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Assessment of dermal exposure to halogenated flame retardants: Comparison using direct measurements from hand wipes with an indirect estimation from settled dust concentrations

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ABSTRACT

There are few studies estimating dermal exposure to halogenated flame retardants in adults. To fill this gap, sixty-one hand wipe samples were collected from a Norwegian adult cohort using gauze pads immersed in isopropanol. BDE-47, BDE-209, bis(2-ethyl-hexyl)-3,4,5,6-tetrabromophthalate (BEH-TEBP) and decabromodiphenylethane (DBDPE) were the most frequently detected chemicals. The highest median mass in hand wipes was that of sumEHFR (570 ng), followed by sumHBCDD (180 ng) and sumPBDE (2.9 ng). The high EHFR level was mainly driven by tetrabromobisphenol A (TBBPA) which accounted for 77% of the total mass. Positive and significant correlations were observed between FR levels in hand wipes and settled dust ($0.26 < r < 0.56$, $p < 0.05$), as well as between FR levels in hand wipes and the number of electronic consumer products at home ($0.27 < r < 0.40$, $p < 0.05$). Significant bivariate associations with number of laptops/tablets and phones/mobiles were further confirmed by multivariate linear regression analyses. Dermal exposure was estimated using the levels measured in handwipes. The estimated median dermal exposure was 2600, 840 and 6.2 pg/kg bw/d for sumEHFR, sumHBCDD and sumPBDE, respectively. Further, we compared these results with the dermal exposure as estimated indirectly by utilizing previously reported FR levels in settled dust collected from the residences of the same studied cohort. With the indirect approach, higher dermal exposures to sumPBDE but lower exposures to sumEHFR and sumHBCDD were observed compared to the direct dermal exposure estimated via hand wipes. Comparable exposure estimates between hand wipes and the indirect method were obtained for α-, β-tetrabromoethylcyclohexane (DBE-DBCH), DBDPE, BDE-28, -35, -49, -99, -153, 154, and -183. For other individual HFRs, the exposure estimates obtained from the two approaches were significantly different (Mann-Whitney U test, $p < 0.05$). Both methods gave similar dermal exposure estimates for many individual FRs. However, it is important to be aware of the value and limitations of each method when using them to estimate human exposure.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDDs) were once among the most widely used flame retardants (FRs) worldwide. However, the use of these chemicals has been restricted due to their persistence, bioaccumulation and toxicological properties (UNEP Stockholm Convention on Persistent Organic Pollutants), leading to increased use of many emerging FRs. Most of these chemicals are used as additives (without bonding to or reacting with the product material), and may leach from FR-treated products during use. Exposure to FRs can occur through dust ingestion and inhalation of contaminated air (Newton et al., 2015; Cequier et al., 2014; Tao et al., 2016). In addition, several studies have highlighted dietary intake as one of the major pathways of exposure to such chemicals (Fromme et al., 2009; Wu et al., 2007; Tao et al., 2017). Very little has been reported about dermal absorption as a potential significant contributor to human body burdens of FRs (Abbasi et al., 2016; Zheng et al., 2017a; Liu et al., 2017).

Estimation of dermal exposure in human study populations can be performed using direct or indirect approaches. The direct methods are further subdivided into three categories: removal (wiping and hand-washing), interception (patch samplers, wristbands), and in situ

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techniques (direct measurement such as video-imaging using a fluorescent tracer) (WHO Environmental Health Criteria 242: Dermal Exposure; Fenske, 1993; van Hemmen & Brouwer, 1995). The indirect methods include monitoring of parent compounds or metabolites in human samples and investigation of the processes before dermal exposure occurs (migration and transfer approaches) (WHO Environmental Health Criteria 242: Dermal Exposure). Due to its low capital cost and ease of use, the hand wipe method has been widely used to assess dermal exposure to various chemicals in human study populations, including FRs (Liu et al., 2017; Stapleton et al., 2012; Stapleton et al., 2008; Hammel et al., 2016). For many situations where measurement results are unavailable for large populations, dermal exposure to FRs may be estimated using the indirect approach. For example, dermal uptake from dust can be estimated from indoor dust concentrations, by using generic values for specific activities (such as dust contact) together with estimates of the time periods and body part surfaces involved (Cequier et al., 2014; Zheng et al., 2017a). However, there are still important gaps in understanding which dermal exposure pathways to FRs are the most biologically-relevant for humans. To fill such data gaps, studies combining and comparing both direct and indirect methods of dermal exposure are needed to reduce the risk of over- or underestimation of the intake levels.

The objectives of this study were to 1) investigate levels and dermal exposure to FRs using hand wipes, and 2) compare a direct (FR mass in hand wipes) with an indirect approach (settled dust concentrations) for estimating dermal exposure to FRs.

2. Material and methods

Information about the chemicals and materials used in this study can be found in the Supporting Information.

2.1. Sample collection

This present study is part of the Advanced Tools for Exposure Assessment and Biomonitoring (A-TEAM) project that aims to develop understanding of a variety aspects related to external and internal exposure to selected consumer chemicals. Hand wipe and settled dust samples (from elevated surfaces from the living room) were collected from a Norwegian adult cohort between November 2013 and April 2014. Details about the study design and population, recruitment, and sampling procedures are given in Papadopoulou et al. (2016). Details about sample clean-up and subsequent instrumental analysis for settled dust samples have been described previously (Papadopoulou et al., 2016; Tay et al., 2017). In short, sixty-one hand wipe samples were collected from a Norwegian cohort between November 2013 and April 2014, typically in the evening in their homes. All 61 participants were instructed not to wash their hands at least 60 min prior to sampling. A sterile gauze pad (3 × 3 in., Swift First Aid Inc. Valencia, CA, USA) immersed in 3 mL isopropanol was used to wipe the palm and the back of the hand from wrist to fingertips. Left and right hands were sampled separately but extracted and analysed together, providing one measurement per participant. Both pieces of gauze pad were stored in a 60 mL amber glass jar at −20 °C until analysis. Field blank samples were taken by soaking a gauze pad in isopropanol and placing it directly into a glass jar. After sample collection, the participants were asked to complete a questionnaire regarding indoor environment characteristics, type and number of consumer products as well as some personal behaviours.

2.2. Sample extraction, clean-up and analysis

A total of 23 PBDE congeners, two Dechlorane Plus isomers (*syn*- and *anti*-DDC-CO), three HBCDD isomers (*α*-, *β*- and γ-isomer) and 20 EHFRs were measured (see Table S1). The extraction, clean-up and analysis of hand wipe samples were performed according to Sahlström et al. (2012) with slight modifications. In brief, hand wipe samples were spiked with isotopically labelled surrogate standards and then extracted three times with 8 mL of *n*-hexane (*n*-Hex)/acetone (1:1, v:v) in an ultrasonic bath for 20 min. The extract was concentrated to 1 mL under a gentle flow of nitrogen, solvent-changed to *n*-Hex and then loaded on a solid phase extraction (SPE) column containing 2 g of silica. PBDEs and EHFRs were eluted in fraction I with 10 mL of 5% diethyl ether (DEE) in *n*-Hex, while HBCDDs and TBBPA were eluted in the second fraction with 10 mL of ethyl acetate. Fractions I and II were further cleaned up with sulphuric acid (98 and 90%, respectively) before being analysed by gas chromatography–electron capture negative ion–mass spectrometry (GC-ECNI-MS) and ultra performance liquid chromatography–mass spectrometry (UPLC-MS), respectively. Details on the instrumental parameters can be found in the supporting information (Table S3).

2.3. QA/QC

All glassware (including Pasteur pipettes) were heated to 450 °C for 4 h and rinsed with acetone before use. No contamination was found in any of the reagent blanks (solvent blanks). Sixteen field blanks were analysed together with the hand wipe samples (4 blanks per batch of 20 samples). TBBPA, BDE-35, -99, -197 and -209 were detected in the field blanks in the range of 13–400 pg, while an average field blank level of 1 ng was observed for BEH-TEBP. Blank correction was applied to the FR measurements by subtracting the mean amount detected in the field blanks from the same batch. One sample was lost in the analytical process, so the number of samples with results was 60.

Method recovery was checked by the analysis of spiked blanks (gauze pad with spiked mixtures consisting of EHFRs, PBDEs, HBCDDs and TBBPA). The recoveries of the target compounds in samples spiked at two different levels were between 67 and 130% (see Table S4 for details). However, the measurement uncertainty for samples with very low and very high masses could be greater. Recoveries of ^{13}C-labelled surrogate standards in the collected hand wipe samples were satisfactory and ranged between 65 and 100% (Table S5). Method detection and quantification limits (mLODs and mLOQs, respectively) for analytes present in the blanks were set to the mean blank values plus 3 and 5 times the standard deviation of the blanks, respectively. For analytes not present in the blanks, mLOQ was defined as a signal/noise ratio of 10 and mLOD as mLOQ divided by 3. The mLODs and mLOQs for each of the compounds are given in Table S6.

2.4. Statistical analysis

Statistical analyses were performed using IBM SPSS statistics 24 (Chicago, IL) and only for analytes with detection frequencies (DFs) above 40%. Masses below the mLOD were replaced with the mLOD divided by the square root of 2 before statistical analyses. Masses above the mLOD but below mLOQ were replaced with the mLOQ divided by the square root of 2. The FR distributions for both hand wipe levels and estimated dermal exposure were highly skewed. Therefore, nonparametric methods were used in the bivariate comparisons (Mann-Whitney *U* test) and Spearman's rank correlation tests for investigation of bivariate correlations (between FR levels in hand wipes and settled dust, and between FR levels and indoor parameters). For multivariate comparisons of FR composition in hand wipes with personal behaviour and indoor parameters, we used the Kruskal-Wallis test and principal component analysis (PCA). The level of significance was set to $p = 0.05$ for all statistical tests. Indoor parameters correlated with hand wipe masses ($p < 0.2$) in the bivariate analysis were then included in multivariable linear regression models of log transformed hand wipe masses. Factors that were found to be significant ($p < 0.05$), after removing the highest *p*-values following a backward selection procedure, were retained in the final multivariable linear regression models.

2.5. Hand surface area calculations

The surface area of the hands was estimated using an equation adopted from the USEPA Exposure Handbook (USEPA, 2011), as given below:

$$SA = a \times weight^{b} \times height^{c} \times 10,000 \quad (1)$$

where SA represents surface area (cm^2), weight and height of the participants in the units of kg and cm, respectively. The variables a, b and c are gender-specific constants obtained from the USEPA Exposure Factors Handbook (USEPA, 2011) (see Table S7), while the value of 10,000 represents a conversion from m^2 to cm^2. Information about individual body weight and height of the participants was obtained from the questionnaires.

2.6. Dermal exposure calculations

Dermal exposure to FRs via the hands (pg/kg bw/d) was estimated for each participant using the masses found in hand wipes as well as levels in settled dust. Direct exposure estimations based on hand wipe and indirect exposure estimations via dust uptake were determined with the following equations:

$$\textit{Dermal exposure using hand wipe} = \frac{C_{hw} \times SA \times AF \times ED \times EF}{BW} \quad (2)$$

$$\textit{Dermal exposure via dust contact} = \frac{C_d \times CF \times SA \times DA \times AF \times ED \times EF}{BW} \quad (3)$$

where C_{hw} is the surface area normalized mass of FRs in hand wipes (pg/cm^2); SA is the hand skin surface area exposed per event (cm^2/event) estimated using Eq. (1); AF is the absorption fraction (unitless) adopted from ex vivo studies (Abdallah et al., 2015; Frederiksen et al., 2016) (see Table S8, it is stressed that the assumption of constant AF over a wide range of dose and the estimation of AF for other FRs based on molecular weight and number of bromines are inherent uncertainties with this approach); ED is the exposure duration in one day (t/24, where t is assumed to be 24 h or 1 day for hand wipe, while for dust contact the average hours spend indoors per day as assessed by questionnaires is used); EF is the exposure frequency (event/day and is assumed to be 1 event/day for both scenarios); BW is the body weight (kg); C_d is the concentration of FRs in dust (pg/g); CF is the conversion factor (1×10^{-3} g/mg); and DA is the amount of dust adhered to the skin (0.011 mg dust/cm^2 for adults' hands (USEPA Example exposure scenarios; Abou-Elwafa Abdallah et al., 2016; Pawar et al., 2017)).

3. Results and discussion

3.1. Levels of FRs in hand wipes

Descriptive statistics of the masses of PBDEs, HBCDDs and other EHFRs in hand wipes are shown in Table 1. Thirty-six out of 48 target analytes were detected in the studied samples. Overall, BDE-47, -99, -197, -209 as well as BEH-TEBP, DBDPE and TBBPA were the most frequently detected FRs (DF ≥ 85%). The median masses of sumPBDE, sumHBCDD and sumEHFR were 2.9, 170 and 570 ng/participant, respectively. Surface-area-normalized median sumPBDE, sumHBCDD and sumEHFR masses were 3.5, 150 and 640 pg/cm^2. The total masses of FRs measured in hand wipes ranged from 94 to 11,000 pg/cm^2, equivalent to 81–12,000 ng/participant. There were no statistically significant differences between the masses of FRs in hand wipes collected from male and female participants.

TBBPA was the most predominant FR, contributing about 77% to the total mass of FRs (median = 570 ng), followed by α-, β-, and γ-HBCDDs (together 21% of total mass, medians of 78, 33 and 53 ng, respectively) and BEH-TEBP (1% of total mass, median = 7.7 ng) (Table 1). The mean TBBPA masses (1300 ng, equivalent to 1200 pg/cm^2) found in this study were much higher than those reported in children's hand wipes in the U.S. (0.4 ng) (Stapleton et al., 2014), but lower than those detected in patch samples attached to worker's clothing at an electronic dismantling facility in Finland (6700 pg/cm^2) (Mäkinen et al., 2009). This finding was unexpected because around 90% of TBBPA is used as a reactive intermediate in the manufacture of epoxy and polycarbonate resins of Flame Resistant 4 (FR-4) printed circuit boards (PCBs), whereas only 10% of TBBPA is used as additive FR in acrylonitrile-butadiene-styrene (ABS) and high impact polystyrene (WHO EHC 172 Tetrabromobisphenol A and derivatives (2017/09/12)). Excessive unreacted TBBPA in the brominated epoxy has the potential to leach out from PCBs into the environment. High levels of TBBPA (up to 1.0% by weight) have been reported in various components of a laptop computer (Kajiwara et al., 2011), but the emissions of TBBPA from personal computers (PCs) into air were very low (0.4 ng/m^2/h), even at elevated operating temperatures (Kemmlein et al., 2003). In other words, the release of covalently bonded TBBPA from treated products is expected to be rather low. On the other hand, the main additive use of TBBPA is found in television casings (around 450 t per year) (Abou-Elwafa Abdallah, 2016). Elevated levels of TBBPA have also been reported from surface wipes of various consumer products containing plastics (e.g. televisions, small household electronic appliances, children's toy and power adaptors, with a maximum level of 160,000 ng/wipe detected for a power adaptor) (Gallen et al., 2014), whereas relatively low levels of TBBPA were detected from surface wipes of mobile phones and PCs (medians of 0.4 and 3.8 pg/cm^2, respectively) (Zheng et al., 2017b). It is therefore possible that direct skin contact with several consumer products, as well as dermal uptake from contaminated dust from surfaces at home, dust on the consumer products and FR-enriched microparticles released through abrasion of the polymer surface could be the main routes of exposure to TBBPA.

Masses of the three HBCDD isomers in the hand wipe samples (means ranged from 200 to 260 ng/participant for the three isomers) were three orders of magnitude higher than those detected in U.S. children's hand wipes (means from 0.11–0.35 ng/participant) (Stapleton et al., 2014). However, these values are not directly comparable since children have different pathways of exposure than adults due to their smaller size and hand-to-mouth behaviour. High levels of HBCDDs have frequently been reported in textiles (DF > 80%, concentration up to 0.54 mg/kg) (Vojta et al., 2017), drapes (up to 43,000 mg/kg) (Kajiwara et al., 2009), electrical outlets and insulation board (up to 23,000 mg/kg) (Kajiwara et al., 2011) and various polystyrene products (such as cooler boxes and building insulation materials with concentrations up to 960 mg/kg) (Vojta et al., 2017; Rani et al., 2014). The emission rates of HBCDDs from flame-retarded curtain and insulating boards made from expanded polystyrene (EPS) and extruded polystyrene (XPS) at room temperature (around 20 °C) were generally low (0.020, 4.0 and 29 ng/m^2/h respectively) (Kemmlein et al., 2003; Miyake et al., 2009), with an overall emission amount of 250 ng per day from household products into indoor air, dust, floor and wall surfaces (Kose et al., 2009). In addition, abrasion of HBCDD-treated curtain fibres directly to dust, as well as direct contact between fabrics and dust particles have been identified as the major transfer pathways of HBCDDs into indoor dust (Rauert et al., 2016; Rauert et al., 2014). The findings from these studies suggest that textile and polystyrene products might be potential sources of HBCDDs in the indoor environment.

Limited studies have measured FRs in adults' hand wipes. The median masses of individual PBDE congeners and other EHFRs in this study are lower than those reported in China (Liu et al., 2017) and the U.S. (Cowell et al., 2017; Hoffman et al., 2014; Hoffman et al., 2015; Watkins et al., 2011) In general, the PBDE congener pattern was dominated by BDE-209 (accounting for 58% of the sumPBDE), which is similar to the pattern for China (Liu et al., 2017) but different from the U.S. measurements (mainly dominated by BDE-47 and BDE-99) (Hoffman et al., 2015; Watkins et al., 2011). These rather contradictory results are probably due to different

Table 1
Descriptive statistics for all FRs measured in hand wipe samples (n = 60).

	DF%	Mass (ng/participant)			Mass per hand surface area (pg/cm^2)		
		Mean	Median	Range	Mean	Median	Range
α-DBE-DBCH	83	0.18	0.084	0.0029–1.7	0.18	0.084	0.0035–2.1
β-DBE-DBCH	47	0.099	0.033	0.028–0.82	0.097	0.042	0.018–1.0
BATE	32	0.0043	0.00085	< 0.00085–0.15	0.0035	0.0010	< 0.00048–0.090
TBCT	10	0.0020	0.0011	< 0.0011–0.022	0.0023	0.0013	< 0.00063–0.027
PBT	2	0.78	0.78	0.72–0.78	0.81	0.90	0.43–1.0
PBEB	2	0.13	0.13	< 0.13–0.39	0.14	0.15	< 0.071–0.43
TBP-DBPE	12	0.0024	0.00064	< 0.00064–0.047	0.0027	0.00074	< 0.00035–0.057
HBB	15	0.033	0.0036	< 0.0036–0.69	0.026	0.0043	< 0.0020–0.43
EH-TBB	63	3.0	0.47	0.12–90	2.5	0.49	0.094–56
BTBPE	7	0.090	0.066	< 0.066–0.91	0.090	0.076	< 0.037–0.56
BEH-TEBP	90	17	7.7	0.0056–150	17	8.3	0.0031–180
OBTMPI	57	0.020	0.013	0.0057–0.15	0.021	0.015	0.0034–0.17
DBDPE	90	1.9	0.61	0.042–20	1.8	0.60	0.050–18
TBBPA	88	1300	570	< 30–11,000	1200	640	< 28–8200
α-HBCD	80	220	78	1.4–4100	240	80	1.7–5000
β-HBCD	57	200	33	6.5–4000	220	33	7.0–4900
γ-HBCD	68	260	53	< 11–5000	300	52	< 5.9–6300
BDE-28	72	0.019	0.0051	< 0.0013–0.35	0.020	0.0049	< 0.00075–0.43
BDE-35	60	0.041	0.0048	0.00037–0.099	0.044	0.0049	0.00033–0.13
BDE-47	97	0.60	0.16	0.015–8.0	0.62	0.16	0.0093–8.8
BDE-49	65	0.053	0.0075	< 0.0013–1.5	0.055	0.0062	< 0.00084–1.8
BDE-66	25	0.041	0.0013	< 0.0013–1.7	0.047	0.0016	< 0.00075–2.1
BDE-77	5	0.0027	0.0011	< 0.0011–0.093	0.0031	0.0012	< 0.00059–0.11
BDE-85	23	0.032	0.0020	< 0.0020–0.76	0.034	0.0024	< 0.0011–0.92
BDE-99	88	1.3	0.33	0.013–18	1.2	0.32	0.012–15
BDE-100	68	0.082	0.018	0.0013–1.9	0.090	0.019	0.0012–2.0
BDE-153	80	0.10	0.029	0.0048–2.0	0.11	0.028	0.0055–2.5
BDE-154	62	0.046	0.011	< 0.0029–0.64	0.047	0.012	< 0.0016–0.69
BDE-183	73	0.097	0.035	< 0.0033–0.84	0.11	0.029	< 0.0018–1.1
BDE-185	17	0.0069	0.0033	< 0.0033–0.06	0.0073	0.0040	< 0.0018–0.068
BDE-197	85	0.072	0.032	0.0079–0.51	0.076	0.029	0.0057–0.64
BDE-203	22	0.32	0.16	0.056–2.2	0.36	0.18	0.068–2.5
BDE-206	45	0.15	0.066	< 0.066–1.1	0.15	0.084	< 0.037–0.68
BDE-207	52	0.12	0.085	< 0.054–0.49	0.12	0.070	< 0.030–0.61
BDE-208	25	0.055	0.042	< 0.042–0.25	0.056	0.051	< 0.024–0.15
BDE-209	92	3.6	1.7	0.11–44	3.5	1.8	0.13–29
sumPBDE		6.3	2.9	0.44–64	6.7	3.5	0.62–40
sumHBCDD		680	180	49–8900	760	150	27–11,000
sumEHFR		1300	570	31–11,000	1200	640	39–8400

The sums of PBDE, HBCDD and EHFR were calculated from individual results. The detection frequency (DF) is the percentage of samples with a mass above the mLOD.

usage patterns of FRs in the U.S. (predominant use of PentaBDE formulation) compared to the rest of the world, as well as the early phase-out of Penta- and Octa-BDE formulations in the EU (UNEP Stockholm Convention on Persistent Organic Pollutants). Significant moderate to high positive correlations ($0.28 < r < 0.84$) were observed among many EHFRs, PBDEs and HBCDDs (Table S9). PCA was applied to identify patterns in the masses of FRs in hand wipes. Three significant principal components (PC) were extracted accounting for 61% of the total variance (Table S10, Fig. S1). PC1 accounted for 27% of the total variance with high loadings of BDE congeners representing commercial PentaBDE formulation (BDE-47, -49, -99, -100, -153 and -154). BDEs in the commercial DecaBDE formulation (BDE-206, -207, -209) as well as EH-TBB, OBTMPI and DBDPE were the dominant FRs in PC2 (18% explained variance). The third principal component (PC3, 16% explained variance) was dominated by α-, β-DBE-DBCH, BDE-183, -197, α-, β-, and γ-HBCDD. Lower loadings for all three PCs were observed for BEH-TEBP, TBBPA and BDE-35, indicating that the sources of these chemicals are different from the other FRs.

3.2. Associations between paired indoor dust and hand wipe samples

Ten EHFRs (α- and β-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP, *syn*- and *anti*-DDC-CO, OBTMPI, DBDPE and TBBPA), α-, β-, and γ-HBCDD, and 17 PBDE congeners were detected in at least 40% of the settled dust samples from the participants homes, as reported previously (Tay et al., 2017). Summary results from that study for the dust samples are given in the supplementary data (Table S11). BDE-209 was the most abundant FR in settled dust, followed by BEH-TEBP and other less volatile FRs such as HBCDDs, DBDPE and TBBPA. The distribution and patterns of PBDEs and EHFRs, except for TBBPA, were similar between settled dust and hand wipes. Positive and significant correlations were found between settled dust and hand wipes for α- and β-DBE-DBCH, EH-TBB, BEH-TEBP, γ-HBCDD, BDE-47, -99, -154, -183 and -209, with a range between 0.26 and 0.56 (Table 2). This indicates that the occurrence of FRs on the skin surface might be a consequence of contact with elevated surface dust in the home. Similar relationships were observed by researchers from the U.S. (Stapleton et al., 2014; Cowell et al., 2017; Hoffman et al., 2015). Interestingly, no associations were seen for TBBPA or DBDPE levels between hand wipes and dust. Although DBDPE has been used as a replacement for BDE-209, the absence of correlation between levels of DBDPE in hand wipes and home dust samples indicates that dermal exposure may be from other microenvironments or from sources other than dust from the living room.

3.3. Effects of type and number of consumer products, personal behaviour and building characteristics

Statistical analysis was carried out to investigate the possible

Table 2
Correlation matrix between FR levels measured in paired hand wipes and settled dust samples (both DF ≥ 40%). Correlations in bold were statistically significant ($p < 0.05$).

		Hand wipe (ng/participant)									
		α-DBE-DBCH	β-DBE-DBCH	EH-TBB	BEH-TEBP	OBTMPI	DBDPE	TBBPA	α-HBCDD	β-HBCDD	γ-HBCDD
Settled dust (ng/g)	α-DBE-DBCH	**0.26**	**0.33**	0.03	0.13	0.00	−0.03	0.03	0.02	0.02	0.15
	β-DBE-DBCH	**0.40**	**0.45**	0.15	**0.26**	0.06	0.09	0.20	0.18	0.11	0.25
	EH-TBB	0.06	0.09	**0.40**	**0.41**	0.00	0.21	0.15	0.11	0.09	0.12
	BTBPE	−0.05	−0.01	0.06	0.11	−0.12	0.07	−0.18	0.07	0.10	0.07
	BEH-TEBP	0.09	0.11	0.08	**0.27**	0.17	0.09	0.00	0.00	−0.02	0.09
	syn-DDC-CO	**0.34**	**0.29**	0.03	0.12	0.02	0.10	0.23	0.22	0.21	**0.31**
	anti-DDC-CO	**0.27**	**0.26**	−0.02	0.09	0.04	−0.03	0.13	−0.03	−0.06	0.10
	OBTMPI	−0.02	−0.15	−0.13	0.05	0.13	0.19	0.12	0.07	0.11	0.10
	DBDPE	0.12	0.02	0.19	0.07	0.03	0.04	0.05	0.02	0.03	0.06
	TBBPA	−0.05	0.09	−0.15	−0.09	−0.15	−0.07	0.16	0.04	−0.02	−0.05
	α-HBCDD	−0.02	0.08	−0.03	0.02	−0.02	0.00	**−0.27**	0.21	0.24	**0.37**
	β-HBCDD	0.07	0.12	−0.17	−0.05	−0.21	0.03	−0.15	0.21	0.25	**0.33**
	γ-HBCDD	−0.04	0.12	0.03	0.09	**−0.31**	0.14	−0.07	**0.33**	**0.31**	**0.56**
	BDE-28	−0.01	0.06	0.04	0.25	−0.05	−0.05	0.18	0.01	−0.01	0.06
	BDE-35	−0.07	−0.07	−0.03	0.24	0.14	0.06	−0.07	0.05	0.07	0.21
	BDE-47	−0.01	0.09	0.09	0.23	−0.14	0.11	0.02	0.06	0.15	0.20
	BDE-49	**0.29**	**0.29**	0.22	0.12	−0.02	0.09	0.16	**0.39**	0.13	**0.30**
	BDE-66	0.13	0.17	0.19	**0.32**	−0.07	0.16	**0.29**	0.07	0.04	0.24
	BDE-99	0.10	0.16	0.04	0.13	−0.14	0.11	0.04	0.01	0.21	0.17
	BDE-100	0.18	0.18	0.18	0.15	0.06	**0.31**	0.15	0.10	−0.09	0.05
	BDE-153	0.09	0.10	−0.15	−0.07	0.01	−0.03	0.05	−0.15	−0.02	−0.04
	BDE-154	0.20	0.17	0.06	0.21	−0.18	0.05	0.05	0.03	0.23	0.23
	BDE-183	0.12	0.07	0.09	0.13	0.01	−0.03	0.02	0.09	0.04	0.13
	BDE-196	0.13	0.11	**−0.27**	0.00	0.00	−0.04	0.15	−0.04	0.16	0.12
	BDE-197	0.02	−0.04	−0.18	0.03	0.10	0.05	0.16	0.00	0.08	0.10
	BDE-203	0.05	−0.02	−0.25	0.17	−0.11	0.07	−0.01	−0.04	0.02	0.16
	BDE-206	0.06	−0.02	−0.11	0.19	0.15	**0.30**	0.22	0.04	0.15	0.18
	BDE-207	0.12	0.09	−0.09	0.18	0.20	0.20	0.19	0.01	0.09	0.16
	BDE-208	0.11	0.09	−0.15	0.11	0.19	0.24	0.16	0.10	0.15	0.16
	BDE-209	0.07	0.06	−0.01	0.20	0.25	0.24	0.17	0.03	0.11	0.20

		Hand wipe (ng/participant)										
		BDE-28	BDE-35	BDE-47	BDE-49	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-207	BDE-209
Settled dust (ng/g)	α-DBE-DBCH	−0.01	0.11	−0.11	0.00	0.01	−0.08	0.06	0.00	0.12	0.02	−0.03
	β-DBE-DBCH	0.14	0.04	0.03	0.07	0.18	−0.04	0.14	0.05	0.19	0.13	0.12
	EH-TBB	0.23	−0.12	0.12	0.04	−0.03	−0.07	0.10	0.07	0.19	0.03	0.03
	BTBPE	0.14	−0.03	0.06	−0.07	−0.01	0.11	−0.03	−0.05	0.01	−0.16	−0.11
	BEH-TEBP	**0.27**	−0.09	0.22	0.03	−0.07	0.05	0.11	0.13	0.20	0.05	0.00
	syn-DDC-CO	0.02	−0.06	0.07	0.12	0.08	−0.12	−0.02	0.03	−0.03	0.10	0.18
	anti-DDC-CO	0.12	0.00	0.14	0.19	0.10	0.10	0.12	0.13	0.06	−0.07	−0.03
	OBTMPI	0.10	−0.03	0.14	0.14	0.07	0.21	−0.13	0.07	−0.14	0.22	**0.33**
	DBDPE	0.22	0.03	0.13	0.15	0.06	0.12	0.16	0.13	0.12	0.16	0.11
	TBBPA	−0.18	−0.10	0.01	0.07	0.24	0.02	−0.13	0.08	−0.10	−0.05	0.14
	α-HBCDD	0.23	0.03	0.19	−0.06	0.22	0.00	0.17	0.08	0.13	−0.10	−0.10
	β-HBCDD	0.14	**0.30**	0.22	0.00	0.24	0.03	0.18	0.09	0.11	−0.15	−0.02
	γ-HBCDD	0.19	0.09	**0.33**	0.05	0.09	0.22	0.21	0.16	0.13	−0.05	0.19
	BDE-28	0.25	0.09	0.14	0.23	**0.28**	0.16	0.07	0.17	0.13	0.14	0.16
	BDE-35	0.19	0.16	0.06	0.03	−0.07	0.00	0.15	0.02	0.18	0.16	0.05
	BDE-47	**0.41**	0.07	**0.48**	0.07	**0.38**	0.18	**0.27**	0.19	**0.30**	0.11	**0.26**

(*continued on next page*)

Table 2 (*continued*)

	Hand wipe (ng/participant)										
	BDE-28	BDE-35	BDE-47	BDE-49	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-207	BDE-209
BDE-49	0.15	0.13	0.17	0.12	0.19	−0.05	0.22	0.05	**0.30**	0.21	0.18
BDE-66	**0.35**	0.16	**0.47**	**0.35**	**0.40**	0.21	0.23	**0.29**	0.23	0.24	**0.36**
BDE-99	**0.36**	0.13	**0.52**	0.11	**0.44**	0.24	**0.28**	0.23	0.18	0.12	**0.31**
BDE-100	0.12	0.02	0.10	0.11	0.13	0.07	−0.04	−0.10	0.06	0.19	0.19
BDE-153	**0.28**	0.02	**0.36**	0.10	**0.27**	0.13	0.24	0.14	0.20	0.24	0.23
BDE-154	**0.42**	0.11	**0.52**	0.20	**0.36**	**0.37**	0.19	**0.27**	0.10	0.19	**0.37**
BDE-183	**0.38**	0.16	**0.31**	0.15	**0.34**	0.19	0.25	0.15	**0.31**	**0.29**	0.23
BDE-196	0.04	0.22	0.10	0.00	0.02	0.03	0.03	0.01	0.06	0.21	**0.36**
BDE-197	0.19	−0.05	0.25	0.18	**0.30**	0.17	0.09	0.12	0.03	0.17	**0.30**
BDE-203	0.12	**0.27**	0.14	0.14	0.14	0.07	−0.12	0.01	0.03	0.09	0.20
BDE-206	0.09	−0.06	0.18	0.21	0.18	0.18	0.03	0.14	−0.10	**0.27**	**0.47**
BDE-207	0.12	0.02	0.12	0.11	0.13	0.17	0.05	0.12	0.12	0.23	**0.44**
BDE-208	0.12	0.02	0.11	0.06	0.12	0.04	0.03	0.08	0.14	0.23	**0.43**
BDE-209	0.09	0.11	0.09	0.14	0.05	0.09	0.09	0.09	0.20	**0.32**	**0.52**

correlation(s) between FR masses in hand wipes and potential contributing factors including numbers of TVs, PCs and mobile phones, personal behaviour (e.g. hand washing and house cleaning frequency), and building characteristics. Masses of BDE-28, 35, -47, -99, -100, -153, -183, -197, -209, sumPBDE, sumHBCDD, α- and β-DBE-DBCH in hand wipes were positively correlated to the number of electronic consumer products at home (i.e. TV, DVD players, tablets, laptops, cell phones and PC screens) (Spearman rank correlation, r ranged from 0.26 to 0.40, $p < 0.05$, Table S12). Positive correlations were found between the number of people inhabiting the house and the masses of β-DBE-DBCH, α- and β-HBCDDs in hand wipes ($0.27 < r < 0.30$), whereas and between the number of electronic appliances/person at home and the masses of BDE-28, -47, -153, -183, and − 197 in handwipes ($0.26 < r < 0.40$).

Multiple linear regression analyses were also performed for α- and β-DBE-DBCH, BDE-28, -35, -47, -99, -100, 153, -183, -197, -207, -209, sumPBDE and sumHBCDD to assess the variation in the hand wipe masses related to household factors (Table S13). The models showed house cleaning frequency to be a relevant contributor to the variation of the levels of α-, β-DBE-DBCH and BDE-28 in hand wipes, but this association was not significant for DBE-DBCH in the Spearman rank analysis (Table S12). Positive associations with number of laptops/tablets, desktops, phones/mobiles, size of apartment and number of cohabitants for many FRs from the bivariate analysis remained significant in the multivariate model. Other factors such as years living in the apartment, number of TVs/video DVDs and PC screens from the bivariate analysis were no longer significant, except for BDE-99 and sumPBDE, which showed negative association with total number of electronic appliances in the models. One possible explanation for this disagreement might be statistical artefacts, due to limited number of samples available in this study.

Congeners of Penta-BDE, BDE-209, EH-TBB, BEH-TEBP and DBDPE have previously been detected frequently in product wipes of small household appliances (Abbasi et al., 2016; Zheng et al., 2017b). Source-to-dust transfer of PBDEs in indoor microenvironments (e.g. from plastic TV casing to the TV interior dust) may also occur through abrasion and direct contact migration pathways (Takigami et al., 2008; Rauert & Harrad, 2015). Positive correlations between FR concentrations and the numbers of electronic equipment in the home were found in our earlier observations for settled dust samples (Tay et al., 2017). Therefore, the presence of these particular FRs in hand wipes could be attributed to a combination of direct transfer of contaminated dust on electronics to hands, transfer of FRs in electronics to dust in the living room and subsequently to hands, and possibly direct transfer from contact with FR-treated electronics and other materials by the hands.

Lower masses of BDE-49 and TBBPA were measured in hand wipes collected from participants with medium and high hand-washing frequencies (4–8 times, > 8 times, respectively), compared to those who washed their hands fewer than 4 times per day (Kruskal-Wallis H test, $p < 0.05$, Table S14). Specifically, participants who washed their hands > 8 times per day had the lowest levels of these FRs on their hands (Mann-Whitney U test, $p < 0.05$). This finding is consistent with those of Stapleton et al. (2014) who reported that the frequency of hand washing for children, especially > 5 times per day, was associated with lower levels of Penta-BDE and EH-TBB. For TBBPA, this result may be explained by its relatively higher water solubility compared to other FRs. For BDE-49 we have no explanation. In addition, lower masses of BDE-100, -154, -209 and BEH-TEBP were found in participants who applied hand cream after hand washing than those who did not (Mann-Whitney U test, $p < 0.05$). This result agrees with the findings of another study in New York (Cowell et al., 2017), in which lower levels of BDE-209 and EH-TBB and BEH-TEBP were detected for those who applied lotion after hand washing, although the differences were not statistically significant. Significant decreases of dermal bioaccessibility from indoor dust in the presence of cosmetics (moisturising cream, sunscreen lotion, body spray and shower gel) have been reported for

HBCDDs (Pawar et al., 2017) and several PCBs (Ertl & Butte, 2012), possibly attributed to retention of the lipophilic chemicals by cosmetic lipids.

3.4. Dermal exposure

The measured levels of FRs from hand wipes and settled dust were used to calculate the exposure from dermal absorption according to Eqs. (2) and (3). The daily dermal exposure estimated from hand wipe data (direct) was the highest for sumEHFR, followed by sumHBCDD and sumPBDE (medians of 2600, 840 and 6.2 pg/kg bw/d, respectively) (Table 2). However, it should be noted that the exposure to EHFRs was mainly driven by TBBPA. While several studies have measured dermal exposure to PBDEs via the skin wipe method (Stapleton et al., 2012; Stapleton et al., 2008; Stapleton et al., 2014; Sugeng et al., 2017), only a few focused on adults (Liu et al., 2017; Hoffman et al., 2015; Watkins et al., 2011). To the best of our knowledge, TBBPA has not been reported in adults' hand wipes previously. Direct dermal exposure of our participants to TBBPA via hand wipes (150–18,000 pg/kg bw/d) was much greater than that reported for workers at a Chinese PCB plant (16–430 pg/kg bw/d, estimated through dust concentrations for face and hands with DA values of 0.096 and 0.2763 g/cm^2, respectively) (Zhou et al., 2014). Our exposure estimates for BTBPE, DBDPE and most of the PBDEs (0.021–2.2 pg/kg bw/d) were lower than those found in China (1.4–360 pg/kg bw/d, recalculated for adults of 70 kg bw), except for BDE-99 which showed comparable values (1.4 pg/kg bw/d) (Liu et al., 2017). Although high daily dermal exposure estimates were observed for TBBPA and HBCDDs through the hand wipe approach, the values were still several orders of magnitude lower than the oral reference dose (RfD) (see Table 2), even when considering the high-end scenario using the 95th percentile masses. However, only considering dermal exposure from the hands may underestimate the total exposure, since significant exposure may also occur from air and clothing (Weschler & Nazaroff, 2014; Morrison et al., 2015). Also, the AFs used for TBBPA (0.30) and HBCDDs (0.27–0.36) (adopted from Abdallah et al. (2015)) (Table S8) were derived under experimental conditions that would lead to underestimates of the fraction absorbed due to the high loadings used. For example, if the measured flux (average of 1.4 ng/cm^2/h from three different in vitro skin models used (Abdallah et al., 2015)) is assumed to be the maximum flux for TBBPA, the corresponding experimental dermal numbers (N_{DERM}, as proposed by Kissel (2011) of this compound for the hand wipe and settled dust approaches are 0.019 and 2.0×10^{-5}, respectively (See SI for detailed calculations). These low dermal numbers (< 1) indicate that at the skin loads observed, the uptake of TBBPA would be supply-limited (i.e. high absorption efficiency of the skin surface) and therefore the hand wipe sampling efficiency may be much lower than expected. This would also be the case for HBCDDs. If AFs of 1 (100% absorption) were used instead, this would lead to 3–10 times higher calculated dermal uptakes for the various FRs derived from both hand wipes and dust. These could still be underestimates as sampling may be missing already absorbed chemicals.

Indirect dermal exposure estimated indirectly from dust concentrations was dominated by sumPBDE, followed by sumEHFR and sumHBCDD (medians of 17, 16 and 9.0 pg/kg bw/d, respectively). A few pharmacokinetic models also revealed that dermal contact with indoor dust made significant contributions to the overall PBDE exposure (Lorber, 2007; Trudel et al., 2011). Our median exposure estimate for sumPBDE (17 pg/kg bw/d through dust contact) was lower than that reported in a similar Norwegian study (140 pg/kg bw/d) (Cequier et al., 2014), China (340 pg/kg bw/d) (Zhu et al., 2015) and the U.S. (340 pg/kg bw/d) (Johnson-Restrepo & Kannan, 2009). Median exposures to single BDE congeners and most of the EHFRs (*α*-, *β*-DBE-DBCH, EH-TBB, BTBPE, BEH-TEBP, DBDPE, *syn*- and *anti*-DDC-CO) in this study (0.026–11 pg/kg bw/d) were much lower than those estimated in 2012 in Norway (0.24–160 pg/kg bw/d) (Cequier et al., 2014). However, a higher dust adherence amount (DA of 0.096 g/cm^2) used for those studies could possibly explain the differences in exposure estimates. For HBCDDs, the exposure value estimated in this study (9.0 pg/kg bw/d) was lower than that found in China (130 pg/kg bw/d, DA = 0.096 g/cm^2) (Qi et al., 2014). Dermal exposures to BDE-209, TBBPA and DBDPE from dust in the present study were lower than those estimated for both Americans and other Europeans (averages of 40–880, 10 and 40 pg/kg bw/d, respectively, DA = 0.01 g/cm^2) (Boyce et al., 2009).

Reasonable agreement was found between the medians of direct and indirect dermal exposure estimates ($<$ 10-fold deviation) for many of the individual EHFRs and PBDEs (Table 3). For *α*-, *β*-DBE-DBCH, DBDPE, BDE-28, -35, -49, -99, -153, -154 and -183, the indirect method provided good agreement between the potential (from dust concentrations) and actual exposure estimates (from hand wipes) (Mann-Whitney *U* test, $p > 0.05$). However, 10 to 1000-times higher exposure was observed for actual compared to potential median exposure estimates for TBBPA, *α*-, *β*-, γ-HBCDD and BDE-100. Between 3 and 9 times higher exposure estimates were obtained for actual (hand wipes) compared to potential (settled dust) exposure for EH-TBB, BEH-TEBP, OBTMPI, and BDE-203, while for BDE-206, -207 and -209 the reverse was found with 3–5 times higher estimates based on concentrations in settled dust compared to estimates based on hand wipe masses. The inconsistency between the two types of exposure estimates for FRs might be related to heterogeneous distribution of FRs in dust depending on their usages and migration pathways (such as BDE-209 and HBCDDs) (Webster et al., 2009; Cao et al., 2015), as well as the impact direct skin contact with FR-treated products has, which was not taken into account in the indirect approach.

Comparison between particle size distribution of hand dust and indoor dust from China showed that dust particles around 20 μm in diameter are selectively adhered to human hands (Cao et al., 2013), while most of the PBDEs and several EFRs (EH-TBB, BTBPE, BEH-TEBP and DBDPE) could be enriched in both coarse and fine dust particles (100–200 and ~10 μm, respectively) (Cao et al., 2014). Our dermal exposure estimates based on dust samples without sieving, however, are still within the same order of magnitude as those estimated via the hand wipe approach for most of the PBDEs and EFRs. These results suggest that hand wipes can capture more information about recent dermal exposures from multiple microenvironments as compared to the indirect method, either through direct skin contact with FR-treated products and/or uptake from dust. The indirect method is also applicable and shows fairly comparable performance in the present exposure scenario for many of the individual FRs, where the dermal exposure is restricted to hands.

3.5. Study limitations and uncertainties

There are several limitations in our study. For example, participants in our study were predominantly women working at the Norwegian Institute of Public Health (NIPH) and thus not representative of the general population in Norway. Only one hand wipe sample was collected per participant for the analysis of FRs and the levels of FRs in the hand wipe samples were assumed to be constant for 24 h on any given day. However, the participants spent part of the day away from the home (at work, traveling etc.) so the hand wipes may reflect integrated exposure from several microenvironments, whereas the dust only reflects the home. Hand wipe sample collection at different times of day paired with simultaneous dust sample collection from different microenvironments the participant is present in may be useful for better understanding of human dermal exposure to FRs. Sampling efficiency with isopropanol was not evaluated. Since we collected hand wipe and dust samples during winter, we assumed our participants were wearing long-sleeved shirts, pants and shoes—limiting the dermal exposure to hands only. Particle size distribution and adherent fractions of settled dust samples were not evaluated, which could lead to bias in estimating

Table 3
Estimated daily dermal exposure (pg/kg bw/d) to FRs for adults from hand wipe and settled dust data compared to oral reference doses, where available.

	Oral RfD	via hand wipe			via settled dust			Mann-Whitney *p*-value (hand wipe vs. settled dust)
		5P	median	95P	5P	median	95P	
TBP-AE		-	-	-	-	-	-	UC
α-DBE-DBCH		0.073	0.29	2.7	0.0024	0.25	1.5	NS
β-DBE-DBCH		0.10	0.16	1.3	0.031	0.24	0.82	NS
BATE		-	-	-	-	-	-	UC
TBCT		-	-	-	-	-	-	UC
PBT		-	-	-	-	-	-	UC
PBEB		-	-	-	-	-	-	UC
TBP-DBPE		-	-	-	-	-	-	UC
HBB		-	-	-	-	-	-	UC
EH-TBB	2.0×10^{7}[a]	0.22	0.75	9.4	0.0065	0.34	2.6	0.039
BTBPE	2.4×10^{8}[a]	-	-	-	0.024	0.60	4.0	UC
BEH-TEBP	2.0×10^{7}[a]	1.2	12	61	0.64	4.2	23	< 0.001
OBTMPI		0.0095	0.021	0.16	0.0024	0.009	0.14	0.008
DBDPE	3.3×10^{8}[a]	0.13	0.83	9.3	0.33	1.1	4.6	NS
TBBPA	6.0×10^{8}[b]	150	2600	18,000	0.49	2.7	21	< 0.001
syn-DDC-CO		-	-	-	0.0058	0.026	0.56	UC
anti-DDC-CO		-	-	-	0.0039	0.092	0.68	UC
α-HBCDD		60	380	2800	0.012	5.0	41	< 0.001
β-HBCDD		76	190	2000	0.0014	0.90	15	< 0.001
γ-HBCDD		34	200	4000	0.14	1.8	18	< 0.001
BDE-28		0.0043	0.021	0.32	0.0043	0.023	0.26	NS
BDE-35		0.0031	0.017	0.49	0.0049	0.066	0.33	NS
BDE-47	1.0×10^{5}[c]	0.12	0.71	18	0.30	0.98	10	NS
BDE-49		0.0058	0.033	0.63	0.0055	0.046	0.76	NS
BDE-66		-	-	-	0.0032	0.022	0.38	UC
BDE-77		-	-	-	-	-	-	UC
BDE-85		-	-	-	-	-	-	UC
BDE-99	1.0×10^{5}[c]	0.14	1.5	32	0.30	1.3	10	NS
BDE-100		0.0083	0.087	0.92	0.0029	0.0078	0.65	0.006
BDE-153	2.0×10^{5}[c]	0.043	0.15	2.0	0.0032	0.14	1.9	NS
BDE-154		0.013	0.061	1.6	0.0034	0.10	0.94	NS
BDE-182		-	-	-	-	-	-	UC
BDE-183		0.0057	0.059	0.65	0.0074	0.076	0.36	NS
BDE-184		-	-	-	-	-	-	UC
BDE-185		-	-	-	-	-	-	UC
BDE-191		-	-	-	-	-	-	UC
BDE-196		-	-	-	0.0094	0.079	0.96	UC
BDE-197		0.023	0.058	0.36	0.010	0.043	0.35	0.028
BDE-203		-	-	-	0.015	0.082	3.0	UC
BDE-206		0.058	0.098	0.48	0.0073	0.28	9.3	0.004
BDE-207		0.051	0.084	0.34	0.070	0.24	4.1	< 0.001
BDE-208		-	-	-	0.037	0.14	1.5	UC
BDE-209	7.0×10^{6}[c]	0.23	2.2	11	2.4	11	41	< 0.001
sumPBDE		2.0	6.2	60	5.8	17	75	
sumHBCDD	2.0×10^{8}[d]	210	840	12,000	1.2	9.0	53	
sumEHFR		170	2600	18,000	6.3	16	39	

-: detection frequency in samples were below 40% and thus no exposure was calculated.
UC: unable to calculate.
NS: no significant difference.
p-values indicate significant differences between exposure values estimated from hand wipes and settled dust data.
The sums of PBDE, HBCDD and EHFR were calculated from individual results.
[a] RfD values used by Ali et al. (2012).
[b] RfD value suggested by Wikoff et al. (2015).
[c] RfD values by IRIS, USEPA (US-EPA Toxicological review of decabromodiphenyl ether (BDE-209); US-EPA Toxicological review of BDE-99; US-EPA Toxicological review of BDE-153; US-EPA Toxicological review of BDE-47).
[d] RfD value by NRC (2000).

dermal exposure to FRs through dust uptake.

We are aware that the estimation of AF using in vivo, in vitro and ex vivo data is mostly an artefact of experimental design, especially at surface loadings that approach or exceed the threshold for saturation of dermal flux (Roberts, 2007). However, due to limited data availability, the AFs used for our risk assessment were mostly derived from such literature data. Since AF can be highly dose and duration dependent (Kissel, 2011; Frasch et al., 2014), the usage of a single, fixed absorption factor is insufficient to indicate the true extent of dermal absorption. Alternatively, dermal exposure to FRs can also be estimated through both experimental-derived and model-estimated dermal permeability coefficients, covering a huge range of exposure scenarios which were not considered in the present study (such as direct contact with FR-treated products, hand to mouth behaviour and indirect uptake through clothing).

Despite its limitations, our study highlights the importance of assessing dermal exposure through measuring FR levels in hand wipes, which cannot be achieved through indirect estimation only from dust concentrations. Levels of FRs in the hand wipes can be an indicator of personal exposure, but do not reflect the actual internal dose, which can

only be assessed through the biomonitoring approach. Dermal exposure occurs from the face, hands, as well as other exposed skin areas and should be taken into account in further studies. Transdermal uptake from air might be significant for FRs with high volatility. Careful evaluation and interpretation of dermal absorption data (absorption fraction) is required to avoid multiplication of underestimation of both potential dose and fraction absorbed. Overall, dermal exposure to FRs is still poorly understood and therefor more studies are needed to address these issues for more accurate estimates of dermal exposure.

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Appendix A. Supplementary data

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