluoroalkane sulfonic acids (PFSAs).

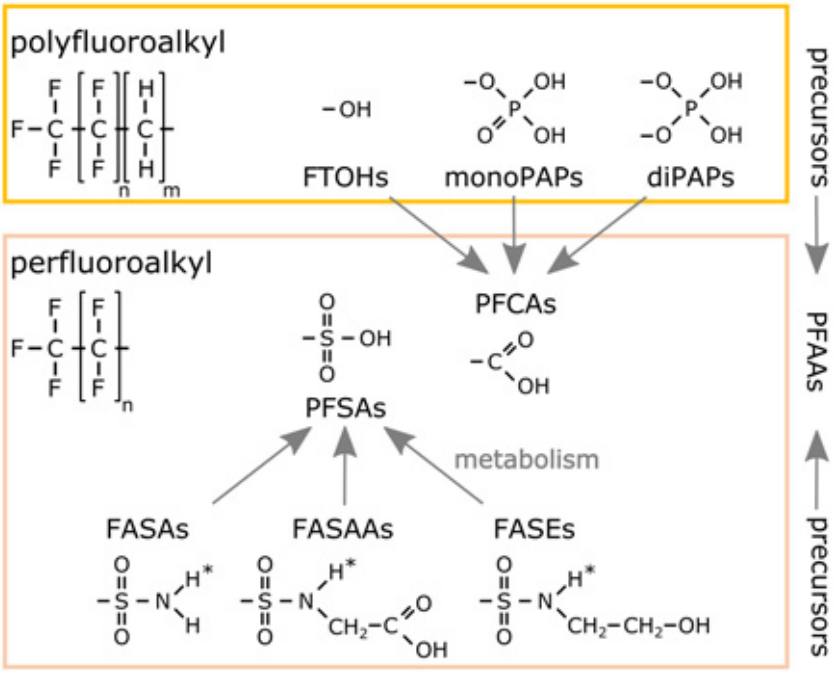

***Figure 1**: Generic chemical structures of PFASs and their division into subclasses relevant for this thesis, including metabolic routes to PFCAs or PFSAs from various precursors; Note for FASAs/AAs/Es: replacing the –H marked with an asterisk (*) by $-CH_3$ (methyl) or $-CH_2$-CH_3 (ethyl) leads to name prefixes "Me-" or "Et-", respectively.*

The per- or polyfluoroalkyl chain can differ in length for all substance classes, according to which the name changes: e.g. the C_8 PFCA is called perfluorooctanoic acid (PFOA), which has 7 perfluorinated carbons as the last carbon belongs to the carboxylic acid; and the C_8 PFSA is called perfluorooctane sulfonic acid (PFOS), which has 8 perfluorinated carbons. Those two PFAAs are the most well studied substances (Wang et al. 2017). Further perfluoroalkyl substance classes of importance for this thesis are perfluoroalkane sulfonamides (FASAs), sulfonamidoethanols (FASEs) and sulfonamidoacetic acids (FASAAs), of which mainly the C_8-compounds were investigated (i.e. "octane=O": FOSA, FOSE and FOSAA). Polyfluorinated compounds like fluorotelomer alcohols (FTOHs), polyfluoroalkyl phosphoric acid esters (PAPs) and fluorotelomer sulfonic acids (FTSAs) have the prefix "n:m" in common, of which "n" indicates the number of perfluorinated carbons and "m" the number of non-fluorinated methylene bridges (-CH_2-), e.g. 6:2 FTOH (Figure 1). The terminology and acronyms of PFASs in this thesis are based on Buck et al. (2011), which are however not consistently applied in literature.

The carbon-fluorine (C-F) bond, is the strongest existing single carbon bond (Smith and March (2001) cited in Mazurek and Schwarz (2003)) and among the strongest single covalent bonds. This provides PFASs with an intrinsic stability, which is highly favourable in many industrial applications, especially under extreme conditions like high temperature, or low/high pH values (Buck et al. 2012). PFAS-based surfactants are unique in lowering aqueous surface tensions at low surfactant concentrations (Buck et al. 2011). Moreover, fully fluorinated carbon chains are simultaneously hydrophobic and lipophobic due to their low surface energies and can thus provide both water and oil/stain repellency (Kunieda and Shinoda 1976). The exceptional combination of physical-chemical properties of PFASs has led to their use in a wide range of industrial and consumer applications (Buck et al. 2011). For example, PFASs can be found in paints and surface treatments of furniture, household products (Kotthoff et al. 2015), cardboard and paper food packaging (Liu et al. 2015; Trier et al. 2011); in textiles, including upholstery, carpets and clothing (Kotthoff et al. 2015; Liu et al. 2015; Vestergren et al. 2015); in cosmetics and personal care products (Fujii et al. 2013) for their emulsifying properties; in floor treatment and cleaning products (Kotthoff et al. 2015; Liu et al. 2015) and in aqueous film-forming foams for extinguishing fires of highly flammable liquids (D'Agostino and Mabury 2014).

1.1.1 PFASs' production history

Since the 1950s, PFASs have been produced via two major processes, electrochemical fluorination (ECF) and telomerisation. ECF is a process during which hydrocarbons of organic raw materials (e.g. $C_nH_{2n+1}SO_2F$ or

$C_nH_{2n+1}COF$) are replaced with fluorine atoms and existing bonds are broken and rearranged (Buck et al. 2011; Buck et al. 2012; Wang et al. 2014). The intermediates are perfluoroalkyl fluorides with residual impurities of multiple chain lengths (odd and even), as well as branched and linear isomers (Buck et al. 2011), that are further reacted to various PFASs. This manufacturing process (ECF) was historically prevailing (Paul et al. 2009). Since 2002, the major PFASs producer, the 3M Company, stopped using it for long-chain PFAAs (PFSAs ≥6 and PFCAs ≥7 perfluorinated Cs, i.e. ≥perfluorohexane sulfonic acid (PFHxS) and ≥PFOA, respectively) (Buck et al. 2011; US EPA 2000). ECF is nowadays still applied for long-chain PFAS production mostly in Asia (Buck et al. 2011; Paul et al. 2009), or for the currently dominating production of short-chain C_4 PFASs (Renner 2006; Ritter 2010).
Telomerisation describes the reaction of a perfluoroalkyl iodide ($C_nF_{2n+1}I$) with tetrafluoroethylene ($CF_2=CF_2$) and the subsequent reaction of the intermediate with ethylene ($CH_2=CH_2$) (Buck et al. 2011). The second part of the reaction introduces the non-fluorinated carbon chain link into the molecule, which can be more easily reacted with different chemical groups to form PFASs (Buck et al. 2012). Due to the lack of rearrangements, telomerisation is a more targeted production process in comparison to ECF. The chosen perfluoroalkyl starting material determines the final chain length and for commercial applications linear homologues are highly favoured (Buck et al. 2011). PFASs can be used in both low molecular weight products (e.g. surfactants) or in high molecular weight polymeric products (i.e. side-chain fluorinated polymers used for oil/water repellency in textiles and food packaging, and fluoropolymers such as polytetrafluoroethylene, i.e. PTFE). PFASs can be released from these products to the environment via multiple pathways (for more details see Buck et al. 2011; Prevedouros et al. 2006). After the millennium, the production of PFASs (especially of long-chain PFASs) shifted from the United States, Western Europe and Japan to China, India, Poland and Russia (Wang et al. 2014).

1.2 Environmental transport and fate

Possible point sources for PFAS emissions into the environment are: industrial sites, including producers and downstream industrial users (Alder and van der Voet 2015), firefighting training sites (Filipovic et al. 2015) and wastewater treatment plant effluents (Filipovic and Berger 2015) as well as landfills (Benskin et al. 2012) where PFASs are released from the amassed consumer products into the environment.
Human activities, such as washing textiles, showering, or rinsing paintbrushes, can release PFASs into wastewater. They can also abrade with fine material particles or fibres from products and/or partition to dust, or can outgas into the air, of which the latter is especially the case for more volatile PFASs

(e.g. FTOHs). Because of the emissions from consumer products, urban air concentrations are higher than rural air concentrations (Gawor et al. 2014; Jahnke et al. 2007). Atmospheric long-range transport is the reason for the detection of PFASs in very remote regions such as the artic (Gawor et al. 2014; Shoeib et al. 2006).
PFAS precursors, e.g. FTOHs, PAPs and FOSAs/Es, degrade eventually via oxidation to the water soluble PFAAs in the environment, which exist in their ionised form at environmental pH values (de Voogt 2010; Ellis et al. 2004). The PFAAs are highly resistant to further degradation in the hydrosphere and can be globally transported in ocean water currents. A global "ocean inventory" of PFAAs (i.e. estimated amount of PFAAs in the world's surface oceans) matched the historical emission estimates (i.e. estimated amount of PFAAs globally released since the 1950s) of four PFCAs around a factor of 1.5 (Wang et al. 2014). This mass balance agreement supports the view that the world's oceans are the greatest reservoir and sink for PFAAs.

Organisms take up PFASs from the environment and with their diet, because of the chemicals' ubiquitous presence and mobility. Long-chain PFAAs bioaccumulate in organisms and biomagnify along the food chain. Hence, predator species have globally higher tissue or body liquid concentrations of PFASs than species at lower trophic levels (Giesy and Kannan 2001; Haukås et al. 2007).

1.3 Human exposure

Humans are continuously exposed to PFAAs and their precursors via several pathways: the inhalation of air; the ingestion of dust, beverages, drinking water and food; as well as the dermal absorption after contact to cosmetics, personal care and other consumer products, such as textiles. The source from which humans receive the contamination is called exposure medium, e.g. dust. The contaminants in the exposure media air and dust originate − as stated above − from household products. Dietary products can be exposure media for humans due to a) uptake of PFASs into crops from contaminated water, soil or fertilisers (Blaine et al. 2014; Lechner and Knapp 2011), b) bioaccumulation in animals' tissues and their products from contaminated feed and the environment (Ahrens et al. 2015; Vestergren et al. 2013) and, c) contamination of food items with PFASs while food processing or from food packaging materials (Begley et al. 2005; Trier et al. 2011). For adults, food ingestion is the major exposure pathway for long-chain PFASs with decreasing importance in decreasing chain lengths (Gebbink et al. 2015a; Vestergren et al. 2012).
External exposure is hereby defined as the contact of humans with chemicals in the exposure media, whereas the *internal exposure* refers to the chemicals'

amount or concentration in the body. Internal exposure is highly influenced by physiological processes such as absorption, distribution, metabolism and excretion.
Exposure of organisms to PFAAs can generally be divided into direct and indirect exposure. Immediate exposure from the exposure media to PFAAs is termed as *direct exposure*, while the exposure to PFAA precursors is referred to as *indirect exposure*. The precursors can be metabolised to form PFAAs in the body after their uptake and thus contribute indirectly to the total body burden of PFAAs (Fasano et al. 2006), which is defined as the total absolute amount of a chemical in the human body. Examples of precursors contributing to the indirect exposure of PFCAs are fluorotelomers (e.g. FTOHs and PAPs), and examples of precursors contributing to indirect exposure of PFSAs are perfluoroalkyl sulfonamides (e.g. FASAs, FASEs and FASAAs; Figure 1).

1.3.1 Estimating the exposure intake

Exposure can be estimated quantitatively by analysing the occurrence of PFASs in different external exposure media and multiplying the measured concentrations with exposure factors of the corresponding media (e.g. inhalation rate). The exposure factors are listed in the exposure handbook (US EPA 2011). Relating the calculated external exposure to bodyweight (bw) results in an estimated daily intake (EDI, example for exposure via air):

$$EDI_{air}\ [ng\ /\ kg\ bw\ /\ day] = \qquad \textbf{\textit{Equation 1}}$$

$$\frac{air\ concentration\ [ng/m^3] \times inhalation\ rate\ [m^3/day]}{bodyweight\ [kg]}$$

The equation above can be extended by further factors, e.g. the absorbed fraction of a chemical, which is the portion of a chemical passing through a membrane into the body. As an example, in the case of chemical exposure via food ingestion: a percentage of the chemicals will not pass intestinal membranes and be readily excreted with non-digestive food parts. Varying values can even be applied for these factors to achieve different exposure scenarios, with low or high absorption etc. (typically: low/intermediate/high exposure scenario). The contribution of direct and indirect exposure to the total PFAA exposure (e.g. PFOA) can be calculated by including the metabolisation rate constants of precursors (8:2 FTOH) to PFAAs into Equation 1 (Gomis et al. 2016). However, the biotransformation of precursors was reported to be of minor importance (2-5 % for PFOS and up to 8 % for PFOA) for the total exposure in an intermediate exposure scenario for adults by Vestergren et al. (2008). It should be emphasised that EDIs are estimates and highly dependent

on the input factors. These are often based on assumptions with inherent uncertainties when transferring uptake or metabolism rates from rodents to humans and extrapolating between different ages.

Another approach to assess human exposure is to determine the internal exposure directly by measuring PFASs in blood or serum samples − so called biomonitoring. For PFASs, this was done by Hansen et al. (2001) for the first time, half a century after the beginning of commercial PFAS production. Blood is the typical sample matrix of choice for the biomonitoring of PFASs, as they bind to and circulate with serum proteins in the body (Beesoon and Martin 2015). This is different from most classical contaminants (e.g. dioxins and polychlorinated biphenyls) that partition into fat (Jensen 1987). An advantage of biomonitoring over the external exposure estimates is that the internal exposure can be accurately determined accounting for all pathways, as well as the absorption, distribution and metabolism in the body and the elimination from the body; whereas the contribution of single exposure pathways and precursors can only be captured via external exposure quantification and EDIs. Serum concentration is however a time integrated measure of current and previous exposure due to accumulation of PFAAs (i.e. slow elimination), caused by their long half-lives of several years (Li et al. 2018; Olsen et al. 2007; Y Zhang et al. 2013). In contrast to that, the measurement of PFAS concentrations in exposure media solely depicts the current external exposure.

1.3.2 Childhood exposure

Children are exposed to PFAAs and their precursors on a daily basis, just like adults. Their exposure already begins in their mothers' womb, where they are subjected to these substances via transplacental transfer from their mother's blood (e.g. Beesoon et al. 2011). After birth, the ingestion of maternal breastmilk also poses a source of exposure to PFASs for the child (Figure 2, p.10 and Fromme et al. 2010). These two pathways have to be additionally considered for children, because of the short time intervals between their developmental stages as well as the PFAS exposure and uptake. Moreover, dust was hypothesised to represent an important exposure pathway for children due to the higher hand-to-mouth and object-to-mouth behaviour (collective term: mouthing behaviour) in comparison to adults (Trudel et al. 2008).

At this point it should be mentioned that in this thesis the terms "child(ren)" and "childhood" are applied for any life stage between birth and adulthood (≤18 years), if not mentioned specifically otherwise; although terms for different age ranges were suggested in a guidance document (EFSA 2011), they were deemed not applicable because neither the behavioural nor the physiological developmental age classification fits these defined terms entirely (US EPA 2005).

The relative importance of different exposure pathways to PFASs is poorly understood for children, as are trends during childhood. Reasons for this are (among others) that existing studies a) mostly survey only single exposure pathways b) mostly sample at a single time point during childhood or pregnancy, c) partly cluster children of different ages or even of different gender, d) have a low number of individuals/samples, and e) are conducted at different calendar years and in different geographical regions.
It is difficult to draw conclusions for children's general PFAS exposure when comparing studies investigating different child ages or age clusters mentioned under b) and c) as well as when the results were based on low sample numbers (i.e. d)). Further complications affecting study comparisons are the many physiological changes occurring throughout the pregnancy and the breastfeeding period. These affect sampling matrices, e.g. serum, in their composition and volume, for both the mother and the foetus/child, which makes the exact time point of sampling essential to consider before study comparison. Additionally, behavioural changes during childhood alter the importance of exposure pathways over time. The combination of the dynamics tied to the physiological and behavioural changes and the fact that mostly single exposure pathways are investigated (i.e. a)) does not allow for a detailed understanding of the relative importance of major exposure pathways or trends. Lastly, temporal and geographical (i.e. e)) differences are of great importance when comparing studies with each other. The production shift of PFASs (see 1.1.1) causes variations in emissions and consumer product concentrations depending on sampling years and locations of the studies. Therefore, the production shift itself leads to an altered exposure of humans to PFASs. Thus, especially for children it becomes extremely difficult to separate the production-related PFAS exposure changes from the possibly simultaneous development-related (i.e. behavioural and physiological) changes in exposure.

1.4 Toxicity of PFASs

The toxicity of PFASs is investigated mostly in laboratory studies as the causal dose-response relationship is evident due to the controllable conditions of most parameters. Toxicological effects in animal or *in vitro* studies are various and mainly reported for C_8 chemicals, as e.g. reviewed by DeWitt (2015) and Stahl et al. (2011). Some precursors or their metabolites are shown to be toxic or even exceed the toxicity of PFAAs (Rand and Mabury 2017), which might be of concern, as the biotransformation of precursors is known for several precursors and species (Butt et al. 2014).
Ecotoxicological effects have been shown to increase with PFAA chain lengths, which might be related to the increasing bioaccumulation potential. Mixture toxicity of PFASs and multigenerational effects have hardly been in-

vestigated (Ahrens and Bundschuh 2014). A systematic review including several mammalian and non-mammalian studies concluded a reduced birth weight after prenatal exposure to PFOA (Koustas et al. 2014). PFOS was shown to affect the neurodevelopment e.g. in rats after prenatal exposure (Zeng et al. 2011). Oral PFOA gavage to pregnant mice caused an increase in the number of pregnancy losses and neonatal deaths and teratogenic effects such as reduced bone formation (Lau et al. 2006). A long-term feeding study of male rats with PFOA's salt (ammonium perfluorooctanoate) resulted in a higher occurrence of benign liver, testis and pancreas tumours (Biegel et al. 2001). The mechanism inducing various toxic effects in the liver was assumed to be receptor dependent (peroxisome proliferator-activated receptor-alpha, PPARα). The receptor has a different structure for humans and these toxic effects were thus assumed to be irrelevant for humans (Kennedy et al. 2004). Recently, liver effects following PFOA exposure were also shown for genetically modified mice without the receptor (Filgo et al. 2015).

Epidemiological human effect studies require a thorough study design and large participant numbers. This prerequisite is necessary in order to separate health effects associated with chemical exposure from health effects based on genetic, environmental, social and life-style factors. The C8 Health Project is probably the most prominent epidemiological study focusing on PFASs (Frisbee et al. 2009). For a long period of time, tens of thousands of people were exposed to elevated levels of PFOA via contaminated drinking water close to a PFAS manufacturing site in the Mid-Ohio Valley, West Virginia. Among the effects that were positively linked to PFOA exposure were testicular and kidney cancer (Barry et al. 2013), higher serum cholesterol levels (Frisbee et al. 2010) and lower levels of sex hormones as well as of a growth factor in children (Lopez-Espinosa et al. 2016). Further, later onset of puberty with increasing PFOS and PFOA exposure was observed for girls; for boys this association was only observed for PFOS (Lopez-Espinosa et al. 2011). Other human studies showed significant evidence for reduced birth weight (Johnson et al. 2014; systematic literature review); effects on cell cycle regulation (Andersen et al. 2008); and evidence for positive associations with effects on later childhood stages after early life exposure to some PFASs, such as adiposity (Braun et al. 2016), thyroid-stimulating hormone levels, i.e. endocrine disruption (Ballesteros et al. 2017), and immune suppression (Pennings et al. 2016). PFOA was recently classified as "Possibly carcinogenic to humans" by the International Agency for Research on Cancer (IRAC 2017).

1.5 Regulation, restriction & risk assessment of PFASs

The environmental fate and toxicological effects of PFASs have led to authority-driven phase outs, classifications or legally binding restrictions of some PFASs and applications:

The 3M Company voluntarily phased out the production and application of PFOS and PFOS-related chemistry in their products by 2002 (US EPA 2000). Eight PFAS manufacturers followed the invitation of the US Environmental Protection Agency (EPA) to join the global PFOA Stewardship Program towards the elimination of PFOA, PFOA precursors and longer chain PFCAs from emissions and products by 2015 and agreed to a reduction by 95 % in 2010 (US EPA 2006). In 2009, PFOS, its salt and ECF starting material were added under Annex B of the Stockholm Convention on Persistent Organic Pollutants (POPs) to achieve a global positive list of certain uses only (UNEP 2009). PFHxS, PFOA, their respective salts and related compounds are currently suggested as candidates for the Stockholm Convention on POPs, of which PFOA already passed the risk profiling (UNEP 2016). Since 2013, PFOA is classified as carcinogenic and reprotoxic under the Classification, Labelling and Packaging (CLP) Regulation (European commission 2013).
Since 2012, several PFCAs (C_8-C_{14}) and PFHxS have been listed as substances of very high concern (SVHC; ECHA 2017b) under the European chemical legislation: Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). The basis for regulation of PFASs is their classification as either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative (vPvB) and or reprotoxic.

The number of restricted or regulated PFASs is however just a minor fraction of the several thousand existing compounds, on which research data are lacking (Wang et al. 2017). At least some novel PFASs seem to have similar properties to the already restricted PFASs (Gomis et al. 2015).
To evaluate the likely potential of a chemical to cause adverse (health) effects, a risk assessment is conducted. A risk assessment is a combination of both an exposure and a hazard assessment (i.e. obtaining the no-observed-adverse-effect level (NOAEL) from response/effect data). The estimated exposure should be below the set threshold from the hazard assessment, to achieve an acceptable risk for possible adverse health outcomes.
In 2008, the European Food Safety Authority (EFSA) set tolerable daily intake (TDI) thresholds of 150 ng PFOS/kg bw/day and 1500 ng PFOA/kg bw/day that should safeguard a lifelong human exposure via food. These TDIs are based on toxicological studies on adult rodents and monkeys (EFSA 2008). In 2015, the Agency for Toxic Substances and Disease Registry (ATSDR) published lower minimal risk levels for PFOS and PFOA (30 and 20 ng/kg bw/day, respectively) based on the most sensitive non-carcinogenic

toxicological endpoint (hepatic). Those levels are however not legally binding (ATSDR; 2015). Attempts are made to set thresholds for the sum of several PFASs, e.g. in Sweden by the National Food Agency with an action level of 90 ng/L drinking water for the sum of 11 PFASs (Livsmedelsverket 2016).

1.6 Objective of the thesis

The overarching aim of this thesis was to improve the understanding of childhood exposure to per- and polyfluoroalkyl substances. This was done by reviewing the current literature (**paper I**), quantifying the external exposure via air and dust in a child-specific indoor environment (**paper II** and **III**) and finally quantifying the internal exposure throughout different childhood stages (**paper IV,** Figure 2).

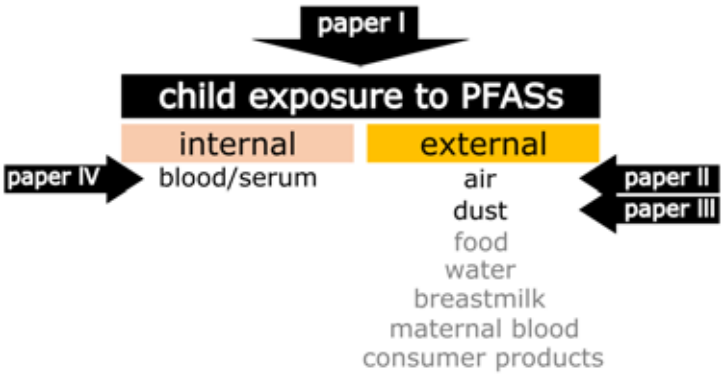

***Figure 2**: Topics of the four papers of this thesis.*

Paper I aimed to investigate the current state of knowledge on early life exposure to PFASs by reviewing the literature both on biomonitoring studies of serum levels in comparison to adults', as well as on external exposure matrices, uptake factors and estimated daily intakes via different pathways. It was investigated whether children are exposed more to PFASs in comparison to adults. Knowledge deficits were identified, based on which future research needs and improvements for the current regulation were suggested.

Paper II aimed at elucidating current indoor air levels of PFAAs and precursors in children's bedrooms and their possible associations with housing and living parameters and production processes.

Paper III aimed at quantifying current indoor dust concentrations for different precursors and PFAAs, using a fast and high throughput method. The relations to living and housing conditions were investigated. The correlations between air concentrations from **paper II** and dust levels were examined. A major aim was also to estimate daily intakes for the individuals via both indoor matrices for 10.5-year-old children and to determine the importance of precursor exposure.

Paper IV aimed to assess the longitudinal internal exposure during childhood of a background exposed population via the measurement of serum concentrations and the calculation of body burdens at 1, 6 and 10.5 years. The trends of the major PFAAs (PFHxS, PFOS, PFOA and perfluorononanoic acid (PFNA)) were analysed and possible causes for trends and differences among compounds were investigated.

2 Methodology

For the review, **paper I,** literature on prenatal and postnatal biomonitoring studies was reviewed in the context of a) geographical and temporal variations due to changes in production of PFASs and b) the influence of individuals' age on serum concentrations, including adults. Exposure factors related to the body weight were plotted over a human's lifetime based on data from the exposure handbook (US EPA 2011). For each exposure pathway, firstly uptake rates and reported PFAS levels of the exposure matrix were reviewed, secondly reported estimated daily intakes were listed and, finally, research gaps were pointed out. This review did not aim at covering the entire literature, but rather on compiling examples for the current scientific state of children's exposure to PFASs to point out research gaps and to highlight how future regulation might benefit form filling these.

2.1 The child cohort and sampling

The individuals participating in **paper II, III** and **IV** of the current study were a subgroup of a longitudinal child study (LUKAS 2) in the area around Kuopio, Eastern Finland (Karvonen et al. 2009). The LUKAS 2 cohort consisted of children living in houses (initial n=224 children), which served as a control group for a European study on children growing up on farms (von Mutius et al. 2006). By following the same individuals through childhood, the study sought to examine effects of mycotoxins from mould and moisture problems on children's health, i.e. allergy and asthma development. Mothers who gave birth at the Kuopio University Hospital between May 2004 and May 2005 were recruited for LUKAS 2 at week 32 of gestation (Karvonen et al. 2009).

For the current study, the parents gave written informed consent to PFAS analysis of the excess serum volume of samples from the LUKAS 2 study of their child at 1, 6 and 10.5 years of age (**paper IV,** Figure 3) and to the additional sampling and analysis of indoor air and dust at the age of 10.5 years, both from the child's bedroom in 2014/2015 (**paper II** and **III**). The Research Ethics Committee, Hospital District of Northern Savo, Kuopio, Finland, approved the study's case (number 48/2004) and the amendments ethically. Samples from about 60 individuals with a balanced gender distribution were received

for each matrix. Information on housing parameters and children's living conditions were noted during sampling (**paper II** and **III**).

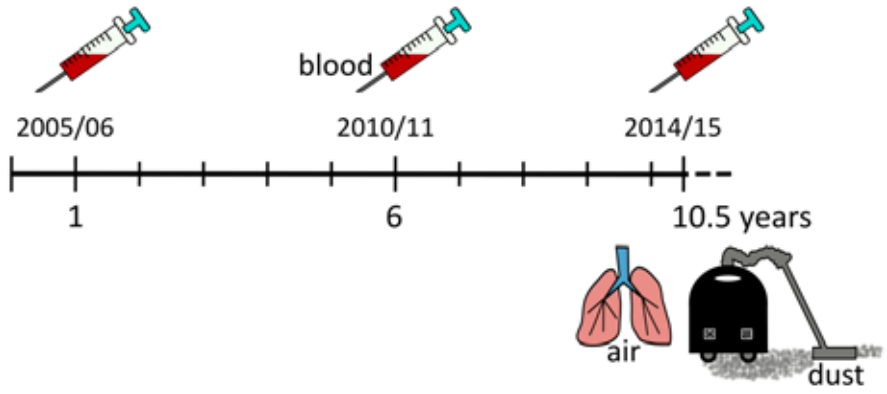

***Figure 3**: Sampling timeline of different matrices with increasing child age.*

The air samples in **paper II** were taken passively in the bedrooms. This sampling technique was chosen, because it is less invasive than active air sampling with pumps and allows for an integrated measurement over a longer time period. Sorbent impregnated polyurethane (SIP) foam disks were used as sampler material. Soaking the pre-extracted polyurethane foam disks with XAD-4 sorbent enabled an even longer sampling period due to a prolonged linear uptake phase and later saturation of the sampler material (Shoeib et al. 2008). This is especially for PFASs with lower air concentrations of importance. The production of SIPs was based on the protocol of Shoeib et al. (2008) and done in their laboratories with minor changes (Winkens et al. 2017a).

The air sampling was stopped after three weeks by transferring the SIP into an airtight jar, which was kept frozen until extraction. At the same time in 2014/2015, the entire floor of the child's bedroom was vacuum cleaned and the dust was collected in a filter sock for later PFAS analysis in dust (**paper III**, Figure 3).

Venous blood samples were taken by nurses in 2005/2006, 2010/2011 and 2014/2015, when the children were 1, 6 and 10.5 years of age, respectively (**paper IV** and Figure 3). The blood was centrifuged in order to obtain the serum fraction and thereafter stored frozen until further treatment.

Drinking water samples (n=12) were taken at each season of all three water suppliers of the study members between November 2014 and September 2015.

2.2 Sample treatment and analysis

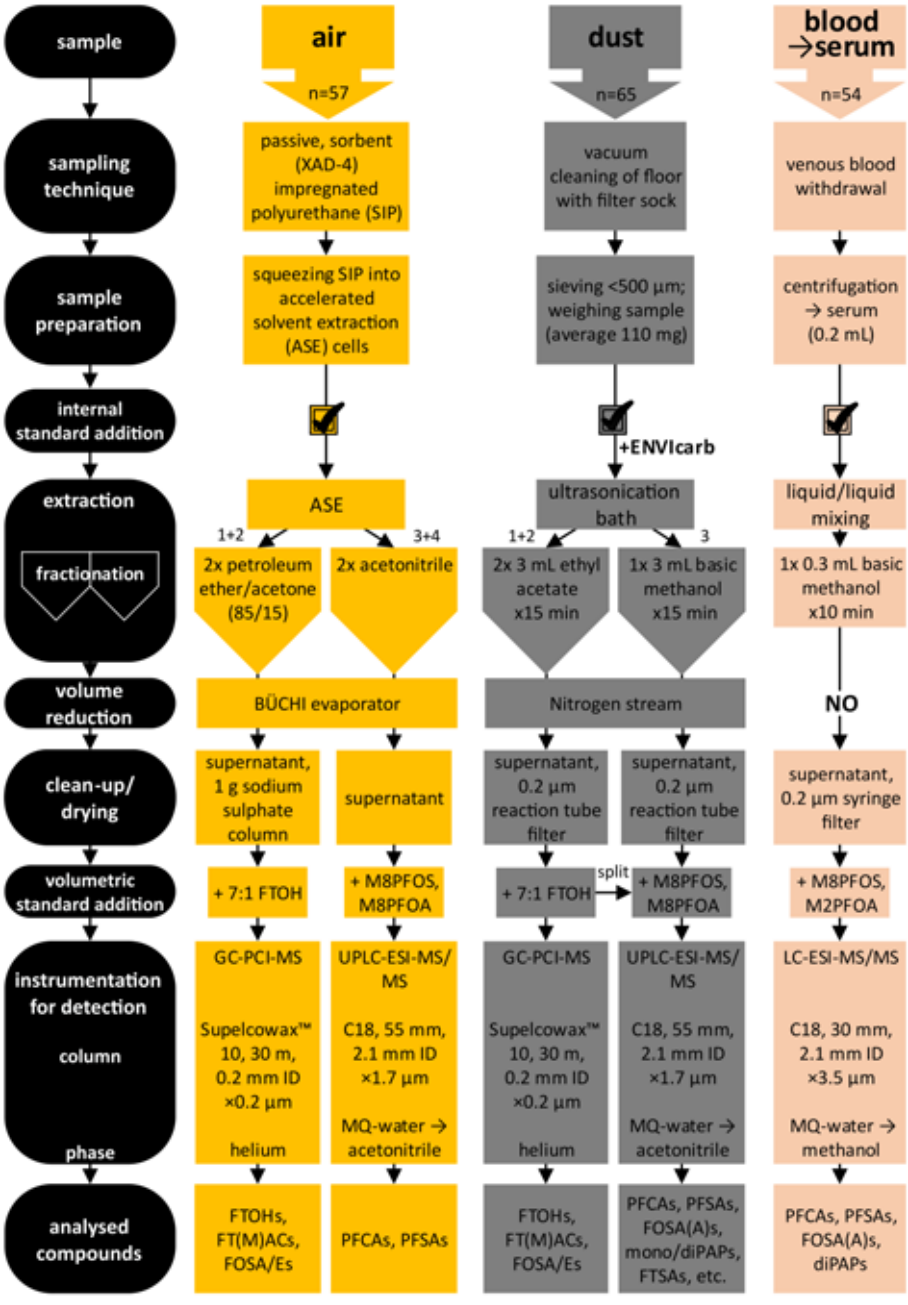

***Figure 4**: Workflow scheme on sample treatment, extraction and analysis.*

The air samplers were extracted via accelerated solvent extraction (ASE) with a method by Ahrens et al. (2013), which was slightly modified for **paper II** (Winkens et al. 2017a). For dust, a new fast method was developed for the analysis of 62 PFASs, combining the methods of Björklund et al. (2009) and Bohlin-Nizzetto et al. (2015), reducing the extraction volume, choosing a nitrogen gas stream for volume reduction and a different kind of extract filtration (**paper III**, Figure 4). See Figure 4, for a rough overview of the treatment, extraction and analysis of the three different matrices.
The analytical method for FTOHs, FOSAs/Es and FT(M)ACs on a gas chromatograph coupled to a mass spectrometer (GC-MS) in positive chemical ionisation (PCI) mode was developed as part of the thesis (Winkens et al. 2017a) and was applied for air and dust extract analyses (**paper II** and **III**). For Ultra Performance Liquid chromatography and triple quadrupole mass spectrometry (UPLC-MS/MS) analysis, existing, in-house methods were applied for PFASs in **paper II** and **III** (for details see Winkens et al. 2017a) and PAPs in **paper III** (Gebbink et al. 2015b). The serum extraction and analysis method in **paper IV** was previously published by Koponen et al. (2013).

For quality assurance and quality control of all matrices (**paper II, III** and **IV**), method blanks were treated in the same way as samples and also solvent blanks were injected. For most compounds, the equivalent internal mass-labelled standard was applied to the samples before extraction, to guarantee an accurate quantification (Figure 4). Recoveries were calculated for each sample relating the internal standards to the volumetric standards. For serum, an in-house control sample and for dust, several standard reference material (SRM 2585) dust samples, were extracted to assure precision (and accuracy) of the methods. The SRM 2585 was not certified for PFASs, but could be compared for 29 compounds with literature (Björklund et al. 2009; Goosey and Harrad 2011; Padilla-Sánchez and Haug 2016; Reiner et al. 2015), aside from the 24 newly reported compounds. For air, one sample extract was repeatedly injected for the control of precision.

3 Results and discussion

The estimated daily intake of PFASs is highly dependent on the concentrations in the exposure media, but also on the magnitude of exposure factors and the bodyweight (Winkens et al. 2017b). Plotting the different relative exposure factors against the body weight over a lifetime (data from US EPA 2011), illustrated that all exposure factors are highest during the first life-stages when considering the entire life (Winkens et al. (2017b)/**paper I** and Figure 5).

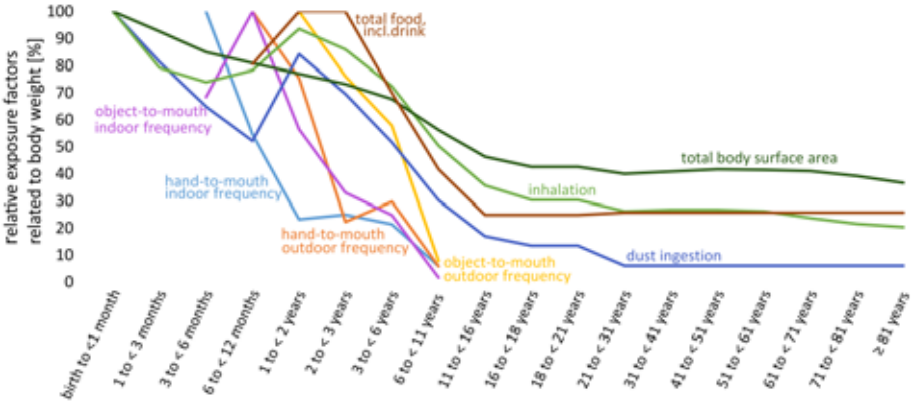

***Figure 5**: Exposure factors over a lifetime; data from US EPA (2011), figure from Winkens et al. (2017b)/**paper I**; reprinted with permission.*

At ages of 16 to <18 years, exposure factors reach the level that is maintained throughout adulthood. This tendency is mainly owed to behavioural and physiological differences of children compared to adults, such as mouthing behaviour or lung volume and breathing rate, but also body weight. As these developmental changes do not occur simultaneously, childhood exposure becomes highly dynamic and the relative importance of certain pathways shifts during childhood.

3.1 Dietary exposure via food and drinking water

The total food category (brown line, Figure 5) was further broken down into different food item categories in **paper I**, which indicated the same trend as

Figure 5 for all categories with the exemption of the total finfish and shellfish consumption (Winkens et al. 2017b). This fish category increases again for the age group of 21 to <31 years (**paper I**) (US EPA 2011). Breastmilk disappears as a food exposure factor for 1- to <2-year-olds. Food as a PFAS exposure pathway for children is hardly studied (Winkens et al. 2017b). Duplicate diet studies for children covering an entire day or days do not exist and mainly food items of the initial life-stages are investigated, such as milk powder, infant formula (Fujii et al. 2012; Tao et al. 2008; Wang et al. 2010) and breast milk (e.g. Mondal et al. 2014; Sundström et al. 2011).

The ingestion of PFAS contaminated drinking water elevates serum concentrations (Gyllenhammar et al. 2016; Hölzer et al. 2008; Wilhelm et al. 2015) (Winkens et al. 2017b). The concentrations in the drinking water samples of the current cohort were among the lowest reported for PFASs worldwide and comparable to levels in Bollebygd and Umeå in Sweden (Filipovic and Berger 2015). Drinking water samples of one waterworks reached above 100 pg/L for some compounds, whereas for the other three waterworks method detection limits of a few pg/L were hardly exceeded by any compound. As drinking water only plays a major role for populations receiving highly contaminated drinking water (Vestergren and Cousins 2009), it was not further considered in this study. Though it should be mentioned that the EDIs via drinking water for PFOS, PFOA and perfluorodecanoic acid (PFDA) were found to be highest among child groups ≤12 years compared to adults (Chimeddulam and Wu 2013) (**paper I**).

3.2 Indoor exposure via dermal contact, dust and air

Consumer products themselves represent an exposure medium during dermal contact. However, intakes via dermal exposure of PFASs are not estimated for humans in exposure studies (**paper I**), though there are several approaches for sampling dermal contact (Gorman Ng et al. 2013). Still, both the sampling methods and the existing models for dermal uptake need further validation (Gorman Ng et al. 2013; Winkens et al. 2017b). Additionally, the influence and importance of the larger skin surface related to the body weight (Figure **5**) and the higher water content of the skin during early life stages (IPCS 2006) on the uptake of PFASs has to be investigated.

The study on PFASs in indoor air (**paper II**) is among the few with a large number of samples (Haug et al. 2011b; Liu et al. 2013; Shoeib et al. 2011). Together with a new study (Padilla-Sánchez et al. 2017) it is rather unique with its recent sampling point, the use of children's bedrooms and the large number of analytes, including two acrylates, of which 6:2 fluorotelomer methacrylate (FTMAC) was detected in 58 % of the samples.

The order of highest median indoor air concentrations in the current study was as follows: 8:2 FTOH>6:2 FTOH>10:2 FTOH (3570, 1310 and 928 pg/m³, respectively, Figure 6 and Winkens et al. (2017a)). The concentrations of FTOHs in children's bedroom air (**paper II**) were in the same ranges and dominating as in previous indoor air measurements that were all conducted in 2007-2008 (Haug et al. 2011b; Liu et al. 2013; Shoeib et al. 2011). The concentration of 6:2 FTOH exceeded 10:2 FTOH's (Winkens et al. 2017a), which was the case in one other European study that also sampled bedrooms (Haug et al. 2011b). Therefore, 6:2 FTOHs might be either predominant in sleeping rooms, or slowly replacing the long chain FTOHs in indoor environments due to production changes, which might be faster in Europe than in America (Winkens et al. 2017a). Though, both explanations are speculative and require corroboration.

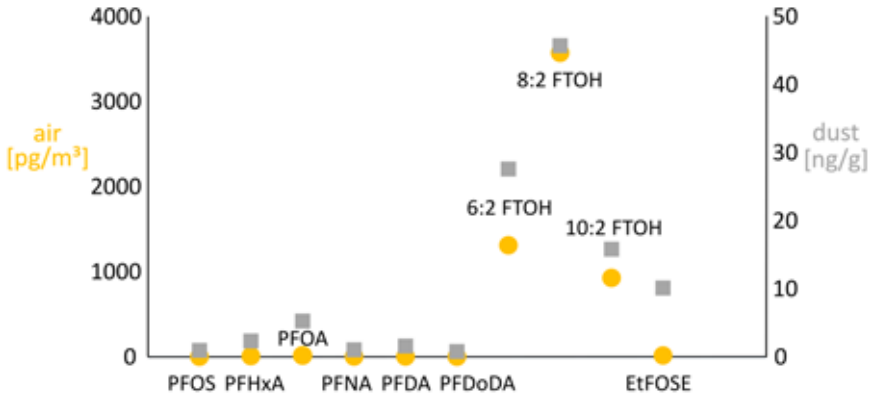

***Figure 6**: Median air and dust concentrations of PFASs in children's bedrooms (n=57 and n=62, respectively); shown PFASs detected in both environments in >50 % of the samples, (Winkens et al 2017a/**paper II** and **paper III**).*

FTOHs were, together with PAPs, the dominating compound group in the dust samples (Figure 6, **paper III**). Dust concentrations were generally comparable to Xu et al. (2013) and Shoeib et al. (2011), which are the only larger studies investigating FTOHs in dust 2008−2009 in Germany and 2007−2008 in Canada, respectively. PAPs in dust samples of the current study compared well with the samples from Sweden (sampled 2013−2014, n=10, Eriksson and Kärrman (2015)), but were up to two orders of magnitude lower than seven years before in Canada (sampled 2007−2008, n=102, De Silva et al. (2012)). Those two studies were the only large studies investigating PAPs at several locations worldwide or in a large number of dust samples, which makes **paper III** not only a valuable piece of information for the FTOHs in dust, but also for the PAPs.

Linear-PFOA was the dominating PFAA with 5.26 ng/g dust and 15.2 pg/m³ air. Among the PFOS precursors, *n*-ethyl-perfluorooctane sulfonamidoethanol (EtFOSE) was most frequently present in dust (57 %, **paper III**) and *n*-methyl perfluorooctane sulfonamidoethanol (MeFOSE) and EtFOSE in air (68 and 95 %, Winkens et al. (2017a)). Air and dust samples contained C_8-chemicals in highest levels among the PFSAs and PFCAs (**paper II** and **III**), even though the phase-out and Stewardship Program of long-chain PFASs were declared more than a decade, or for the latter some years ago (US EPA 2000, 2006). Nevertheless, a literature comparison revealed that air concentrations of FOSAs/Es, especially for MeFOSE, were several orders of magnitude lower in the current study compared to 2002/2003 (Shoeib et al. 2005); and lower than data from 2007/2008 (Haug et al. 2011b; Shoeib et al. 2011), acknowledging other influencing parameters as e.g. region and sampling technique (Winkens et al. 2017a).

Correlation coefficients were partly significantly positive among compounds of the same chemical class or between precursors and their PFAAs (Winkens et al. (2017a)/**paper II** and **paper III**). This was valid within the sample matrix, but also between dust and air. The correlations are likely causal, as the compounds might have originated from the same products both as intended chemicals or as production residues, or had similar indoor fate and partitioning to the exposure media (see also Figure 6). The steady-state partitioning between dust and air was supported by the linear regression line between the logarithm of the ratio between dust and air concentrations of the same PFAS plotted against its octanol-water partition coefficient (log K_{oa}, **paper III**).

Some housing parameters were investigated for association with indoor media levels, among which the floor material was most meaningful. The indoor concentrations were significantly higher ($p<0.05$) for rooms with plastic floor material in comparison to laminate for EtFOSE in air and in comparison to wood for PFOS in dust (Winkens et al. (2017a)/**paper II** and **III**). EtFOSE and PFOS might be present in plastic flooring or their treatment products. They likely occurred together, as EtFOSE is an impurity of PFOS in the ECF production process (Buck et al. 2011). EtFOSE is presumably transferred from floor material to air because it is semi-volatile, whereas the involatile PFOS is more likely to be transferred from floor material to dust. Ingredients of applied floor treatment products were correlated to dust levels in another study and had a major influence on serum levels of a Canadian family (Beesoon et al. 2012). Floor treatment products were assumed to be the major reason for product related uptakes of PFOS in North America (Trudel et al. 2008). Though, in the present study none of the bedrooms had carpet as a flooring material. Especially in the first <16 years of life (Figure 5) dust poses an important exposure medium due to the mouthing behaviour, sitting/playing on the

ground and possibly even due to children's proximity to dust in being smaller height compared to adults (Winkens et al. (2017b)/**paper I**).

3.2.1 Estimated daily intakes via air and dust

Estimated daily intakes from air and dust (EDI_{air} and EDI_{dust}) were considered in the current study via inhalation and ingestion, respectively (**paper II** and **III**). Due to the high uncertainties tied to dermal uptake (**paper I**), dust uptake via the dermal exposure route was not taken into account. The total EDI of a PFAA, e.g. ∑l-PFOS, was defined as the total daily intake via the PFAA itself (direct exposure) and the PFAA amount that resulted from precursor metabolism (indirect exposure, **paper III**). The EDI_{air} and EDI_{dust} in the intermedia exposure scenario were similar for the intake of each ∑l-PFOS, perfluorohexanoic acid (∑PFHxA), ∑l-PFOA, ∑PFNA and ∑PFDA (**paper III**). The ∑l-PFOA intake was the highest of all total PFAA intakes, both via air and dust in the intermediate scenario. The contribution of precursors to the ∑PFAAs EDI was higher for the intake via air than via dust (Figure 7), even though more precursors have been analysed in the dust samples (**paper III**).

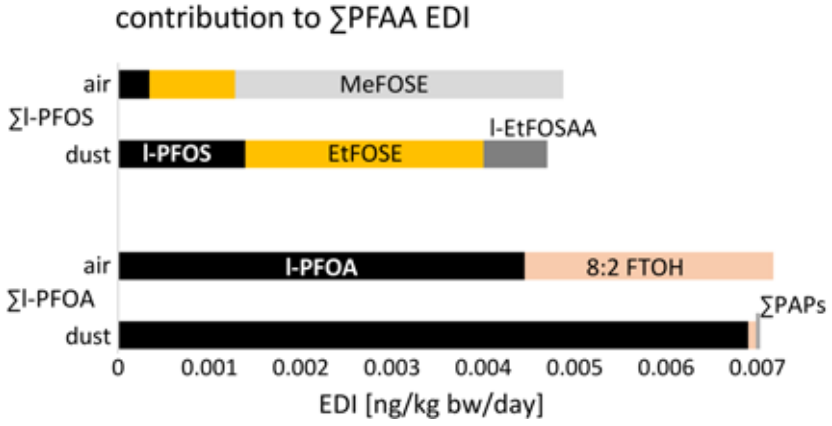

***Figure** 7: Contribution of different PFASs to the total (∑) l-PFOS and l-PFOA estimated daily intake (EDI) via air and dust at the intermediate exposure scenario.*

The ∑l-PFOS was impacted to a high extent by precursor metabolism (i.e. precursor contribution via air 90 % and dust 69 %), which was much lower for PFCAs (e.g. ∑l-PFOA, 38 % precursor contribution via air, Figure 7 and **paper III**). For the ∑PFHxA EDI_{dust}, 6:2 diPAP had the highest contribution among the precursors (**paper III**).

In the high exposure scenario, the ∑PFAA for each substance intake increased, due to the assumed higher absorption and metabolism rates. Therefore, the importance of indirect exposure via precursors increased in the high

exposure scenario (**paper III**). The sum intake of all ∑PFAAs and via both exposure pathways at the worst-case scenario, i.e. the EDIs at the 95th percentile of the high exposure scenario, was 0.46 ng/kg bw/day (**paper III**). This worst case EDI is several orders of magnitude below the TDIs of PFOA or PFOS, respectively (EFSA 2008). However, a problem resulting from the comparison of EDIs and TDIs is that only food ingestion is considered for the TDI determination. Additionally, the effects of different PFASs might vary from the effects caused by PFOS and PFOA alone, on which the TDIs are based. Therefore, summing up all PFASs to an overall estimated daily intake is a very simplistic approach. It was applied because TDIs for other PFASs are missing. Further, it has to be considered, that the toxicity following uptake from different pathways and entry ways into the body might vary.
For children, the consideration of TDI as a safe level for total life-time exposure might not apply for these vulnerable early life stages, as their susceptibility and exposure differs from adults'.

3.3 Serum concentrations and body burdens

Serum concentrations of PFASs have mostly been investigated for adults, as child studies have more obstacles (Winkens et al. (2017b)/**paper I**). Especially time trends based on more than two time points during childhood of the same individuals have rarely been studied. The exception are two recently published longitudinal studies of background-exposed infants/toddlers (Fromme et al. 2010; Mogensen et al. 2015) and one study of exposed children (Gyllenhammar et al. 2016). Studies on mother-child cohorts investigating prenatal exposure became lately more frequent. The transplacental transfer efficiency of PFASs from mother to child, i.e. the ratio between maternal and foetal/newborn blood or serum concentration, is varying within and in between studies and is highly dependent on the sampling time point during pregnancy (Winkens et al. (2017b)/**paper I**). Generally, PFSAs are less well transferred than PFCAs and long-chain PFCAs less well than short- and very long-chain PFCAs (Beesoon et al. 2011; Kim et al. 2011; Pan et al. 2017; T Zhang et al. 2013).
In the present study, there were also discrepancies among PFASs of different chain lengths for the internal exposure during childhood at 1, 6 and 10.5 years of age. Serum concentrations were decreasing significantly with age for PFOS, PFOA, PFNA and PFHxS (Figure 8; **paper IV**), which were all detected in ≥60 % of the samples at each sampling point (1, 6 and 10.5 years). For PFHxS, there was no difference between 1 and 6 years (**paper IV**).
In contrast to the decreasing serum concentration, the body burden was even increasing for PFNA and PFHxS between 1 year and 6 years as well as 1 year and 10.5 years (Figure 8). The body burden of PFOA and PFOS stayed constant between 1 and 10.5 years (**paper IV**). The body burden trends imply

continued uptake of PFASs throughout childhood, as known rates of elimination would otherwise lead to detectable decreasing body burden trends over time.

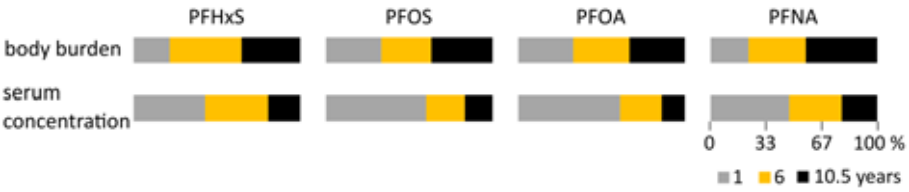

***Figure 8**: Body burden and serum concentration distribution among 1, 6 and 10.5 years of child age in [%].*

The discrepancy between decreasing serum concentrations and increasing or constant body burdens is owed to growth dilution; which is the dilution of the PFAS concentration in serum as a result of an increase in body mass and blood volume when the child grows. Other possibly affecting collinear temporal changes are discussed in detail in **paper IV**. Reasons for the different body burden trends among PFASs need further investigation.

3.3.1 Breastfeeding, air and dust influence on internal exposure

The breastfeeding duration correlated significantly positively with serum concentrations of the children at 1 year of age (**paper IV**), which supports the importance of breastfeeding as an exposure pathway for early life stages reported in several other studies (e.g. Haug et al. 2011a; Mondal et al. 2014; Papadopoulou et al. 2016; Trudel et al. 2008). Breastmilk is a highly variable medium and PFAS concentrations are depending on several factors that are reviewed more detailed in Winkens et al. (2017b) (**paper I**). Among those are the efficiency of PFASs crossing the lactational barrier and even if the mother has delivered a child before, as this reduces maternal serum concentrations.

There was no significant correlation between PFAS concentrations in air and in serum (all sampled at 10.5 years, **paper IV**). Between dust and serum, there were a few weakly positive and weakly significant ($p<0.05$) associations. However, their intrinsic stability prevents PFAAs from breaking down to shorter PFAAs in the body and therefore their correlation cannot be causal. The same was true for a few weak correlations between the body burden of PFAAs and dust or air concentrations of different PFCAs (**paper IV**). The only weak correlations with a likely causality based on the metabolism of precursors to PFAAs were between air concentrations of 8:2 FTOH and MeFOSE and body burdens of PFNA and PFOS, respectively (**paper IV**). This was also

supported by the EDI calculations and the high contribution of these two precursors to their respective acid (see **paper IV** and Figure 7). Other studies showed correlations for the same precursors in air and PFAAs in serum, though with higher correlation coefficients (Fraser et al. 2012; Makey et al. 2017). The association between indoor media and body concentrations is therefore less coherent for Finnish children than compared to North American adults (**paper IV**). Indoor air might be relatively less important for children than for the investigated adults. However, the serum concentration of adults might behave differently than the body burden of children as a considered parameter in the correlation. Further, in one of the studies, occupational exposure was investigated rather than bedroom air (Fraser et al. 2012). It has to be considered that indoor samples solely reflect current chemical levels, whereas the serum also reflects previous exposure and is an integrated measure of internal exposure via all exposure pathways (**paper I** and **IV**).

4 Conclusions

In **paper I**, strong evidence was found that children will receive a higher exposure to PFASs than adults, based on higher relative exposure factors following behavioural and physiological differences and a lower body weight. Though, how children's serum levels compare to adults' differs for the age of the children, the sampling year, the geographical region and the PFAS compound, of which some examples were shown in Winkens et al. (2017b). The major research deficit is the lack of longitudinal exposure studies that simultaneously quantify different exposure pathways and internal serum concentrations of PFASs at different childhood stages. Estimated daily intakes are highly dependent on the concentrations in the exposure media, which differ geographically and temporally for studies. Further, EDIs are difficult to compare across studies, because (detailed) information on included factors, on made assumptions and on the actual values for the factors is often missing (Winkens et al. (2017b)/**paper I**). Therefore, it was not possible to quantify the overall PFAS exposure of children by simply combining literature data for single pathways.

In the air and dust of children's bedrooms, a wide range of PFASs was successfully quantified (**paper II** and **III**). An easy and fast method for the inclusion of many precursors in one dust extraction protocol was presented in **paper III**. FTOHs and PAPs − which have often not been analysed in earlier indoor dust studies − were shown to dominate in this study. Plastic as a floor material seemed associated with increased air and dust concentrations of single PFASs that were produced via ECF. Distance to the city centre was judged not a sufficient predictor for remoteness, but showed positive or negative correlations for some PFASs, likely caused by other co-correlating factors (**paper II** and **III**). Even though PFOS was phased out more than a decade ago, this compound and its precursors are still present in homes (**paper II** and **III**), which hint towards a slow turn-over of building materials and furniture (**paper II**). Their continuous detection in indoor environments underlines the importance of the precautionary principle. Compounds of the same PFAS group as well as FTOHs and PFCAs correlated with each other, likely because they originate from the same consumer products that contained related PFASs as impurities or remnants from the production process (**paper II** and **III**).

Estimated daily intakes revealed for 10.5-year-olds that both air and dust exposure are of similar importance for the intake of single PFAAs, when including precursor metabolism (i.e. ∑PFAA). Precursors had a higher contribution to the ∑PFCA intake for single compounds via air than via dust, although fewer precursors were analysed in air than in dust (**paper II** and **III**). Further investigation is needed, as analysing air samples for more precursor compounds, could reveal a higher importance of ∑PFCA intake via air than via dust. The ∑PFOS intake is driven to a great extent by the precursor intake, especially following air exposure, which was partly supported by correlating PFAA body burdens and precursor air concentrations (**paper IV**).

Paper IV demonstrated decreasing serum concentrations of PFASs with the age of the child (1, 6 and 10.5 years) − not to be misinterpreted as a decreasing trend in PFAS intake during childhood. The calculated body burdens were constant or even increasing with age. This discrepancy between decreasing serum concentrations and increasing PFAS body burdens was, aside from other temporal changes, mainly based on growth dilution (**paper IV**). Serum concentrations at the age of 1 year correlated with the duration of breastfeeding, supporting that breastmilk is the major exposure pathway during infancy. Further, PFOA and PFOS body burdens stayed constant whereas PFHxS' and PFNA's increased between 1 and 10.5 years (**paper IV**). Reasons for this discrepancy between the compounds need to be investigated by multiple exposure pathway assessments. However, part of the reason might be compound specific differences in the efficiency of transplacental and breastmilk transfer, historical exposure of the mother and changes in PFAS production.

5 Future perspective

Advances are needed in several fields to allow for a better understanding of childhood exposure. This knowledge is necessary to develop strategies for minimizing children's exposure to PFASs and to ensure effective regulations and assessments:

- Detailed monitoring studies and a mechanistic understanding of the interaction between the mother (from before conception) and foetal life stages are needed, as well as for early life stages after birth (i.e. breastfeeding period). The influence on PFAS transfer from the mother to her child is poorly understood, as numerous dynamic processes and physiological changes during pregnancy and the nursing period occur both on maternal and foetal/infant side. A high temporal resolution of data is required as exposure during certain "windows of vulnerability" may strongly impact the child's development (Bruckner 2000; Holsapple et al. 2004; IPCS 2006; Scheuplein et al. 2002).

- Longitudinal exposure studies following the same individuals throughout childhood need to be conducted to quantify the importance of different exposure pathways over time, ideally with a high sampling frequency.
  Dermal uptake (from dust/products) has probably been the least studied exposure pathway, as sampling techniques and processes require advances in general understanding and reliable quantification (**paper I**). Therefore, dermal absorption of compounds from dust was not considered for the EDI calculation in the current study, which might increase the importance of dust as an exposure medium (**paper III**).
  Though dietary questionnaires existed for the current cohort, they were not investigated in this thesis. In combination with reported concentrations in food items, they could give valuable insights into the importance of food ingestion as an exposure pathway to PFASs in comparison to dust and air. Child-specific food exposure studies are to date mostly focusing on early-life periods covering infant formula and breastmilk, even though children have different dietary preferences than adults (**paper I**).

- Physiological parameters that influence the absorption, distribution, metabolism and elimination of PFASs und thus body concentrations have to

be investigated for early-life stages. Most of the current studies are limited to adult animal species and adult humans exposed at their workplace, though the parameters might vary during an individual's development and vary for different entry pathways into the body, of which mostly ingestion and inhalation are researched.
In the current study, urine samples of the 10.5-year-old children were archived and could give better insights into the elimination of PFASs at this life stage.

- Existing pharmacokinetic models would benefit from all the points above by enabling the use of more defined model input parameters for PFAS exposure during childhood. Valuable insights can be gained by the goodness of fit between measured and predicted data and the exclusion/inclusion of certain pathways or processes and display a) where further research refinement is needed, b) where major body burden contributions originate and, c) how/why these processes change over time.
With our data set, refinement of the model presented by Verner et al. (2016) is planned.

- The diversity of PFASs requires the inclusion of a wider range of compounds into scientific studies, as the major focus lies on classical PFCAs and PFSAs (Wang et al. 2017). This also calls for new analytical (recovery) standard mixtures for correct substance quantification and the use of highly sensitive analysis techniques in order to detect low concentrations.

- Global production and trade markets pose an extreme challenge when tracking and controlling the use of chemicals, which is reflected by the global production shifts of PFASs (Paul et al. 2009; Wang et al. 2014). Consumers need to be educated on chemicals' properties and risks to enable them to make informed purchase decisions as their demand is the major steering force of the market. The current non-transparency of ingredients in consumer products makes this difficult. However, companies are aware of the increased consumer interest in "environmental friendly/safer" products and partly use labels like "xy-free" as marketing strategies. Some of them are misleading though and in case of PFASs e.g. just cover PFOS and/or PFOA, which underlines the importance of consumer education.

- Regulation is the key tool to control the industrial production of chemicals and therefore reduce their release, application and exposure to humans. Some progress has already been made in this regard, e.g. with the European-wide chemical legislation since 2007. However, regulations constantly need improvement supported by research:

1. Toxicity tests are mostly conducted on adult test-species, missing effects on developmental stages (including not only early life, but also sexual maturation), which exclusively can be fully covered in two-generation tests (chapter 6, IPCS 2006). Their inclusion into future assessments would protect early life-stages by adapting thresholds if needed.
2. Mixture toxicity has been discussed for long and needs to be better understood even within the highly diverse class of PFASs. Chemicals with similar toxicological mode-of-actions could be grouped to achieve thresholds for a sum of compounds and pathways.
3. Today's bioaccumulation criteria need to be expanded by new standard tests for chemicals that deposit elsewhere than classical POPs, or that are airborne, and respective new thresholds must be set. The guidance section on "organic substances that do not partition to lipid" does not offer a clear solution (ECHA 2017a), whereas the proposed PMT (persistent, mobile and toxic) and vPvM (very persistent and very mobile) criteria for implantation into REACH do (Neumann and Schliebner 2017). Bioaccumulation cannot be failed to consider for slowly eliminating chemicals, as previous exposure still contributes to current internal body concentrations (cumulative risk assessment).
4. The contribution of different exposure pathways to the internal exposure needs to be understood and considered. Among these pathways are the exposure via breastmilk and transplacental transfer, which could be included into risk assessment for the early life stages by modelling human equivalent doses based on rodent data, as e.g. presented by Kieskamp et al. (2018). Accounting for other pathways than food ingestion would lead to a decrease of the TDIs based on increased total intakes (aggregate exposure assessment).

Finally, the Environmental Health Criteria 237 report (IPCS 2006, p. 6) puts the absolute importance and necessity of childhood exposure research for a continued healthy existence of humankind in a nutshell:

"The development of risk assessment strategies that address the developmental life stages through which all future generations must pass is essential to any public health strategy. Protection of children is at the core of the sustainability of the human species. It should be a priority of all countries and international and national organizations to provide safe environments for all children and reduce exposure to environmental hazards through promotion of healthy behaviours, education, and awareness raising at all levels, including the community, family, and child."

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