Brominated Flame Retardants in UK Human Milk; Relationship to External Exposure

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Introduction

➢ **Several studies have reported levels of various BFRs in both biotic and abiotic matrices from different parts of the world in the past few years.**

➢ **The only available information on BFRs in UK human samples is for tri- to hexa-BDEs (median = 6.3 and 4.18 ng/g lw in human milk and serum samples collected in 2003) . In addition, BDE-209 was detected in 11 out of 153 serum samples at concentrations from 15-240 pg/g lw).**

➢ **Consequently, very little is known about the exposure of nursing infants to BFRs via breast milk in the UK and how it compares to the dietary exposure of other age groups.**

Introduction

➢ **Very little is known about the extent to which the known contamination of indoor environments with BFRs influences human body burdens.**

Correlation between the levels of BFRs in food or indoor dust and their concentrations in human milk or serum.

Significant	Non-Significant
Wu et al.[1]	Roosens et al.[3]
Roosens et al.[2]	Toms et al.[4]
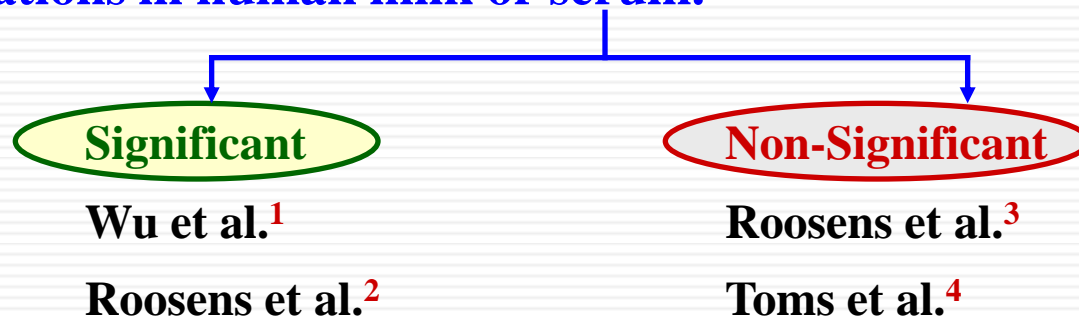
➢ **An alternative approach was adopted by Lorber[5] who applied a simple pharmacokinetic (PK) model to predict the body burdens of PBDEs in American adults using intake data from different exposure pathways.**

(1) Wu, N., *et al.*, *Environ Sci Technol* **2007,** 41, 1584-1589. (2) Roosens, L., *et al.*, *Environ Health Perspect* **2009,** 117, 1707-12. (3) Roosens, L., *et al.*, *Environ Sci Technol* **2009,** 43, 3535-41. (4) Toms, L. M., *et al.*, *Environ Int* **2009,** 35, 864-9. (5) Lorber, M., *J Expo Sci Env Epid* **2008,** 18, 2-19.
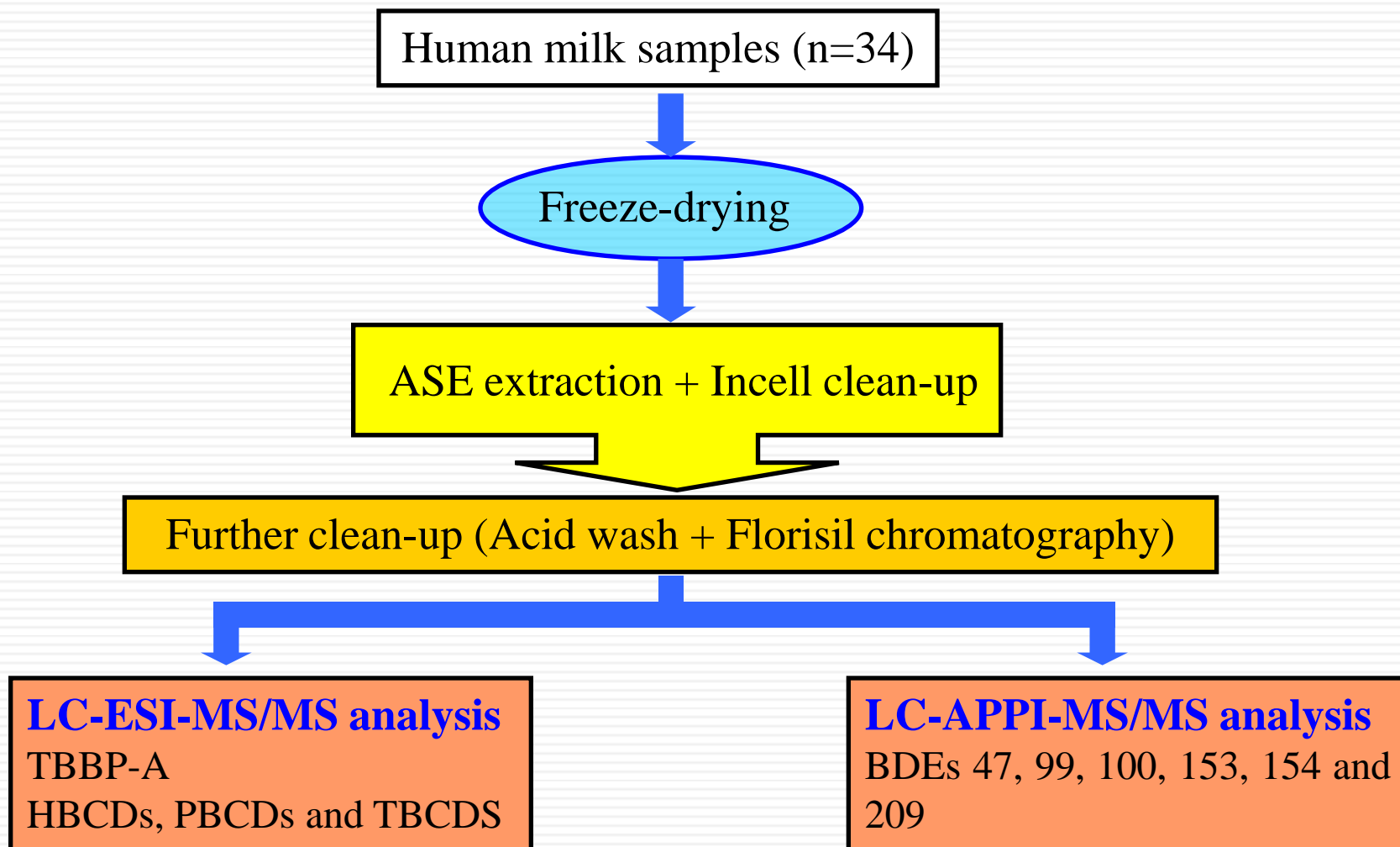
Aims

➢ Determine of the levels of TBBP-A, BDE-209, Σtri-hexa BDEs (Penta-BDE), HBCDs and their degradation products in 34 human milk samples from Birmingham, UK.

➢ Estimate the dietary exposure of nursing infants to the studied BFRs using different scenarios.

➢Apply a one-compartment PK model to predict the body burdens of the studied BFRs in UK adults (using indoor air and dust levels previously reported by our group for Birmingham, UK) and compare the model predictions to the concentrations of target compounds measured in the analyzed human milk samples.
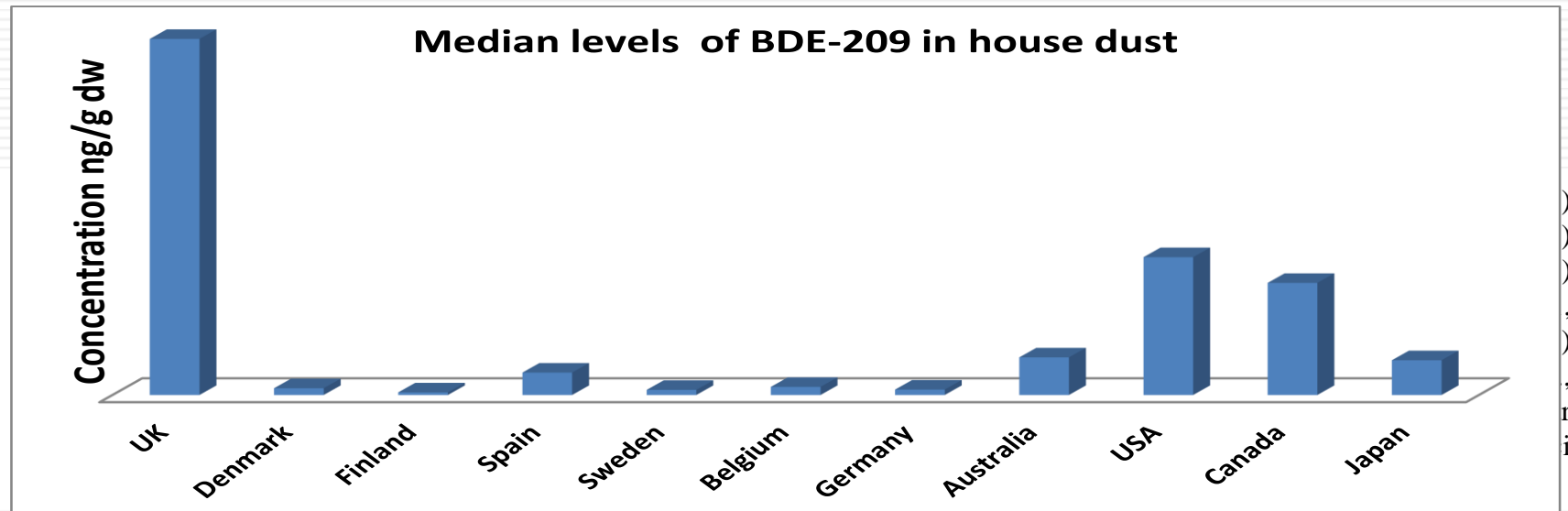
Methodology*

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┌─────────────────────────────────┐
│   Human milk samples (n=34)     │
└─────────────────────────────────┘
              │
              ▼
      ╭───────────────╮
      │ Freeze-drying │
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              │
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┌─────────────────────────────────┐
│ ASE extraction + Incell clean-up│
└─────────────────────────────────┘
              │
              ▼
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│ Further clean-up (Acid wash + Florisil chromatography)│
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        │                               │
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LC-ESI-MS/MS analysis
TBBP-A
HBCDs, PBCDs and TBCDS

LC-APPI-MS/MS analysis
BDEs 47, 99, 100, 153, 154 and 209

- Abdallah, M. A.; Harrad, S., *Environ Int* **2011,** 37, 443-8.
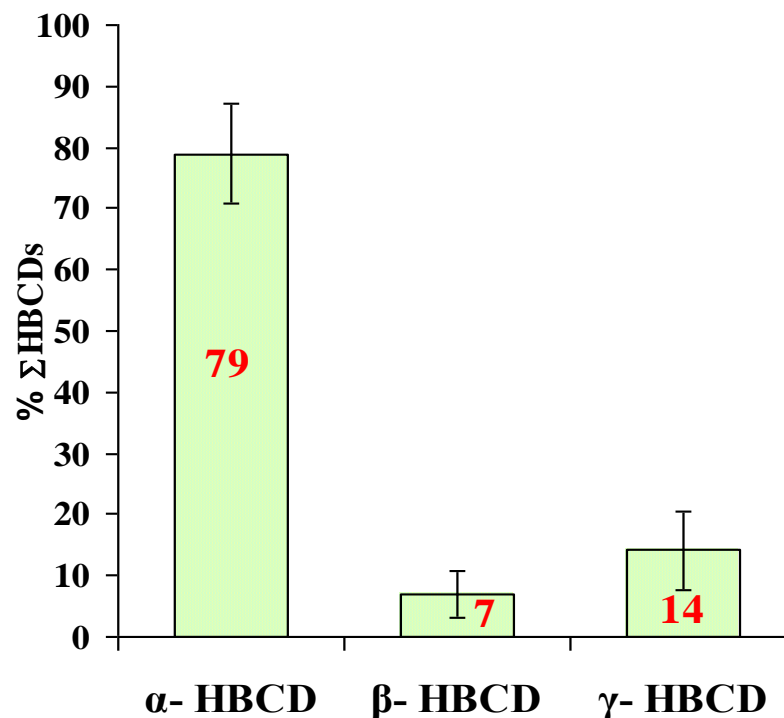- Abdallah, M. A.; Harrad, S., *Environ Int* **2014,** 63,130-6.

Average concentrations (ng/g lw) of BFRs in Human milk

	UK*	Norway	France	Spain	Sweden	USA	Canada	Australia	China
TBBP-A	**0.06**	0.07[1]	0.47[2]						0.93[3]
∑tri-hexa BDEs	**5.95**	2.34[4]	2.51[5]	2.14[6]	3.57[7]	34.0[8]	42.8[9]	7.6[10]	2.53[11]
BDE-209	**0.31**	0.61[12]	1.62[5]	2.9[13]		0.92[8]	0.43[14]	0.31[10]	3.0[11]
∑HBCDs	**5.95**	1.7[12]	2.2[15]	47[16]	0.45[17]	0.5[18]	3.8[18]		2.4[3]

Median levels of BDE-209 in house dust

Concentration ng/g dw

UK, Denmark, Finland, Spain, Sweden, Belgium, Germany, Australia, USA, Canada, Japan

HBCD diastereomer profiles in human milk

Average % contribution of HBCD diastereomers to ΣHBCDs (error bars represent 1 standard deviation).

Possible reasons:

➢ *Preferential metabolism[1].*

➢ *Diasteromer profile in dust[2].*

➢ *Higher bioavailability of α-HBCD[3].*

➢ *Higher adipose tissue deposition and lower fecal elimination rate of α-HBCD[4].*

(1) Zegers, B. N., *et al.*, *Environ Sci Technol* **2005,** 39, 2095-100. (2) Harrad, S., *et al.*, *Environ Int* **2009,** 35, 573-9. (3) Abdallah, M. A., *et al.*, *Organohalogen Compounds* **2009,** 71, 100-104. (4) Hakk, H., *et al.*, *Organohalogen Compounds* **2010,** 72, 182-186.

HBCD enantiomer profiles in human milk
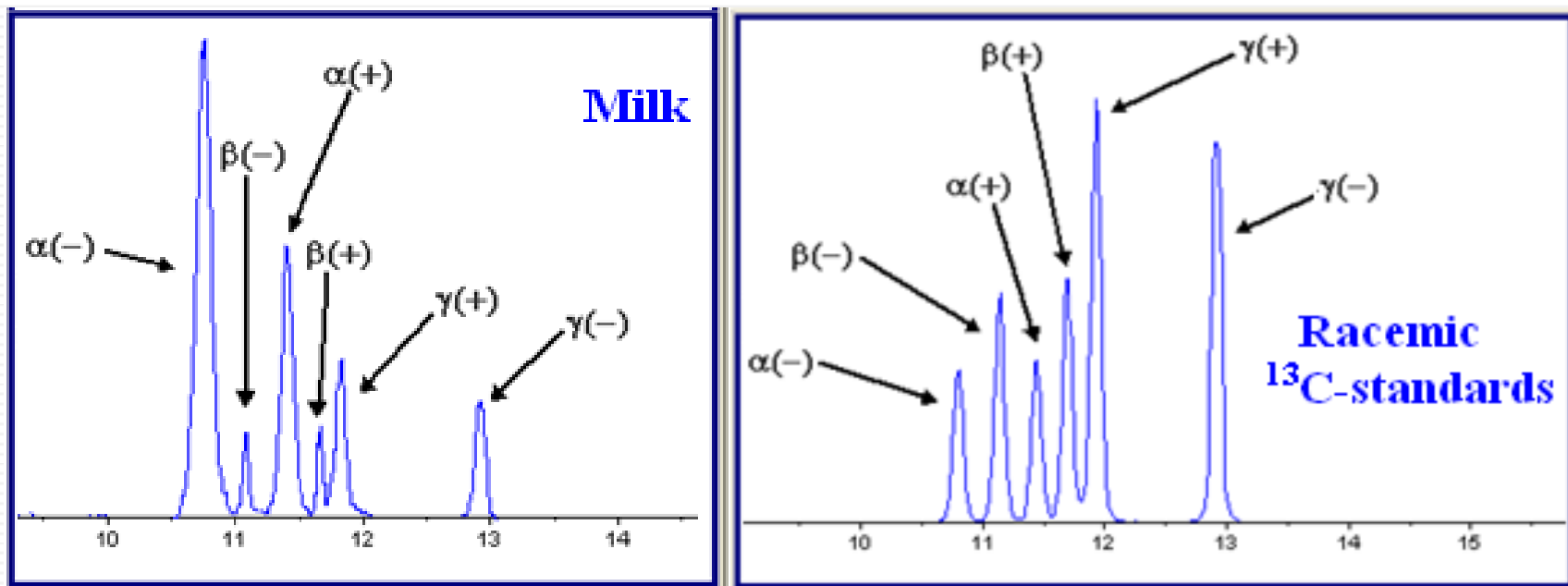
➢ Significant enrichment of the (-)-α-HBCD enantiomer (Average EF=0.29).

➢ Given the previously reported racemic chiral signatures of HBCDs in indoor dust[1] and diet[2], This indicates the presence of potential enantioselective processes involved with the absorption, metabolism and/or excretion of HBCDs.

(1) Harrad, S., *et al.*, *Environ Int* **2009,** 35, 573-9. (2) Roosens, L., *et al.*, *Environ Health Perspect* **2009,** 117, 1707-12.

HBCD degradation products* in human milk
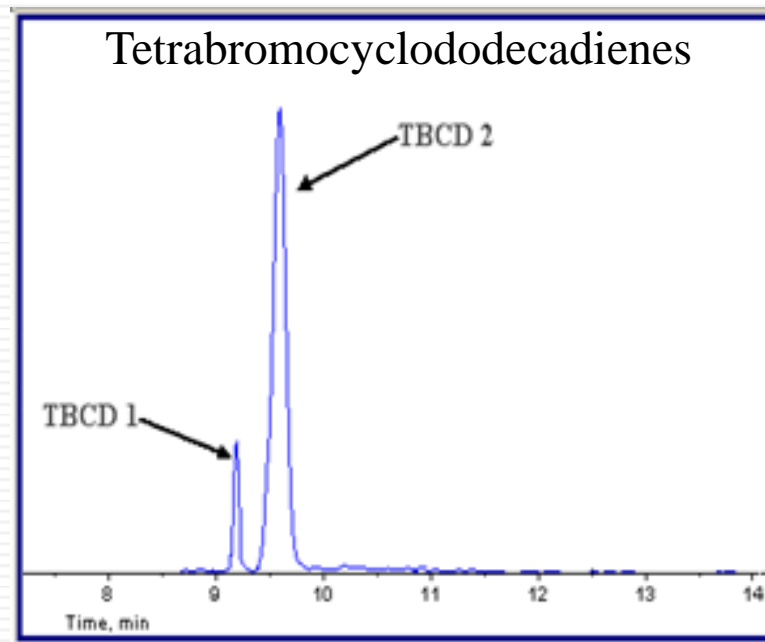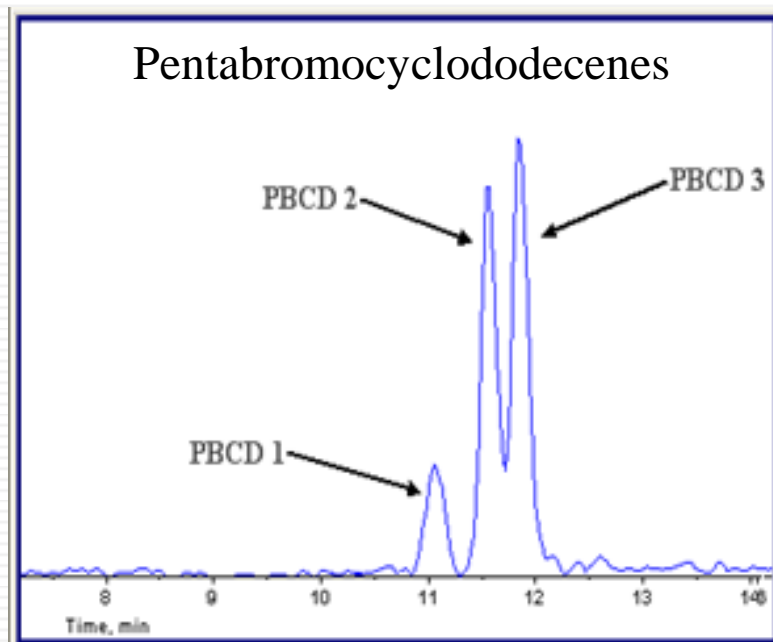
Concentration (ng/g lw) of HBCD degradation products in human milk.

	Average	Range	Frequency
ΣPBCDs	0.04	<0.03-0.20	26%
ΣTBCDs	0.15	<0.03-0.36	73%

* Abdallah, M. A., *et al.*, *J Chromatogr A* **2008,** 1190, 333-41.

Nursing infants' dietary intake of BFRs via breast milk

$$Di = \frac{C_{BFR} \; x \; F_{lipid}}{Bw}$$

Parameter	Definition
D_i	The estimated dietary intake (ng/kg bw/day).
C_{BFR}	The concentration of target BFR in milk (ng/g lw)
F_{lipid}	The daily lipid intake via breast milk (g/day)
B_w	The infant's body weight (kg)

The U.S. EPA (2002) guidelines suggest an average intake of 702 mL milk/day for a 1 month old infant weighing 4.14 kg.

The median lipid content of the analyzed milk samples was 3.47 g/100 mL resulting in a daily lipid intake of 24.4 g lipid/day.

Nursing infants' dietary intake of BFRs via breast milk

Estimated exposure (ng/kg bw/ day) of a 1 month old infant to the target BFRs via breast milk under different scenarios.

	5th %ile	Average	Median	95th %ile
α- HBCD	6.44	28.62	18.49	89.02
β- HBCD	0.5	1.84	1.75	3.88
γ- HBCD	0.87	4.24	3.25	12.33
Σ HBCDs	9.77	34.71	22.32	104.97
Σ PBCDs	<LOQ	0.6	0.48	1.04
Σ TBCDs	<LOQ	1.08	0.91	2.05
TBBP-A	<LOQ	0.98	0.63	2.74
Σtri-hexa BDEs	3.12	35.08	29.88	78.01
BDE-209	<LOQ	2.56	2.52	4.91
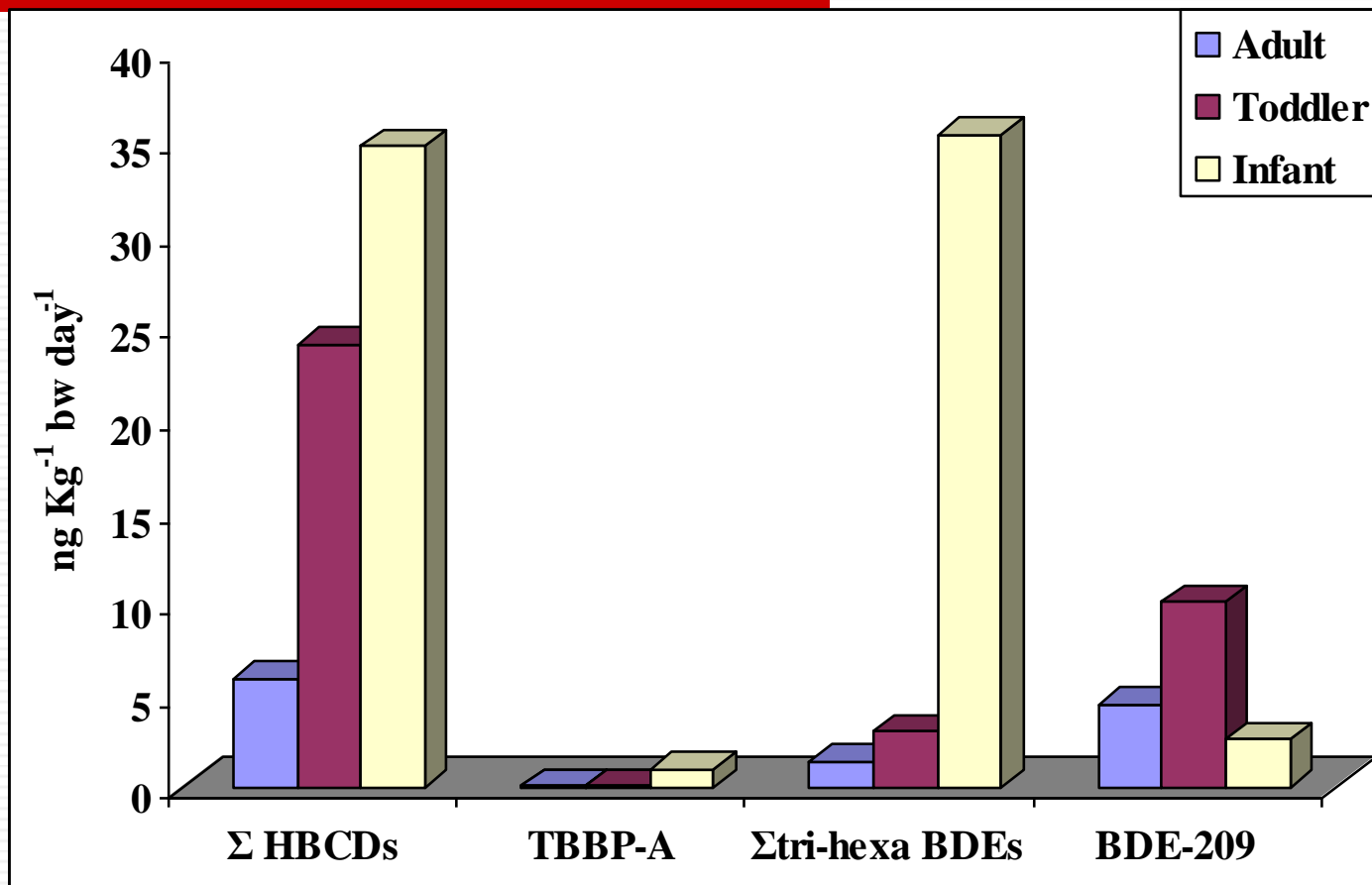
Average estimates of dietary exposure (ng/kg bw/day) of UK adults, toddlers and infants to the target BFRs.

Comparison of BFR intake to human body burdens

➢ Our research group have previously reported on UK adult intake of target BFRs via inhalation, dust ingestion and diet using data obtained from the analysis of a few hundred samples of indoor air and dust from homes, offices, cars and public microenvironments from Birmingham, UK[1-5] in addition to the data published by UK FSA[6].

➢ To compare the estimated BFR intakes of UK adults to the body burdens measured in human milk samples, a simple one-compartment, first order pharmacokinetic (PK) model was used where BFRs were hypothesized to accumulate in lipids (the single compartment in the model).

(1) Abdallah, M. A., *et al.*, *Environ Sci Technol* **2008,** 42, 6855-61. (2) Abdallah, M. A.-E.; Harrad, S., *Environ Int* **2009,** 35, 870-6. (3) Harrad, S., *et al.*, *Environ Int* **2008,** 34, 1170-5. (4) Harrad, S., *et al.*, *Environ Sci Technol* **2006,** 40, 4633-4638. (5) Abdallah, M. A.; Harrad, S., *Environ Sci Technol* **2010,** 44, 3059-65. (6) UK FSA, *http://www.food.gov.uk/multimedia/pdfs/ fsis 1006.pdf,* **2006**.

Comparison of BFR intake to human body burdens (Continued)

➢ The following final equation was used to predict the body burdens of the target BFRs assuming a steady state concentration was reached.

$$C_{BFR} = \frac{(I_{BFR} \; x \; AF_{BFR})}{BL \, x \, K_{BFR}}$$

| Parameter	Definition
C_{BFR}	The target BFR concentration in lipids (ng/g lw)
I_{BFR}	The daily intake of the target BFR (ng/day)
AF_{BFR}	The absorption fraction of the target BFR
BL	The body lipid mass (g)
K_{BFR}	The compound specific first order dissipation rate (day^{-1}) = $0.693/t_{0.5}$

Comparison of BFR intake to human body burdens (Continued)

	I_{BFR} (average) ng/day	I_{BFR} (median) ng/day	AF_{BFR}[1]	$t_{0.5}$ (days)[2]	BL (g)
α-HBCD	251	213	0.91	165	
β-HBCD	121	108	0.80	55	
γ-HBCD	185	135	0.71	55	
TBBP-A	5	2	0.94	21	25% body fat for an average adult weighing 70 Kg[4].
BDE-47	37	35	0.58	1516	
BDE-99	32	31	0.41	1953	
BDE-100	6	6	0.50	1243	
BDE-153	7	7	0.48	2850	
BDE-154	3	3	0.31	2460	
BDE-209	4589	3476	0.14	7[3]	

(1) Abdallah, M. A., *et al.*, *Organohalogen Compounds* **2009,** 71, 100-104. (2) Geyer, H. J., *et al.*, *Organohalogen Compounds* **2004,** 66, 3867–3872. (3) Hagmar, L., *et al.*, *Organohalogen Compounds* **2000,** 47, 198-201. (4) (U.S. EPA, 1997).

Comparison of BFR intake to human body burdens (Continued)
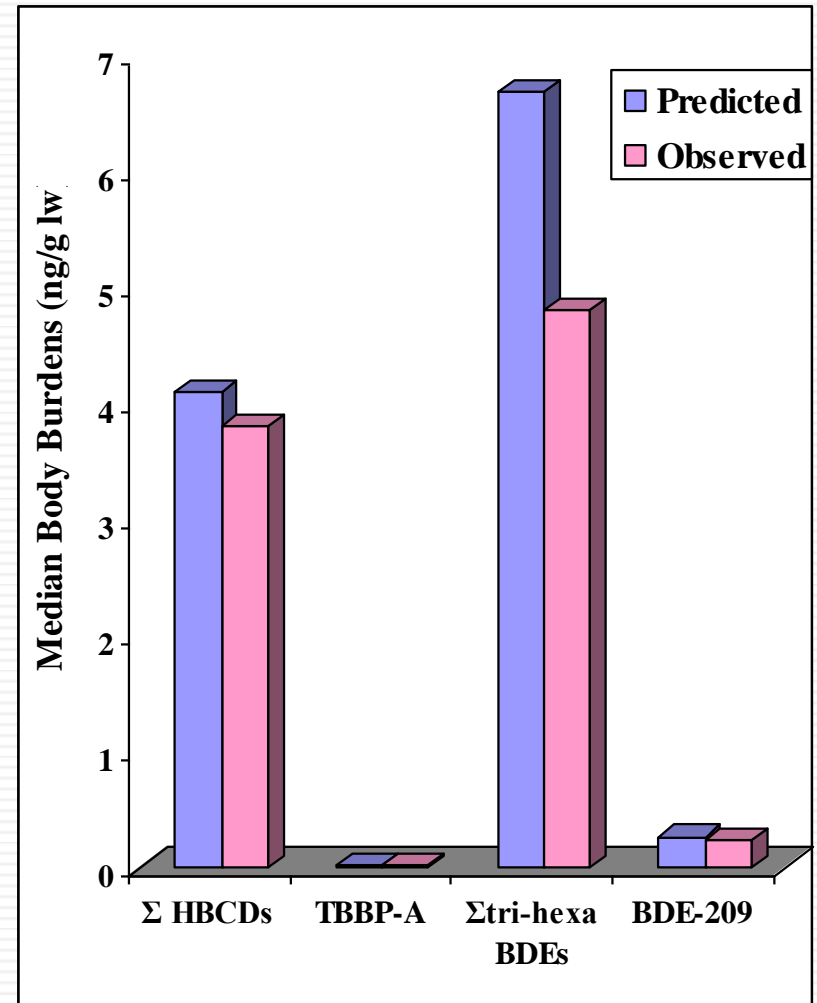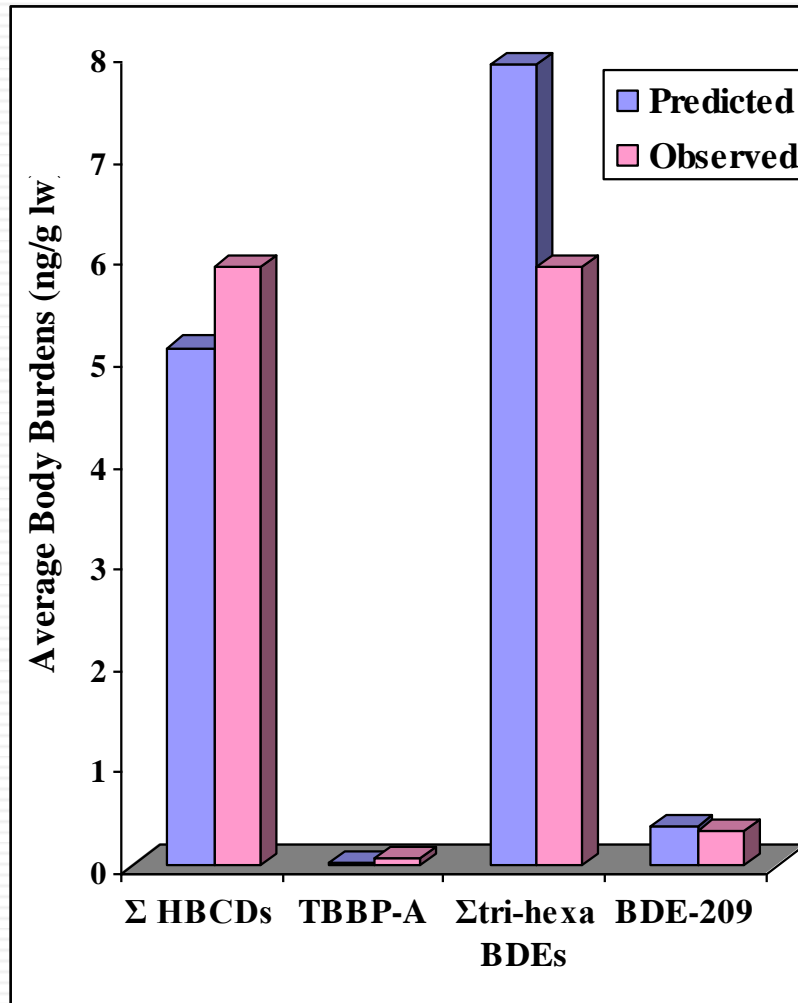
Conclusions

➢ BDE-209 concentrations in human milk were at the lower end of those previously reported from other European countries despite the higher levels of BDE-209 in UK indoor dust.

➢ α-HBCD was the predominant HBCD diastereomer in all the studied human milk samples.

➢ Enrichment of (-)-α-HBCD in human milk; as opposed to external exposure to racemic matrices, indicates the presence of enantioselective processes associated with HBCD absorption, metabolism and/or excretion.

➢ Lower brominated HBCD derivatives were detected in human samples for the first time. The potential toxic effects of these derivatives (PBCDs and TBCDs) are yet to be elucidated.

Conclusions (continued)

➢ The estimated exposure of nursing infants to HBCD, TBBPA and Σtri-hexa BDEs via milk exceeded adults and toddlers dietary intakes.

➢ The pharmakokinetic approach to understand the relationship between external human exposure to BFRs and internal body burdens provided promising results. However, more research is required to:

❖ Determine the half-life of different BFRs in various tissues of both males and females.

❖ Assess the bioavailability of various BFRs to humans from different matrices and via different exposure pathways.

❖ Develop more reliable multi-compartment models which integrate other important pharmakokinetic parameters like tissue distribution and variable metabolic and elimination rates of different BFRs.

ACKNOWLEDGEMENT

THANK YOU