Are brominated flame retardants a threat for humans?

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Presentation Outline:

- Background on Brominated Flame Retardants (BFRs)
  - uses, commercial formulations
  - toxicology
- Exposure to BFRs
  - human body burdens
  - dietary exposure vs. indoor exposure
  - identify sources of exposure
- Recent (own) results
- New/alternate BFRs

Classes of flame retardants (FRs)

- Brominated FRs **- polybrominated diphenyl ethers (PBDEs)**

- hexabromocyclododecanes (HBCDs)

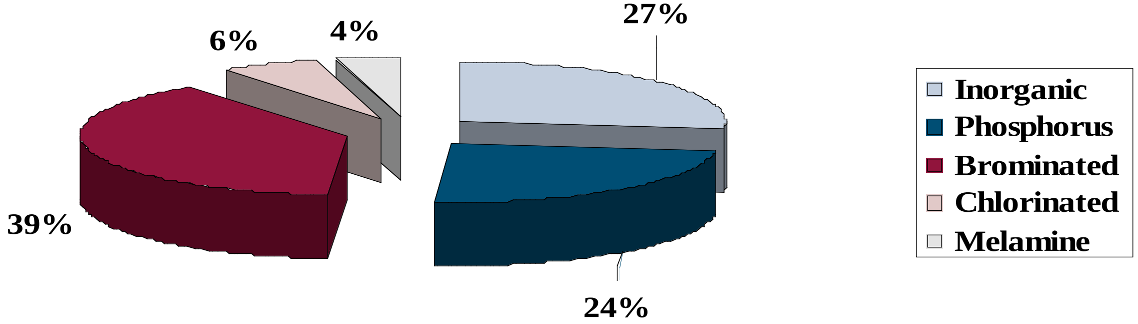
- tetrabromobisphenol-A (TBBP-A)

- others ("alternate" BFRs)

- Chlorinated FRs: **- polychlorinated alkanes (PCAs)**

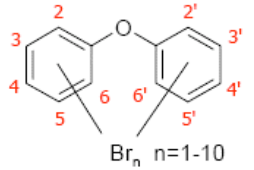
- Phosphorus FRs: **- halogenated and non-halogenated**

- Inorganic FRs: **- antimony oxide, hydrated aluminium**



Polybrominated diphenyl ethers (PBDEs)

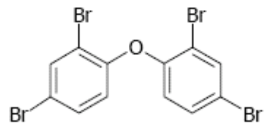
PBDE Nomenclature



Polybrominated Diphenyl Ether (PBDE)

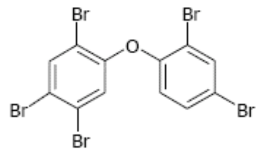
- 3 commercial products
- Penta-, Octa-, and Deca-BDE
- low number of congeners in the mixtures

PentaBDE Congeners:



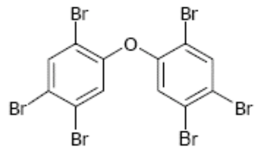
2,2',4,4'-tetrabromodiphenyl ether

BDE-47



2,2',4,4',5-pentabromodiphenyl ether

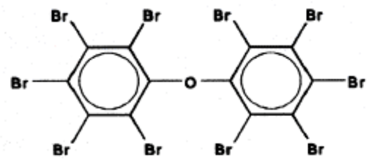
BDE-99



2.2',4,4',5,5'-hexabromodiphenyl ether

BDE-153

DecaBDE:



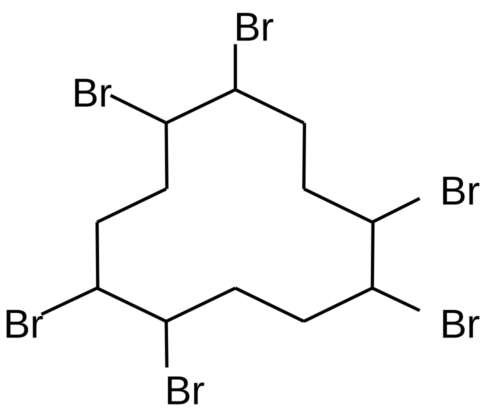
BDE 209

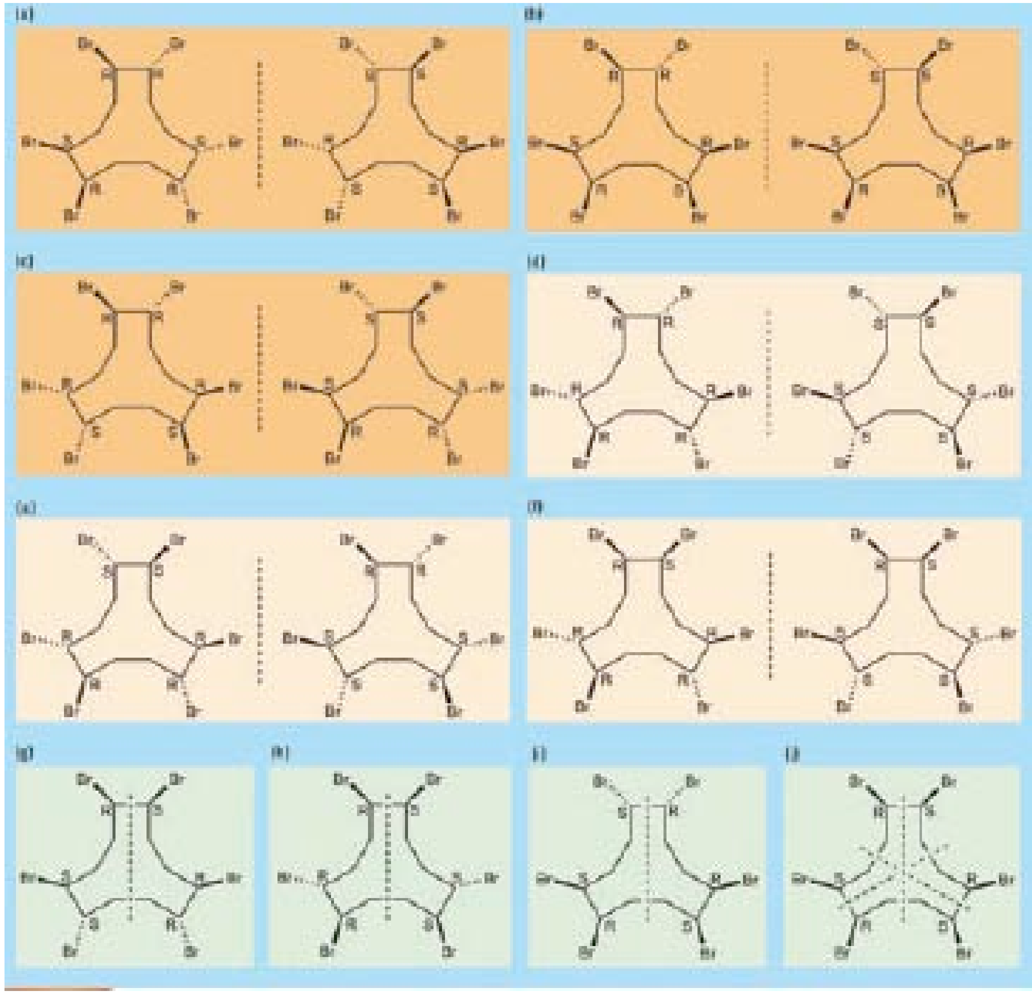
- used only as additive FRs at concentrations of 2-30% in polymers

Hexabromocyclododecanes (HBCDs)

- Additive FR

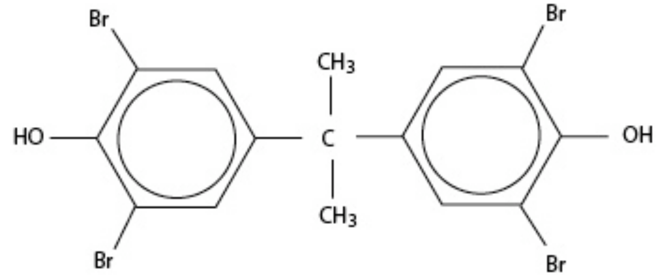
– α-, β- and γ-HBCD present in the technical mixtures





Law et al., ES&T 2008

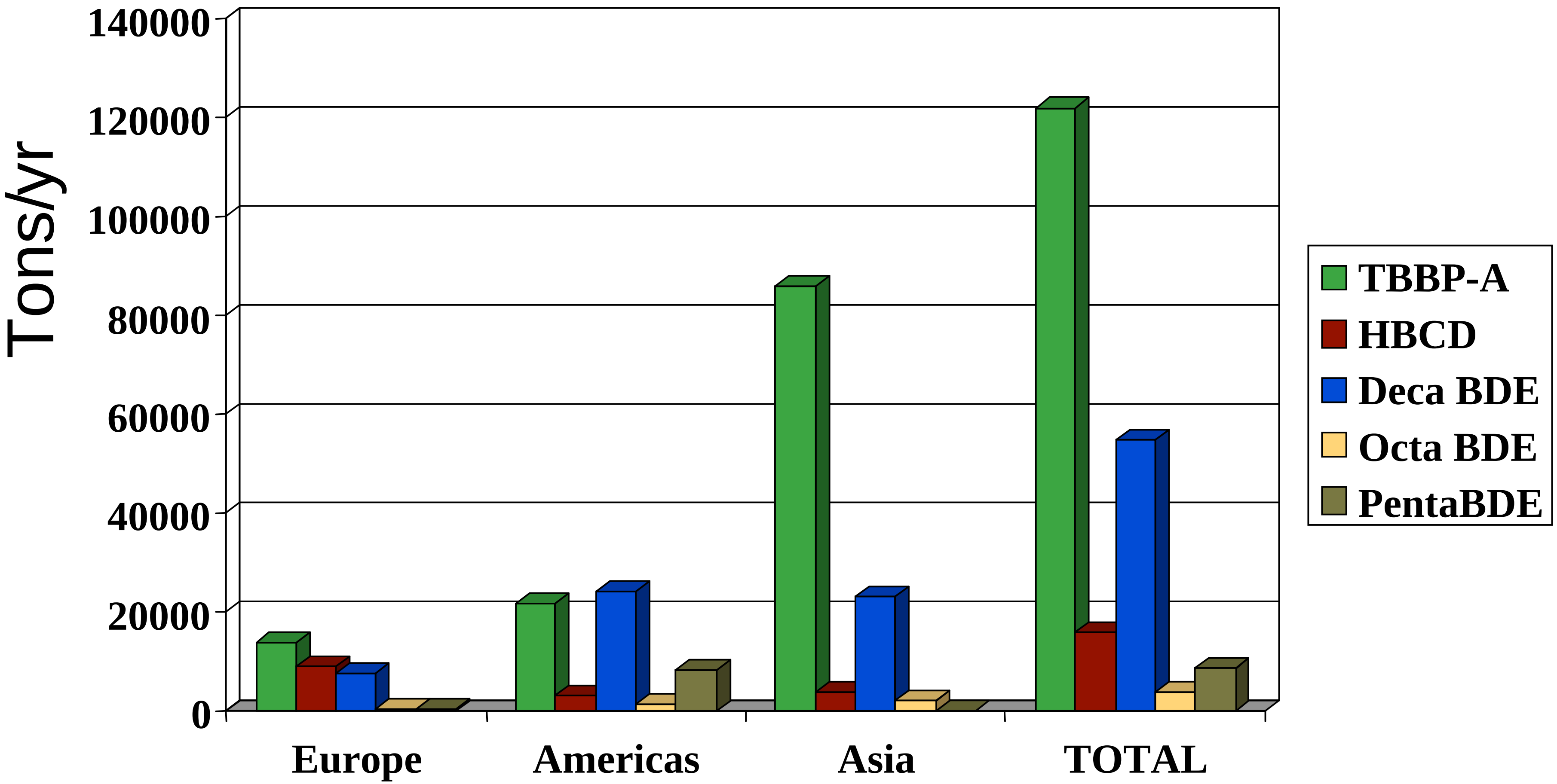
Tetrabromobisphenol-A (TBBP-A)



- mostly used as reactive FR in printed circuit boards and laminates
- also as additive FR in ABS plastic housing
- also in production of other BFRs

- EU risk assessment and WHO have established that TBBP-A presents no risk to human health

BFR market demand in 2001



Applications

- Penta-BDE:	**Flexible polyurethane foam**
	Upholstery textile in furniture
- Octa-BDE:	**Electronic and electrical equipment**
	- housing and small components
- Deca-BDE:	**Electronic and electrical equipment**
	- housing and small components
	Upholstery textiles
- HBCD:	**Polystyrene (roof isolation) and textile backcoating**
- TBBP-A :	**Electrical and electronic equipment**
	- printed circuit boards and housing

BFRs ARE EVERYWHERE

Home and Office
Televisions
Cell phones
Fax machines
Audio and video equipment
Computers
Printers
Scanners
Photocopiers
Remote controls
Lamp sockets
Hairdryers
Fans
Upholstered sofas
Upholstered chairs
Polyurethane foam
Building materials (walls, cellars, roofs)

Home and Office
Mattress
Curtains
Drapes
Carpet padding
Ovens and stoves
Stove hoods
Refrigerators
Dishwashers
Washing machines
Clothes dryer
Microwaves
Toasters
Coffee makers
Water heaters
Wires and cables
Circuit breakers
Electrical outlets

Transportation (car, train, airplane)
Instrument panel
Battery case and tray
Electrical connectors
Engine control
Computer system
Stereo
GPS system
Upholstery
Sun visor
Head rest
Insulation

Regulatory frame

EU
- Penta-BDE and Octa-BDE banned in the EU since August 2004
- Deca-BDE banned in the EU from July 2008

- Penta-BDE proposed as "candidate" for the Stockholm POP's list

- TBBP-A – passed EU risk assessment
- HBCD – completed EU risk assessment

US
- Penta-BDE and Octa-BDE banned/phased out
- Deca-BDE banned/will be banned in some states
- HBCD and TBBPA not restricted

ASIA
- BDE-209 and HBCD not restricted

PBDEs

Health hazards of PBDEs identified in animal models

* binding to thyroid hormone receptor
* disrupt <u>thyroid hormone</u> pathways (decrease of T4 levels)
* low estrogenic activity (BDE-100), higher activity for HO-PBDEs
* (very) weak inducers of CYP 1A1 activity
* (reduced) evidence of carcinogenicity (BDE-209)
* impaired immune system?

* <u>neurotoxicity and neurodevelopmental disorders</u>
- decreased IQ in offspring
- hyperactivity
- skeletal malformations

HBCDs

Health hazards of HBCDs identified in animal models

* direct acute and chronic toxicity of HBCD are low
* antagonistic effect on detoxification enzymes and may thus increase the toxicity of other compounds
* may induce cancer by a non-mutagenic mechanism
* may disrupt the <u>thyroid hormone</u> system
* low endocrine-disrupting activity
* alter the normal uptake of the neurotransmitters in rat brains

* neonatal exposure can induce <u>developmental neurotoxic effects</u>, such as aberrations in spontaneous behaviour, learning, and memory function.

TBBP-A

Health hazards of TBBP-A identified in animal models

* low acute toxicity in rats and mice

* <u>thyroid hormone-like and estrogen receptor-mediated effects</u>

* potent *in vitro* inhibitor of the sulfation of estradiol, resulting in increased bioavailability of estradiol, and thus in weak estrogen-like properties.

* *in vitro* inhibition of the binding of T3 or T4 to thyroid hormone receptors. The binding of TBBP-A is 10 times stronger than T4.

* immunotoxic, through *in vitro* inhibition of proliferation of activated T-cells.

* neurotoxicity through *in vitro* inhibition of dopamine uptake

* interferring with cellular signaling pathways.

* disorientation, lethargy, decreased egg production and reproductive success observed in a partial life-cycle test with zebrafish

sources → micro-environment → personal exposure → internal dose → health effects

sources	micro-environment	personal exposure	internal dose
electronics textiles	dust air diet	ingestion dermal inhalation	serum milk

Goals:

-understanding exposure to BFRs from *product* to *person*

-linking exposure to possible adverse effects

Internal dose

Questions to tackle

- what are the current levels in human serum/milk?

- are there geographical trends?

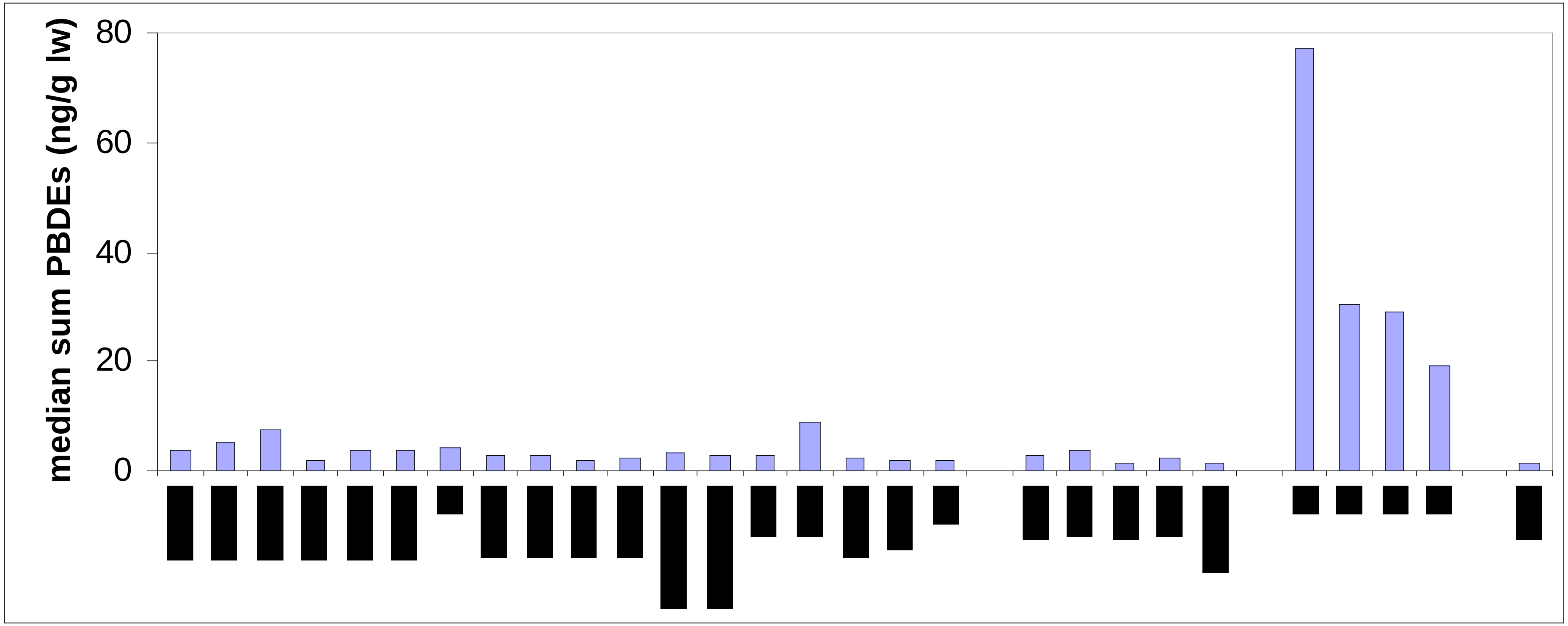
- occupationally-exposed workers?

- is there a relationship with age?

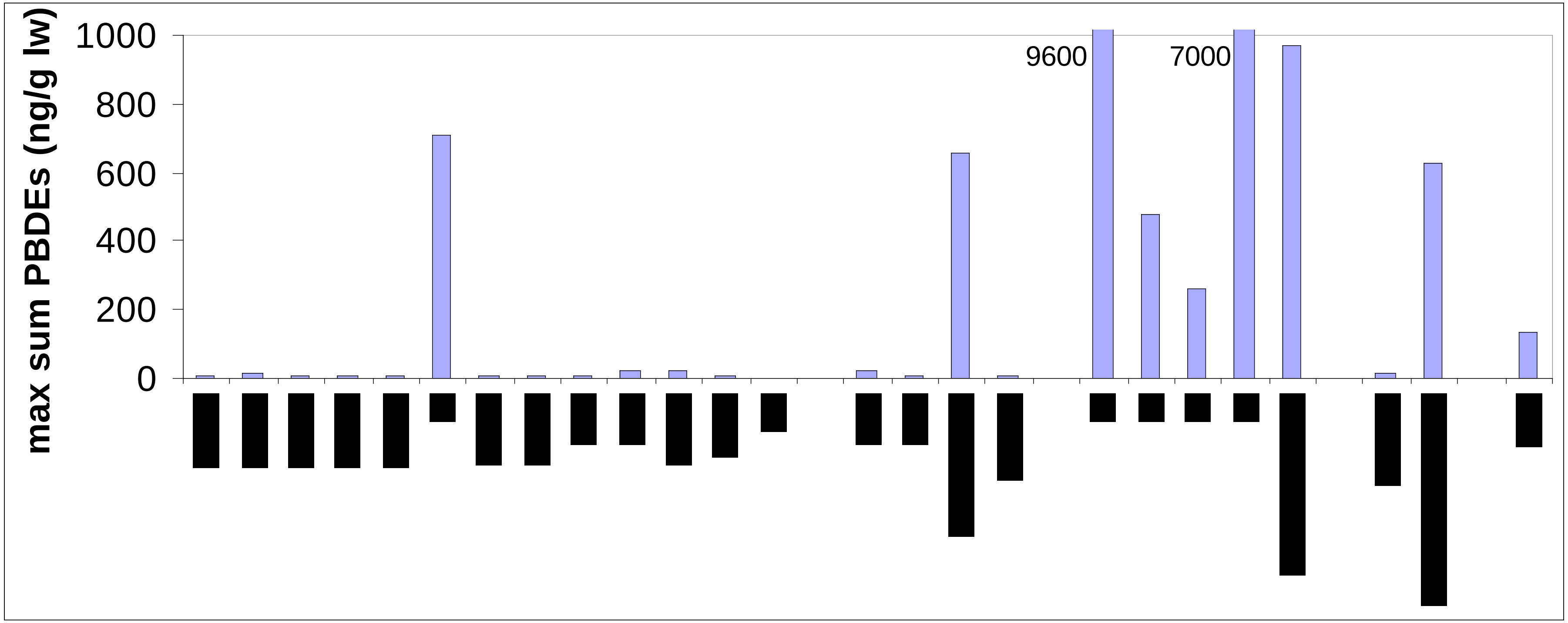
- are there temporal trends?

- are BFRs persistent in the human body?

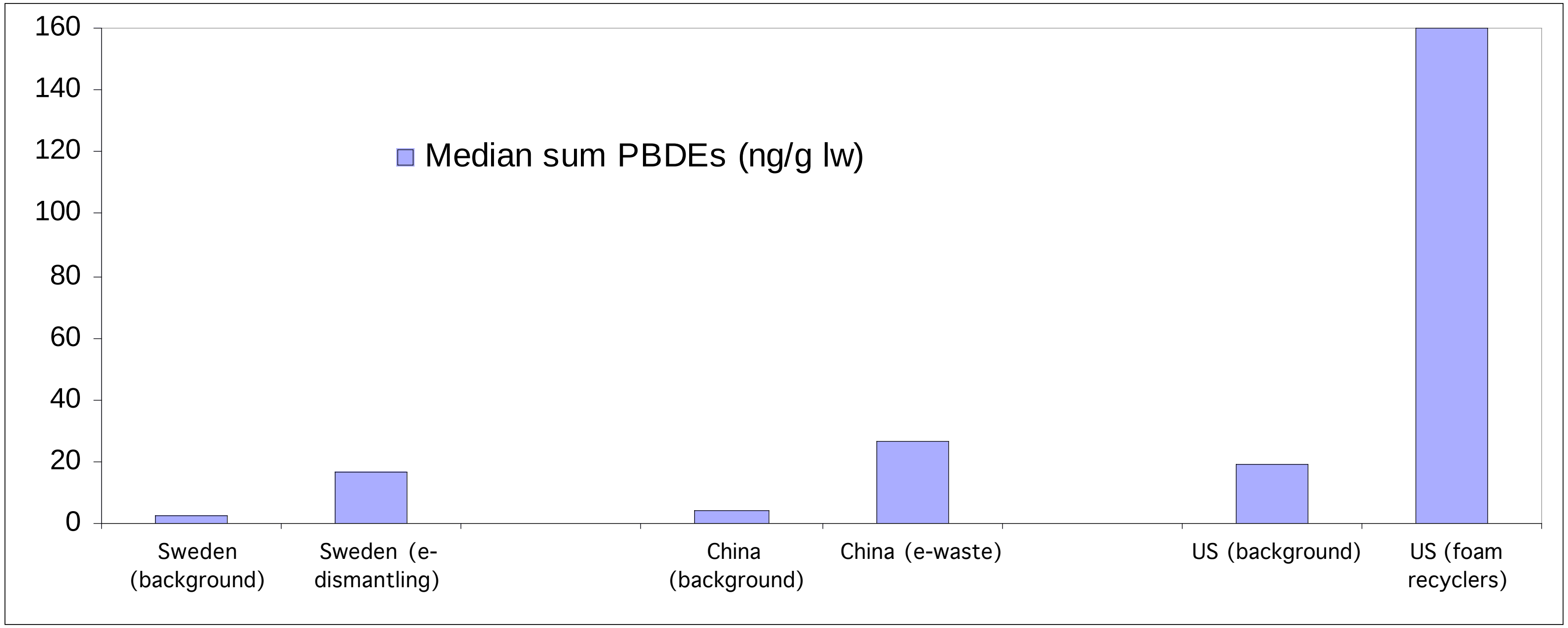
Geographical trends



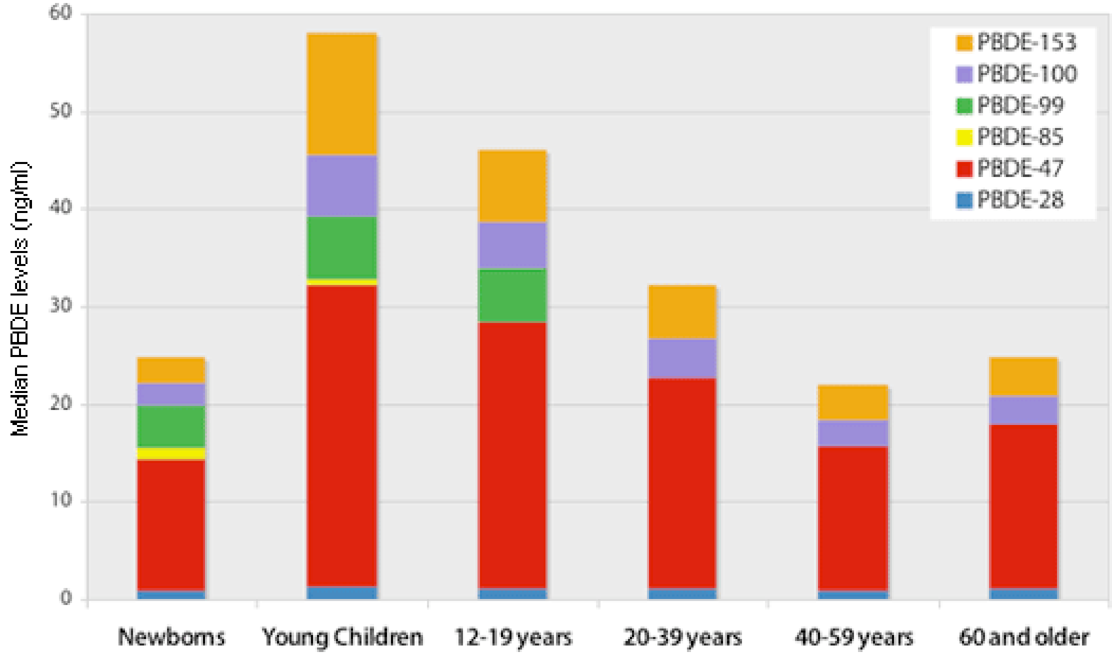
- Penta-BDE are one order of magnitude higher in the USA



- some individuals can have very high concentrations (also in Europe)

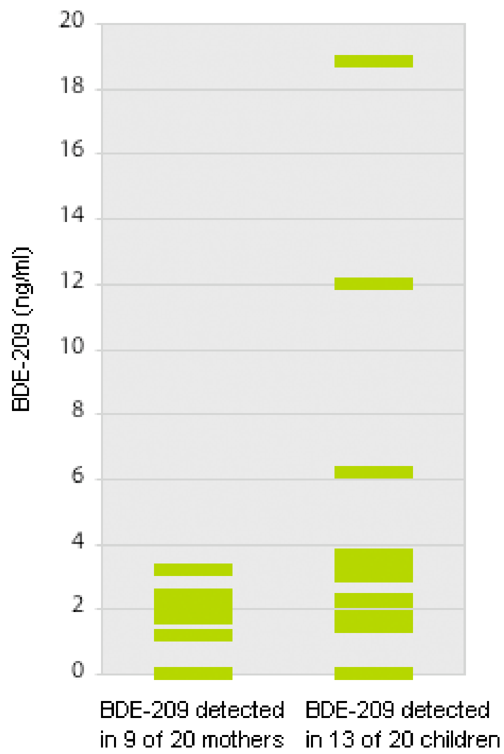


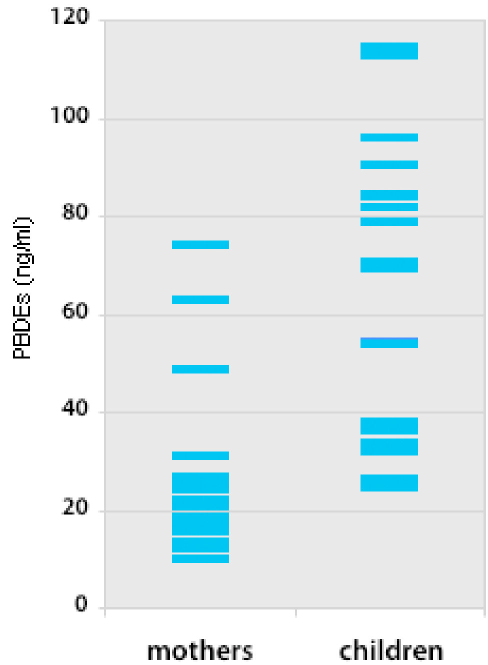
- higher levels in occupationally-exposed individuals



- 300 umbilical cord blood samples (Herbstman et al. 2008)
- 20 children aged 1 to 4 yrs old (EWG, 2008)
- 2,000 Americans aged 12 and older (NHANES, Sjödin et al. 2008).
- BDE-209 was not reported in newborn and adults, but estimated at ~ 2 ng/ml in both groups.

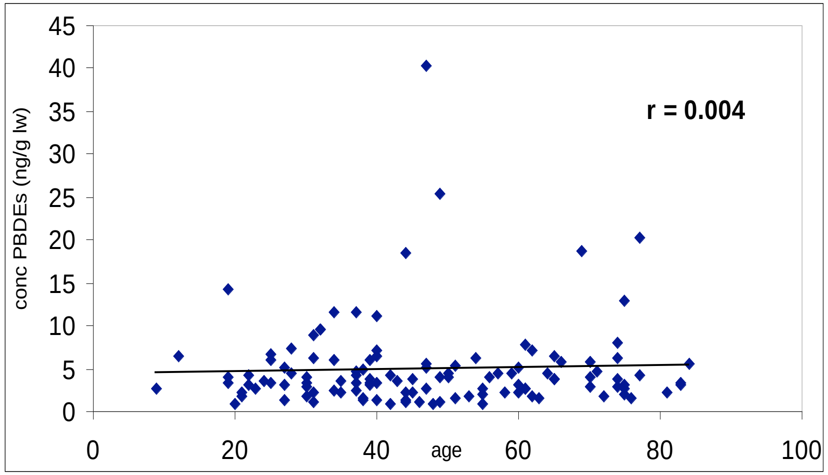
Age relationship



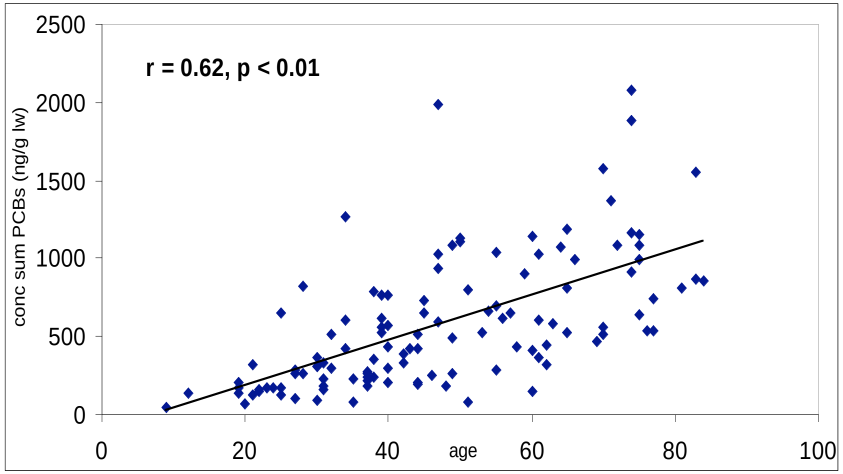


- 20 mother-children pairs ages 1 to 4 years old (EWG, 2008)
- higher medians of PBDEs in children
- yet, similar exposure (food + indoor)??

Age relationship



PBDEs



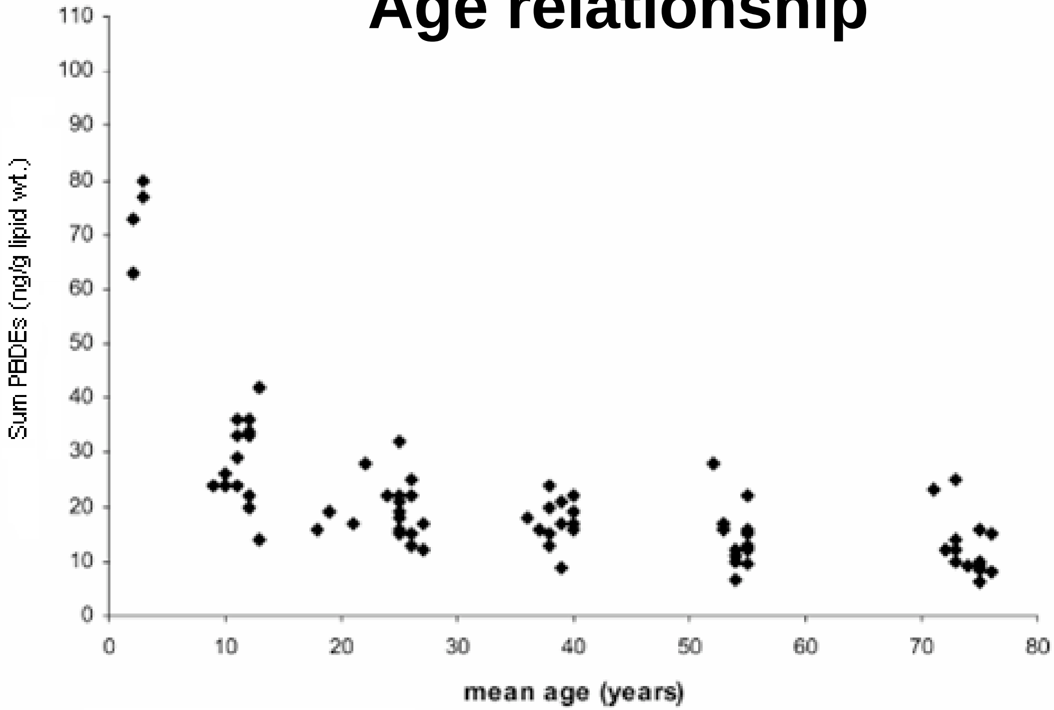
PCBs

n = 100 (serum and fat results) - Belgium

- No age correlation for PBDEs – metabolisation + different exposure pathways for PBDEs

- Relationship with age for PCBs

Age relationship



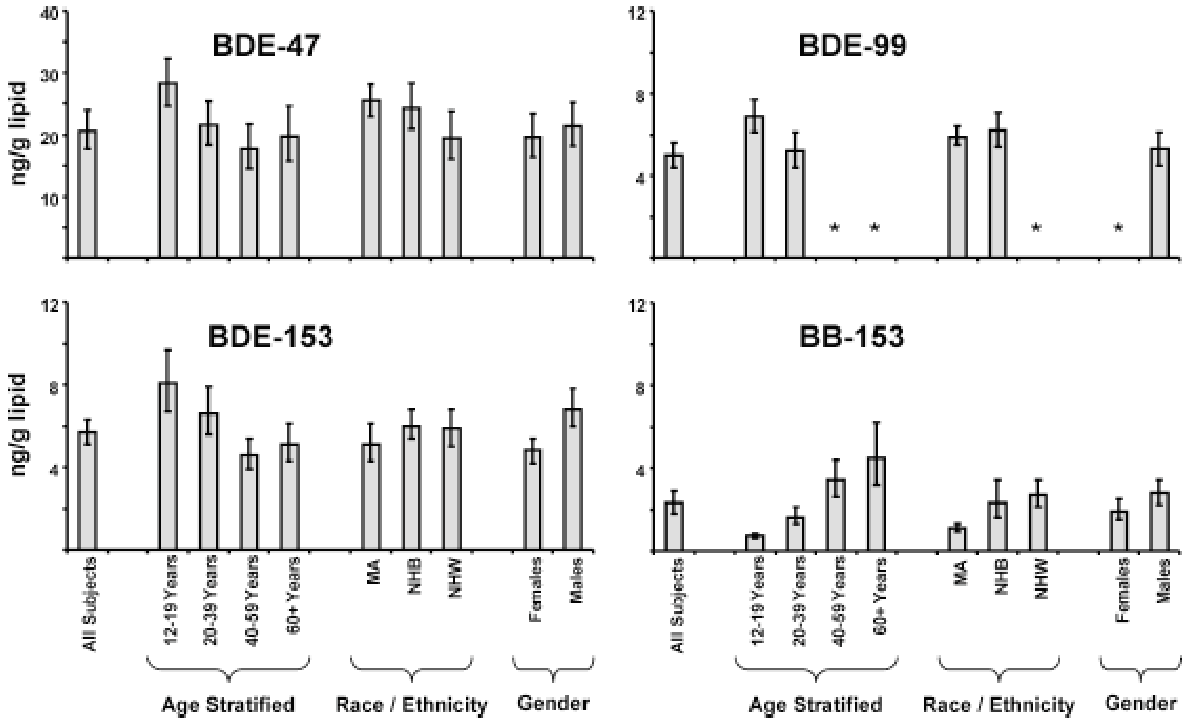
Each data point represents a pool up to 100 serum samples

- During the first years, children undergo extraordinary cell growth, so there are more opportunities for toxic compounds to disrupt the cells.

- Animal tests show that fetuses and newborns are the most susceptible to harm from many chemicals.

Toms et al. ES&T 2008

Age relationship



- congener-specific differences!!

- BDE-99 easier metabolized in adults?

NHANES data (2003-2004)

- **BDE-99 is metabolized in humans to HO-PBDEs and brominated phenols**

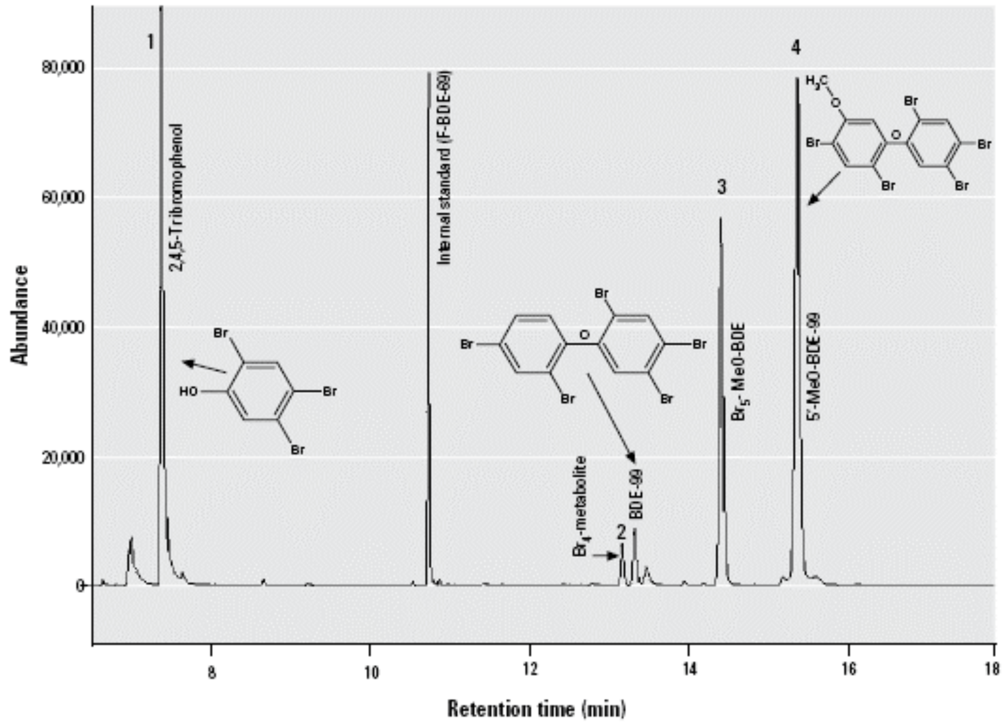


Figure 1. GC/ECNI-MS chromatogram (m/z 79 and 81) of the derivatized phenolic fraction isolated from fresh hepatocytes incubated with 10 µM BDE-99, identifying the four metabolites 1–4.

Stapleton et al., EHP 2009

Half-Lives in Human Serum

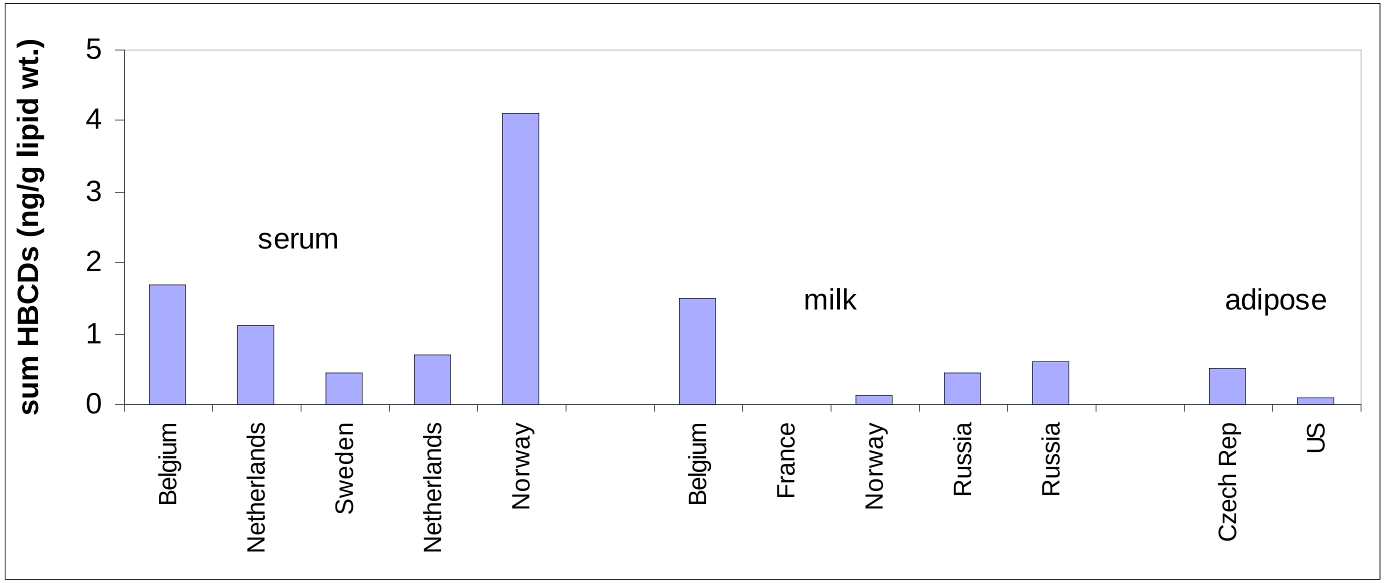
Congener		Half-life in Serum (days)
BDE 209		15
BDE 208		28
BDE 207		39
BDE 206		18
BDE 203		37
Octa-1		72
Octa-2		85
Octa-3	(Thuresson et al., 2006)	91
BDE 153		2340
BDE 100		576
BDE 99		1044
BDE 47	(Geyer et al. 2004)	648

- BDE-99 estimated $t_{1/2}$ is incorrect!
- BDE-153 most persistent, followed by BDE-47

HBCDs

Median

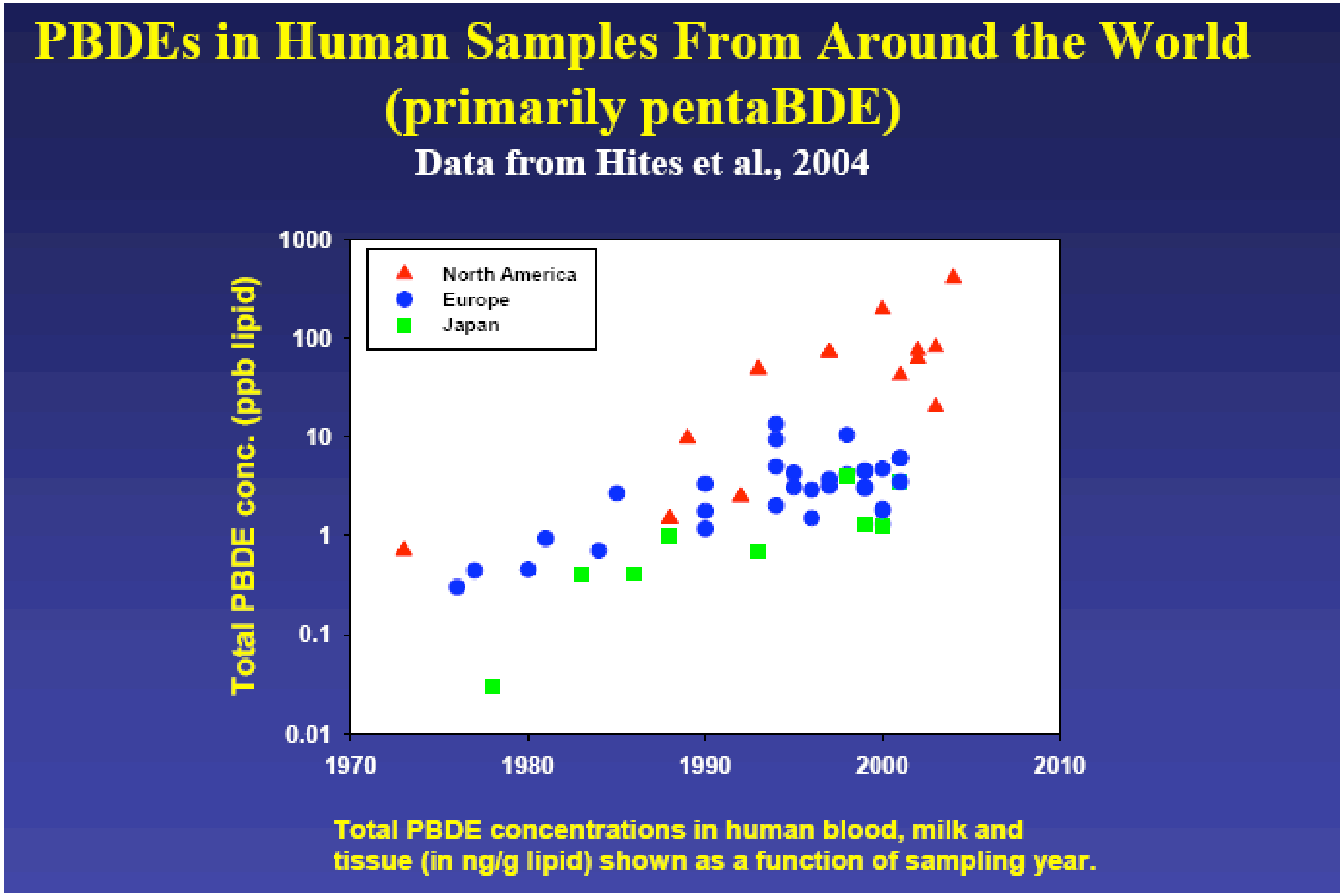
values



- no clear patterns

- HBCD measurements are not so frequent as for PBDEs

Time trends


PBDEs in Human Samples From Around the World
(primarily pentaBDE)
Data from Hites et al., 2004
Total PBDE conc. (ppb lipid)
1000
100
10
1
0.1
0.01
1970
1980
1990
2000
2010
North America
Europe
Japan
Total PBDE concentrations in human blood, milk and
tissue (in ng/g lipid) shown as a function of sampling year.

- **Partial conclusions**: concentrations of BFRs in humans

-Background concentrations of tri-hepta PBDEs in Europe are an order of magnitude lower than in US, but similar with those from Asia/Australia

-Trends in BDE-209 are not clear due to low amount of reported data.

-Conc of TBBP-A are very low in humans (low exposure)

-Background concentrations of HBCDs are relatively low, but occasional higher concentrations can be found – specific sources of exposure.

What are the exposure sources for humans ??

Exposure pathways

- BFRs are present in dust, air and food (principal sources of human exposure)

- <u>Direct</u> causal relationship between exposure pathways and human concentrations of PBDEs/HBCDs have been established in some cases:

  - food and serum (males) – PBDEs (Knutsen et al. MNFR 2008)
  - food (fish) and serum (fishermen) – PBDEs and HBCD (Thomsen et al. EST 2008)
  - dust and maternal milk – PBDEs (Wu et al. EST 2007)

- <u>Indirect</u>: - dust and serum – California (Zota et al. EST 2008)

DIET

- market-basket studies

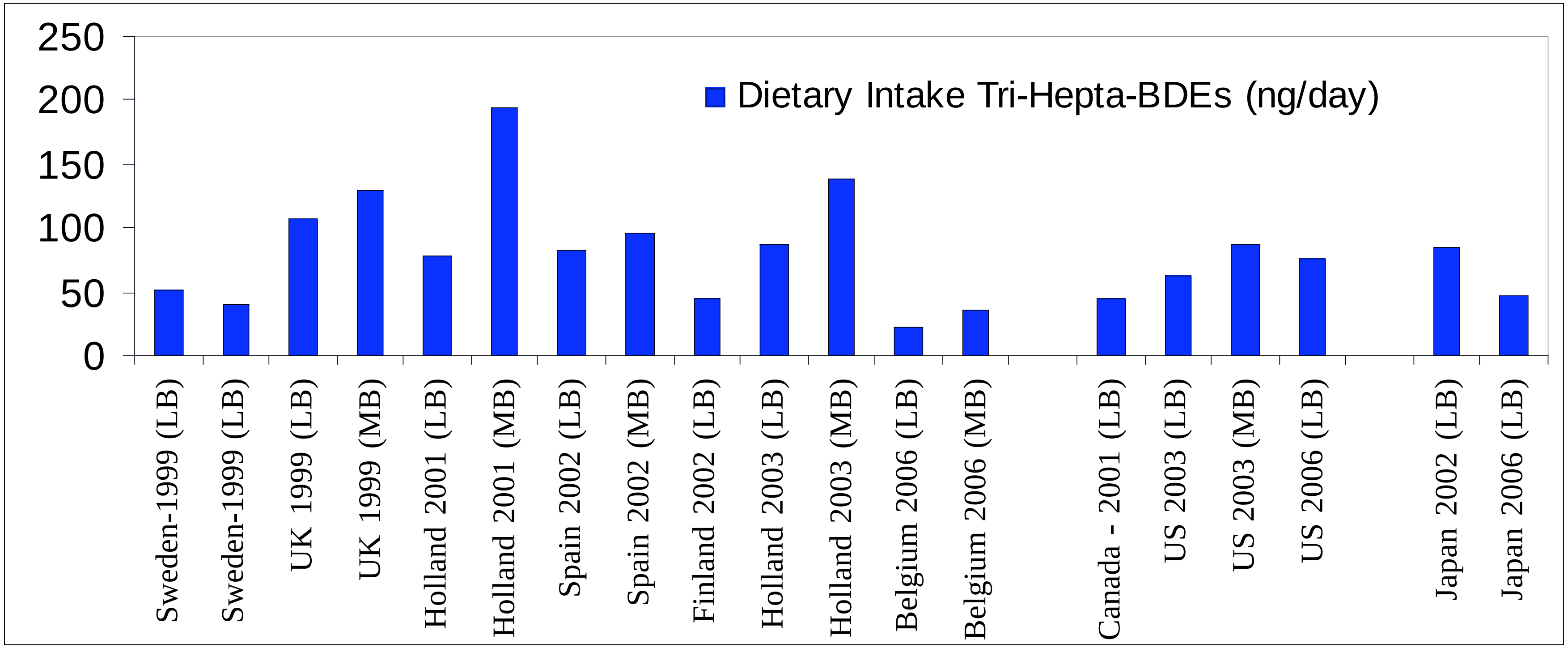
 - uncooked food

 - only a part of the full meal is represented

- duplicate diet studies

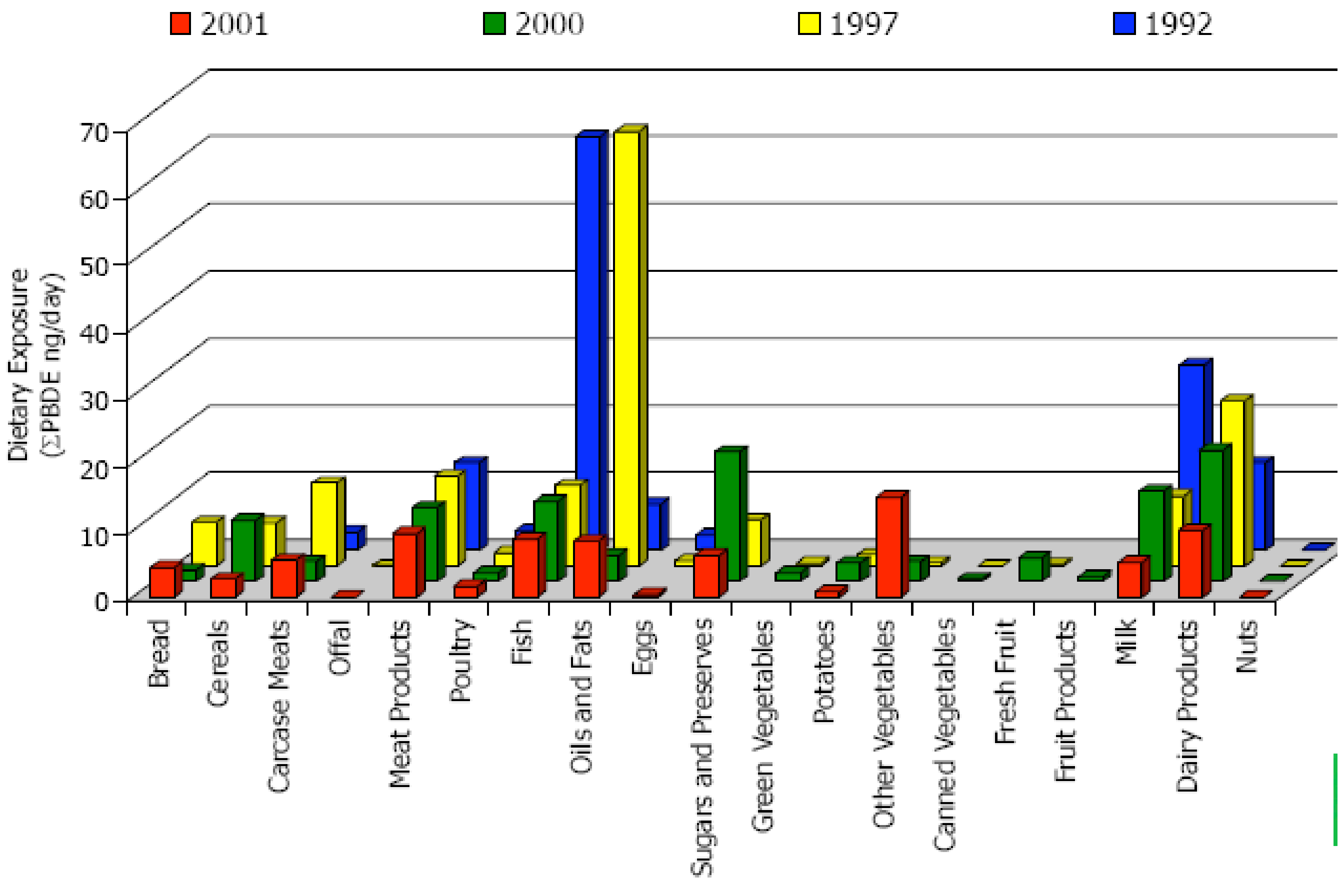
- more realistic picture

- much more difficult to follow on a longer time (typically 1-4 weeks)



- There is only little variation between countries

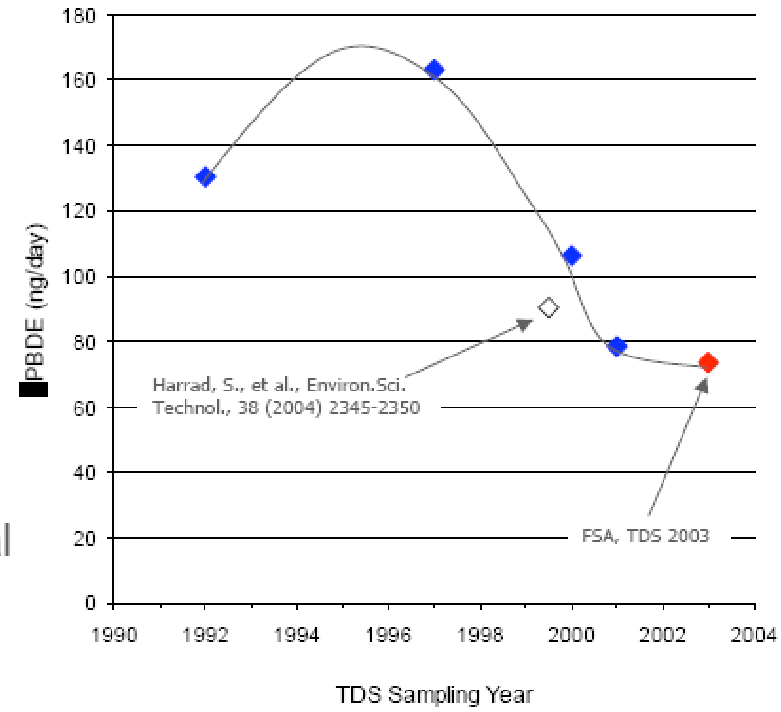
- It does not explain the differences in body burdens



- fish, fats/oils, dairy products and meat are predominant contributors

Trends in UK dietary exposure to PBDEs

- PBDEs "appear" to be **decreasing** in the diet
- Exposure maxima possibly between 1993 and 1996?
- Is there other evidence to support environmental decrease of PBDEs?



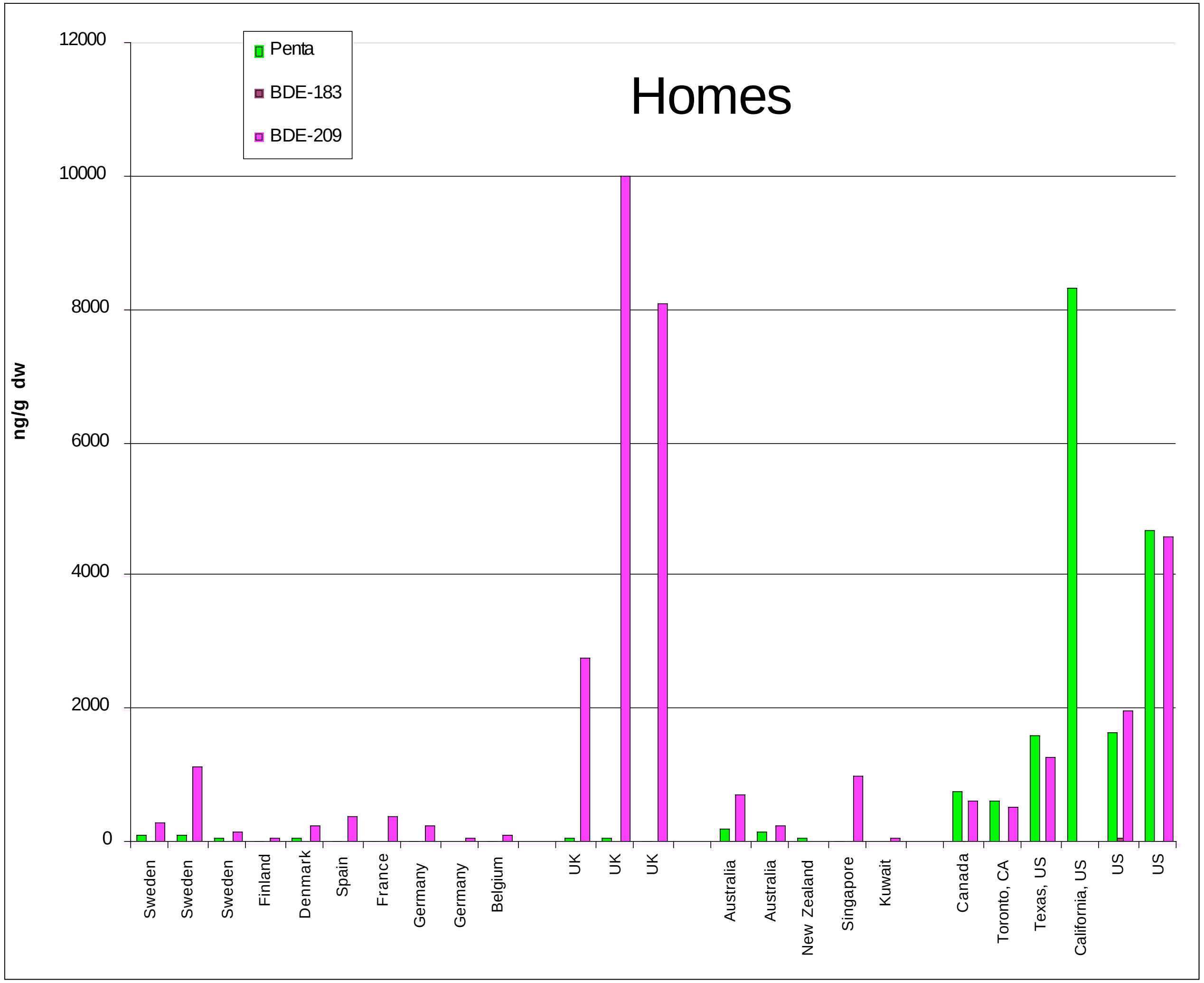
Similar to trends in European human milk and serum

DUST

- **Only recently (2005) identified as potential exposure pathway for BFRs, especially for children/toddlers**

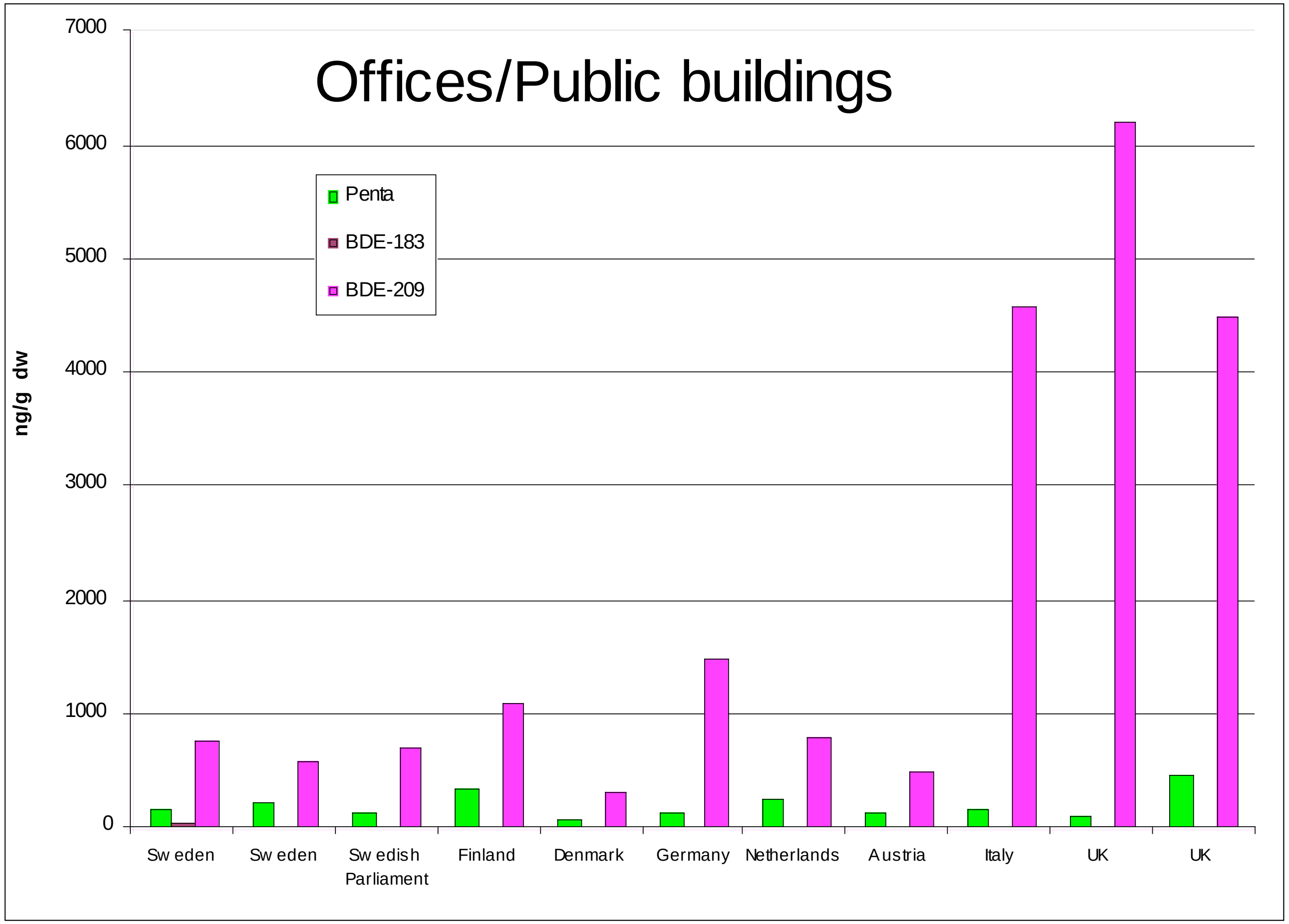
- **Since, an increasing numer of studies have been published covering most continents and BFRs.**

DUST (ng/g dw)
PBDEs



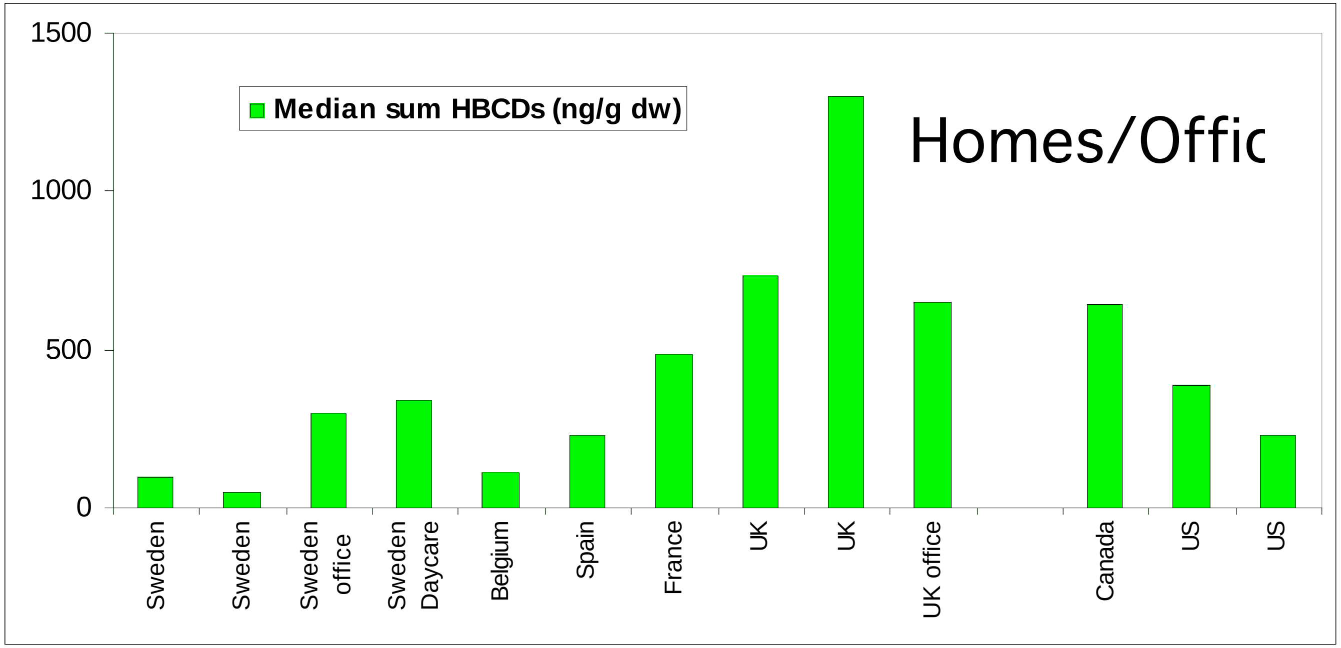
- **Penta-BDEs: US >> EU**
- **BDE-183: low levels**
- **BDE-209: UK > NA >> Europe**

DUST
PBDEs

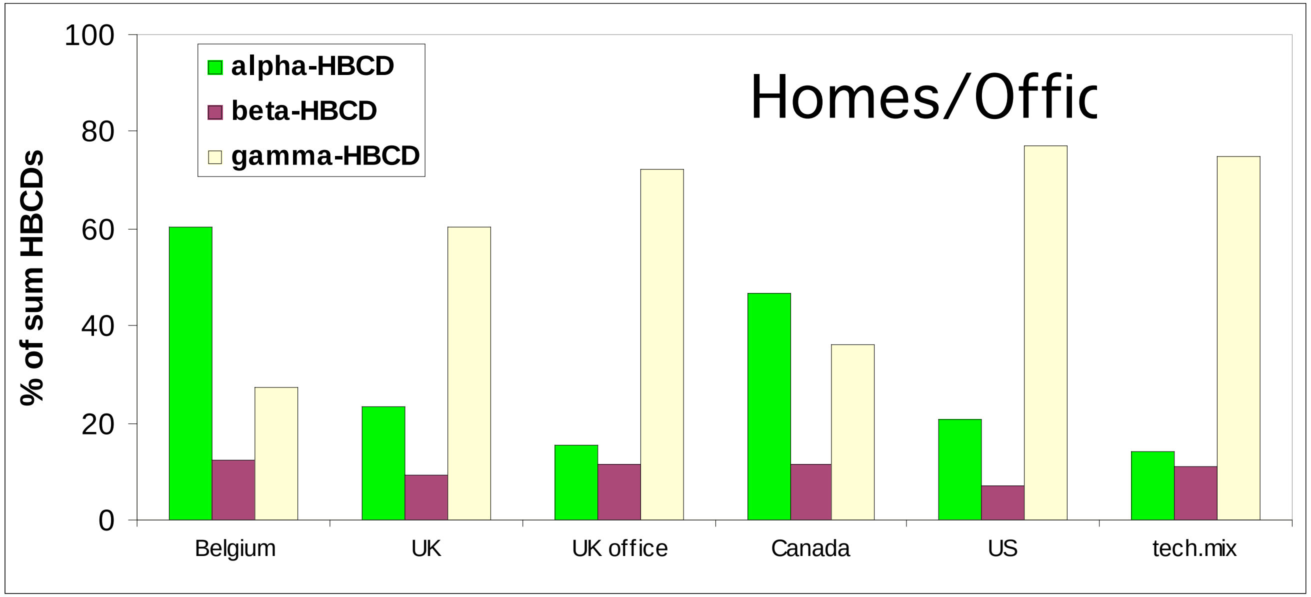


- Penta-BDEs: relatively similar in EU
- BDE-183: low levels
- BDE-209: dominant. UK > rest EU

DUST
HBCDs



Concentrations



Profiles

DUST
TBBP-A

Indoor dust

Domestic dust Hokkaido, Japan

490–520 ng/g

Pooled domestic dust	UK	190–340 ng/g
Office dust	EU offices	5–47 ng/g
Newly constructed building	USA	0.4–2 ng/g
Dust inside computers	China	8.9–39.6 μg/g

DUST ingestion - caveats

-Dust sampling :

- vacuuming time, space, room, pooling
- vacuum bag?

- Uncertainty in estimating dust ingestion

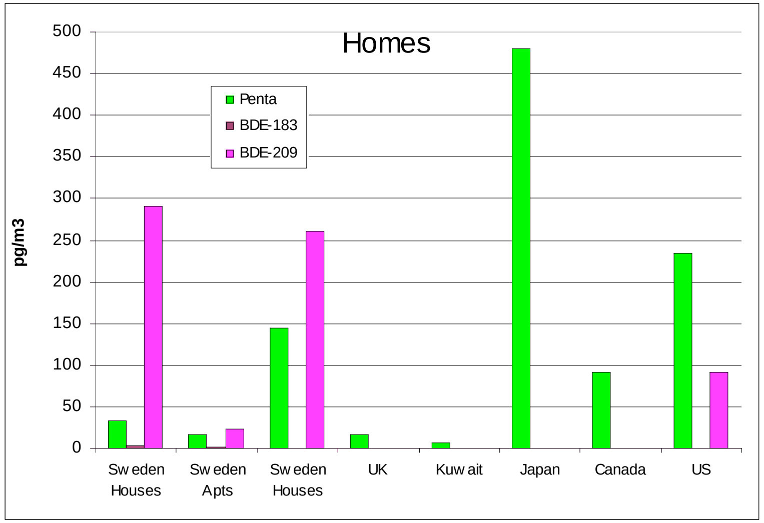
Adults – range 1 – 100 mg/day, most realistic 20 mg/day

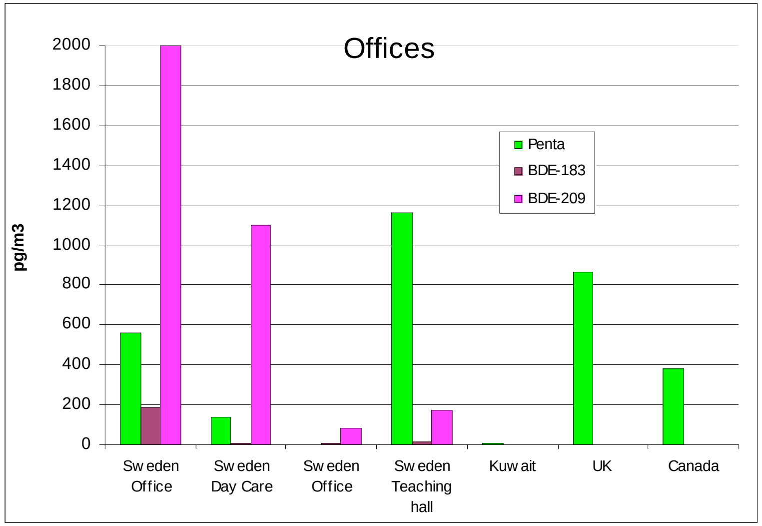
Children – range 20 – 200 mg/day, most realistic 50 mg/day

Air (pg/m³)
PBDEs

- **mixed patterns**
- **lower brominated PBDEs in gas phase**
- **higher brominated PBDEs on particles**

- **indoor air 1-2 orders of magnitude higher levels than outdoor air**





Daily adult exposure to PBDE via Inhalation (ng person^{-1})

$$\sum Exposure = [(C_H F_H) + (C_O F_O) + (C_p F_P) + (C_C F_C) + (C_{OA} F_{OA})]\, R_R$$

% time spent in each microenvironment

-**Homes**	**64%**
-**Office/school**	**22%**
-**Public**	**5%**
-**Transportation**	**4%**
-**Outdoor**	**5%**

-**Respiration rate (adult)** **20 m³**

Air

- Even for high concentrations: e.g.~500 pg/m³, the daily exposure is < 10 ng/day.

- Combined dust + food exposure is in the range 50-200 ng/day.

– Air is a minor contributor to human exposure to BFRs, even in contaminanted environments.

RECENT STUDY - Belgium

Aims:

- **investigating the contribution of food and dust to total intake of BFRs**
- **relating exposure to concentrations of BFRs measured in serum**

PBDEs:
- tri- to hepta-BDEs
(28, 47, 99, 100, 153, 154, 183)
- BDE 209

HBCDs:
- sum HBCDs
- α-HBCD, β-HBCD, γ-HBCD
- HBCD enantiomers

Roosens et al. ES&T 2009
Roosens et al. EHP, submitted

Sampling

- Volunteers (n=20) – students at the University of Antwerp, age 20-25y

- **Duplicate diets** (morning, noon and evening)
  - analysed separately to be able to identify the highly contaminated food
  - Period : 1 week

- **Dust** – their rooms at the end of the week
  - Most had bare (wooden) floors
  - Sampling (as in Harrad et al. 2008) – 4 m² of bare floor vacuumed for 4 min

Other sources are not accounted for
- food outside the principal moments of the day
- drinks
- dust from parental home (weekend) + cars and other microenvironments

- **Serum** (10 ml blood) at the end of the study period

RESULTS - PBDE/HBCD - levels

Duplicate diets

- concentrations are lower than in samples from market-basket studies
- reduction of levels by cooking
- highest concentrations in fish/meat-based diets

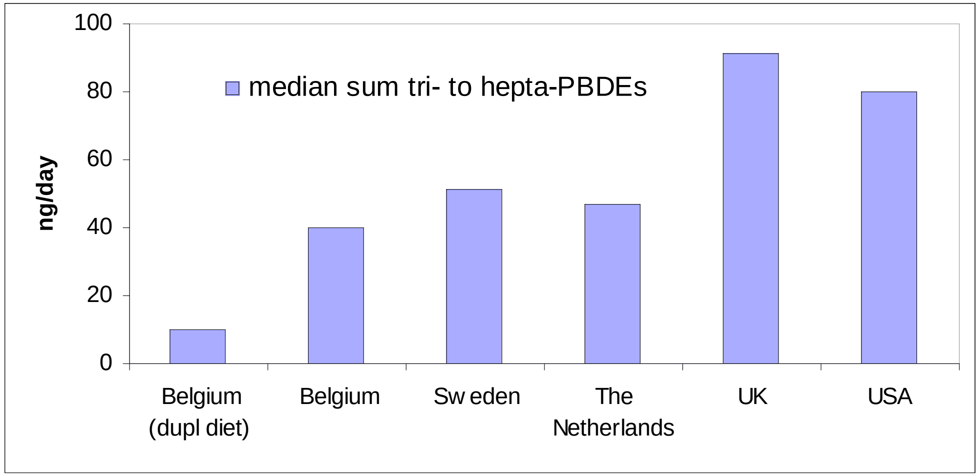
Dust

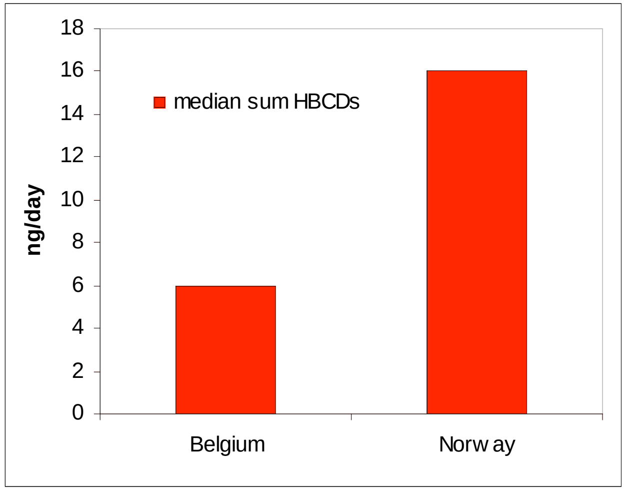
- concentrations at the lower end of European studies
- dominated by BDE-209 and HBCD

Serum

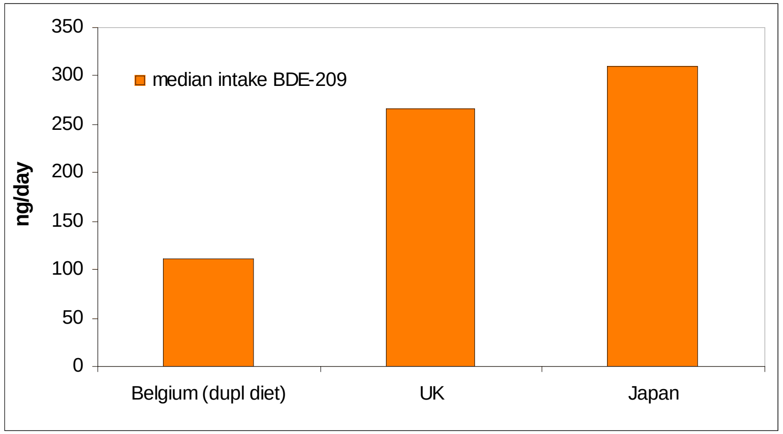
- concentrations at the lower end of European studies (background levels)
- dominated by BDE-47, BDE-153 and HBCD.

PBDE/HBCD intake - food (ng/day)



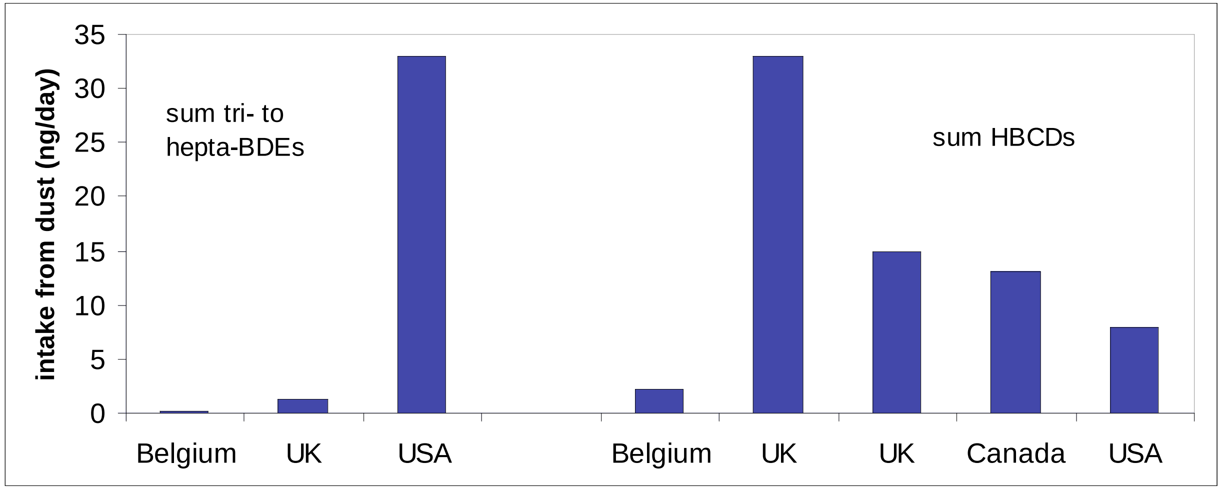


- Intake via food is at the low end of reported food intakes (from market-basket studies)
- Low variation between individuals
- High number of diets with non-detected for HBCDs (~90%) and BDE-209 (~75%)



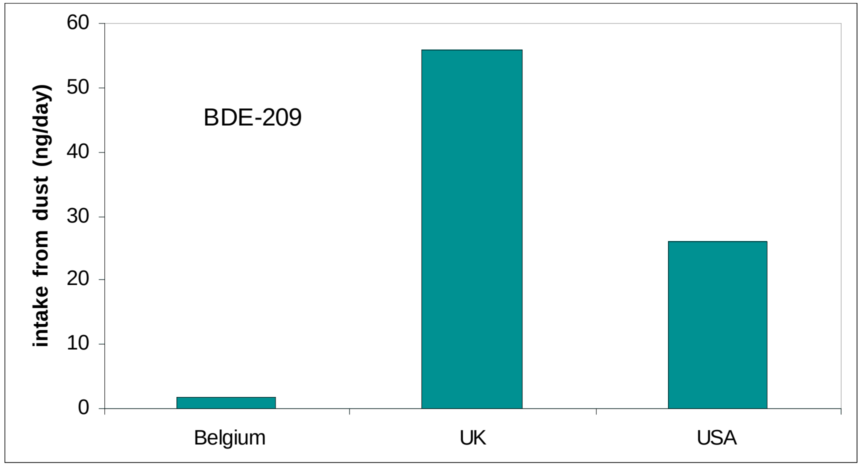
PBDE/HBCD intake from dust (ng/day)

Dust ingestion
-**Average: 20 mg/day**
-High: 50 mg/day
(Jones-Otazo et al. 2005)

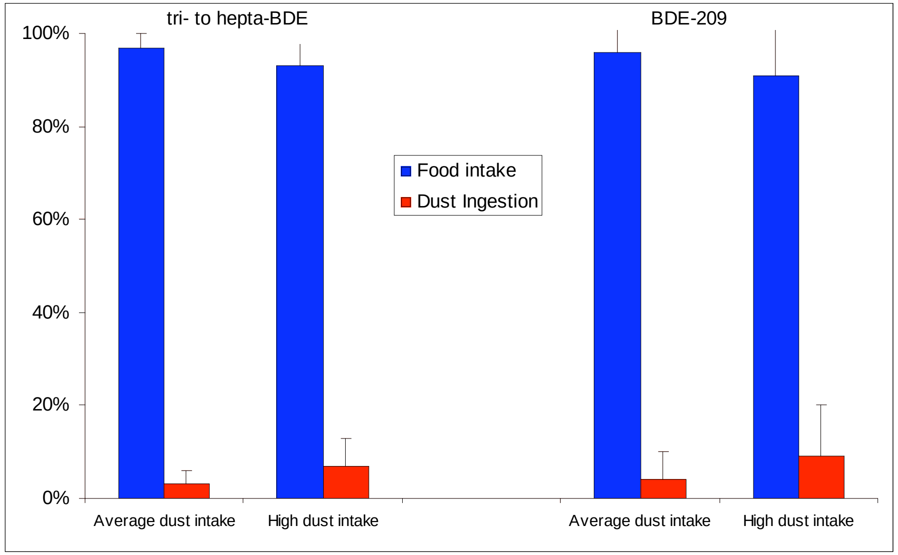


Intake (in Belgium) via dust ingestion is low, due to low dust concentrations

-Higher intake of tri- to hepta-PBDEs in USA
-Higher intake of HBCDs and BDE-209 in UK

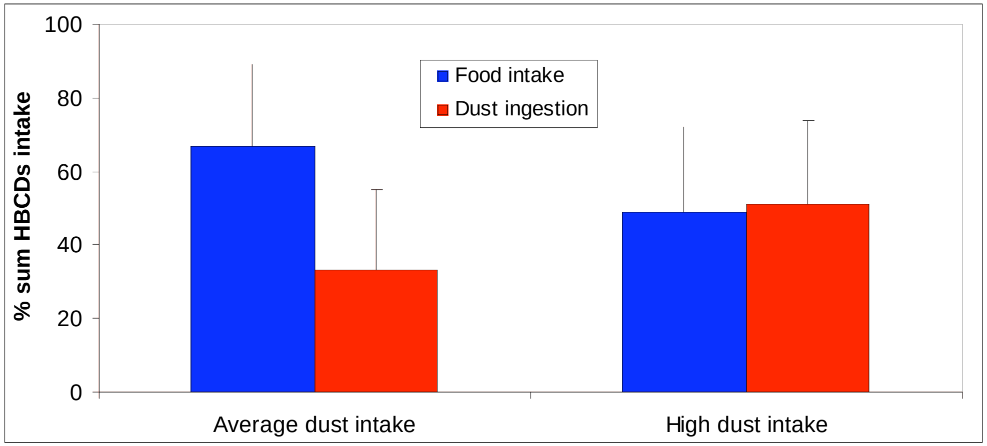


PBDE/HBCD intake – food and dust (ng/day)



		Median	Range
_tri-hepta	average	10.4	6.0 – 22.4
	high	10.8	6.3 – 23.0
BDE 209	average	95	61 – 240
	high	96	62 – 244

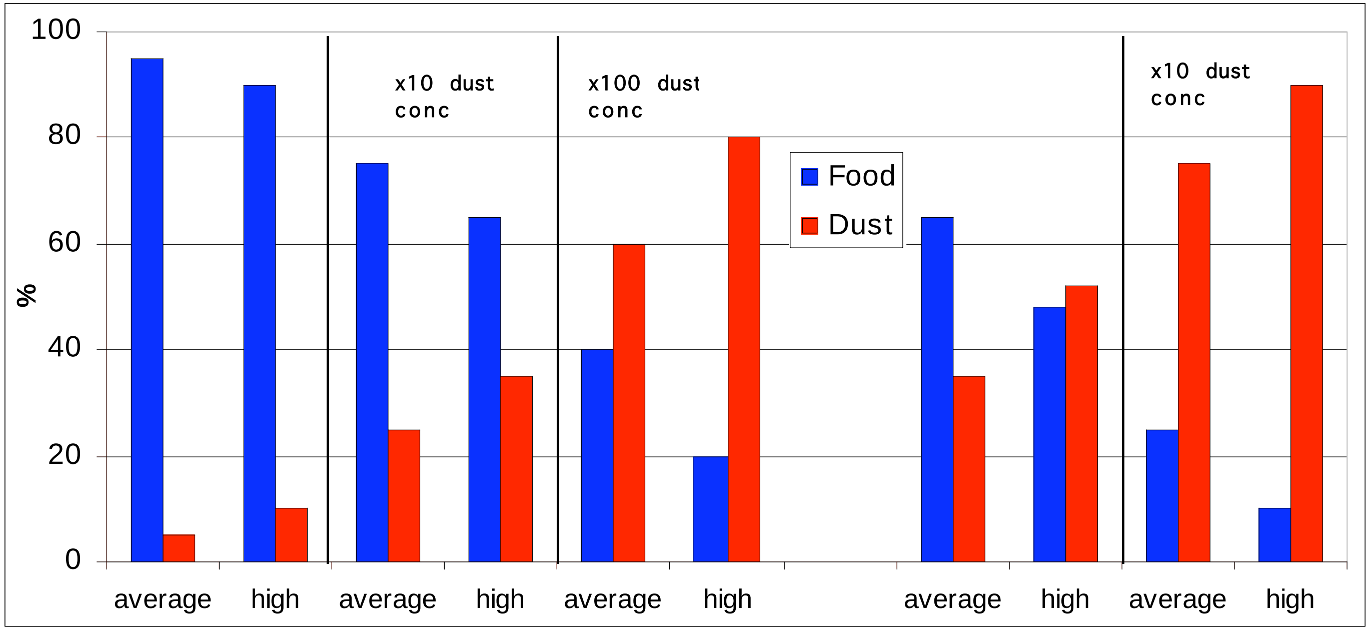
Intake via food predominant > 90%



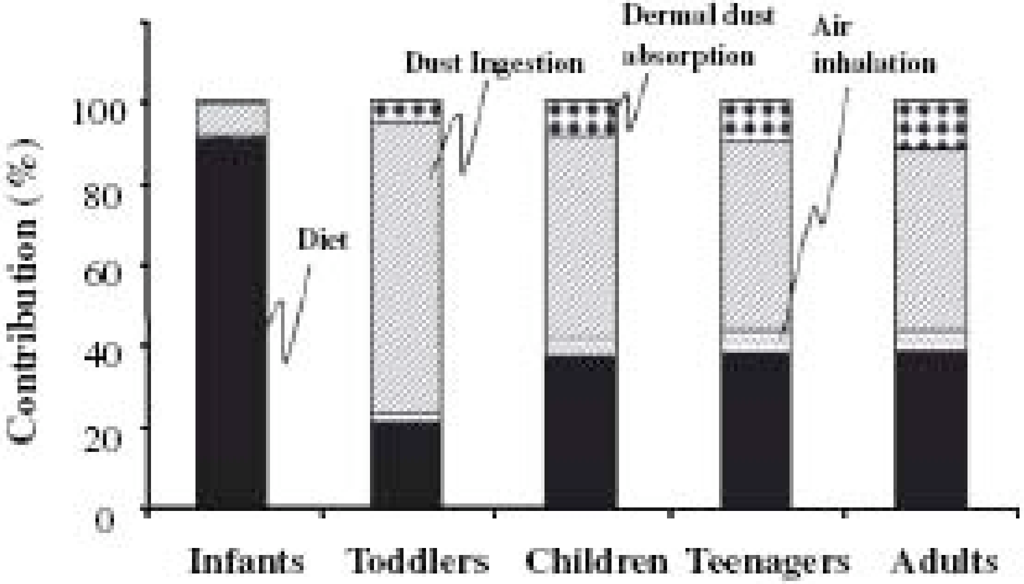
		Median	Range
HBCDs	high	13	5.2 - 42
	average	8	3.6 - 20

Dust becomes a more important contributor

Combined food and dust (ng/day)



- dust ingestion becomes the dominant exposure pathways when concentrations are rising (x10 or x 100)



- This is seen in the US population, where dust ingestion is a more important pathway, due to higher dust levels

Kannan et al. Chemosphere 2009

SERUM

PBDEs:

- similar to background-exposed populations in Europe
- lower than in US or Canada
- much lower than in ocupationally-exposed individuals
- BDE-209 not detected

HBCDs:

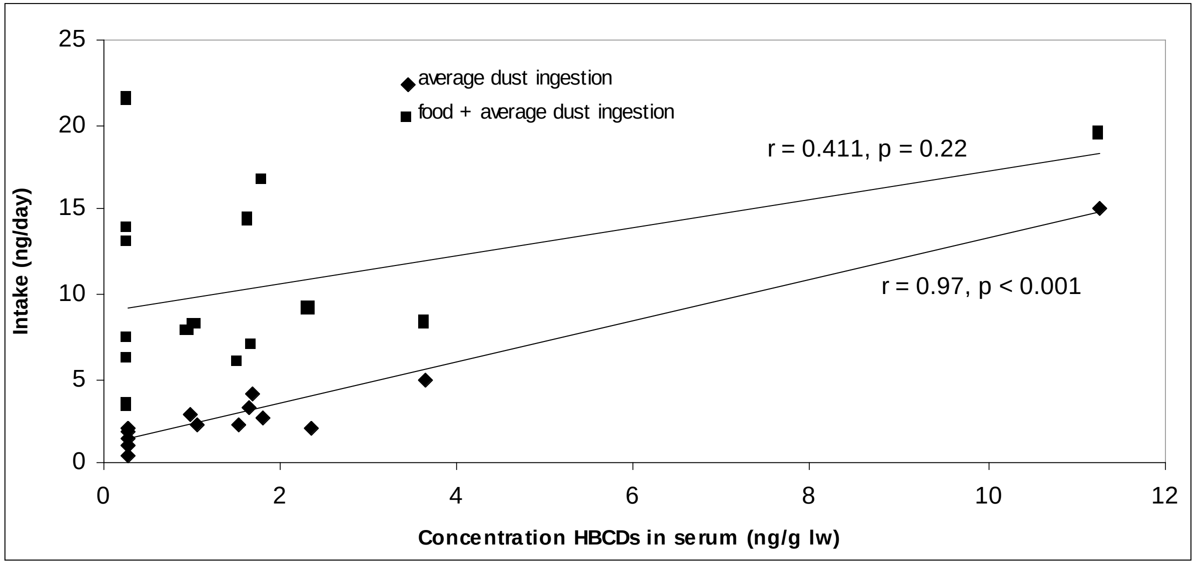
- similar to background-exposed populations in Europe
- lower than ocupationally-exposed individuals

PBDEs

- **Concentrations of tri-hepta-BDEs in serum did NOT correlate with:**
  - **intake via food**
  - **intake via dust**
  - **intake via combined dust + food**

- **Absence of correlations is probably due to:**
  - **exposure before the study period**
  - **exposures not accounted for**
  - **occasional spikes in exposure which can drive the serum levels**

HBCDs



Correlations serum-food-dust:

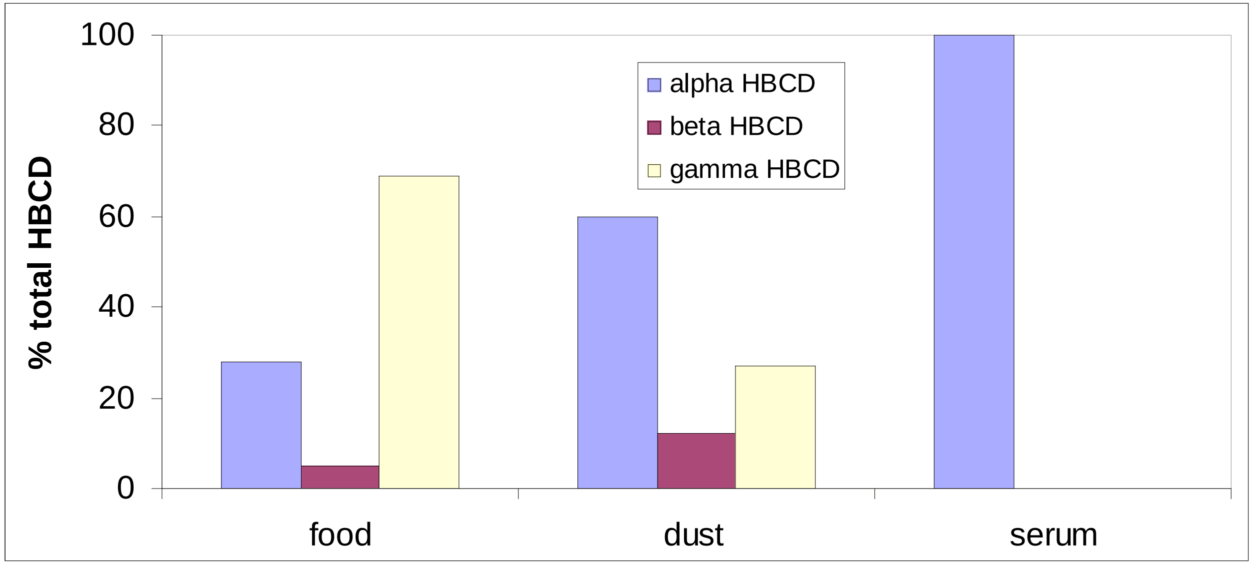
-no correlation serum-food intake

-r = 0.411 – serum – combined food/dust intake

-r = 0.97 – serum – dust

-r = 0.42 – serum – dust (after eliminating the high value)

HBCD – isomeric profile

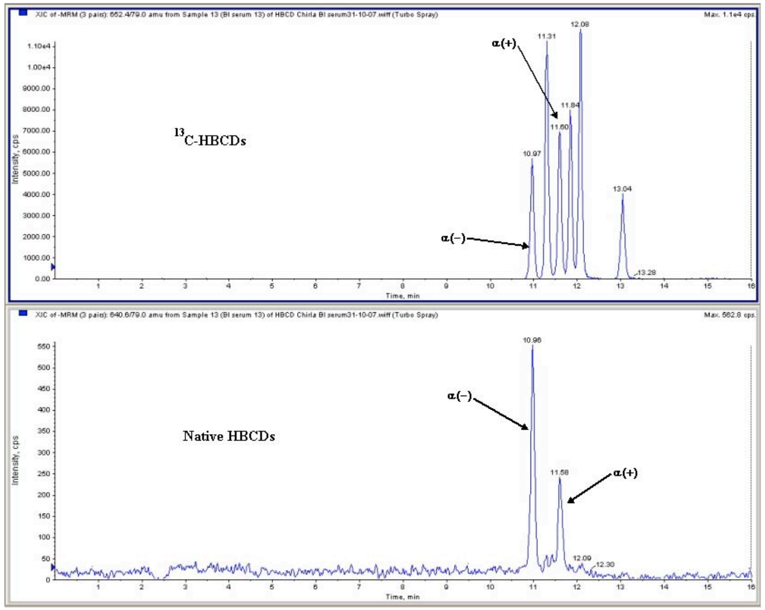


Food: gamma > alpha

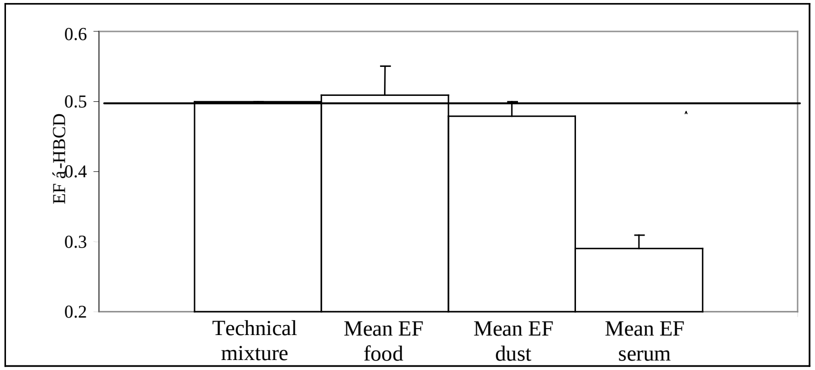
Dust: alpha > gamma

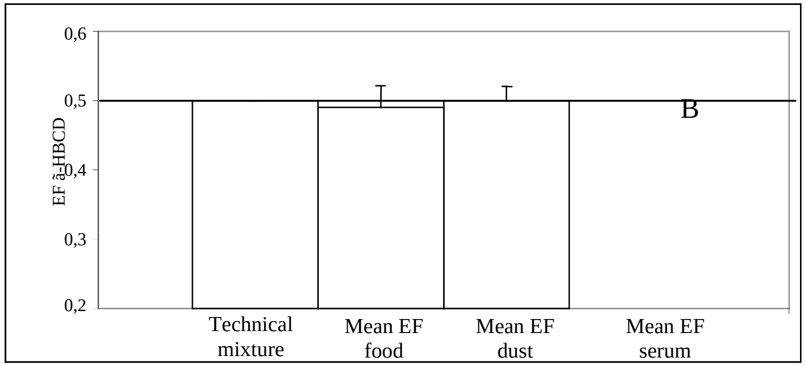
Serum: ONLY ALPHA !

HBCD – isomeric profile



serum





alpha-HBCD: food and dust – racemic, serum – dominance of (-) alpha

gamma-HBCD: food and dust racemic, not detected in serum

▪ food dominates exposure, but at background levels, does not drive serum levels

▪ dust becomes important at higher concentrations

▪ serum levels correlate with an exposure pathway only if the exposure are high enough to drive the relationship

▪ for low exposure (background exposure), serum levels are driven by spikes in exposure (e.g. eating a contaminated meal)

▪ selective biotransformation of HBCD isomers in humans (only α-HBCD in these serums amples, yet low levels), non-racemic EFs.

or

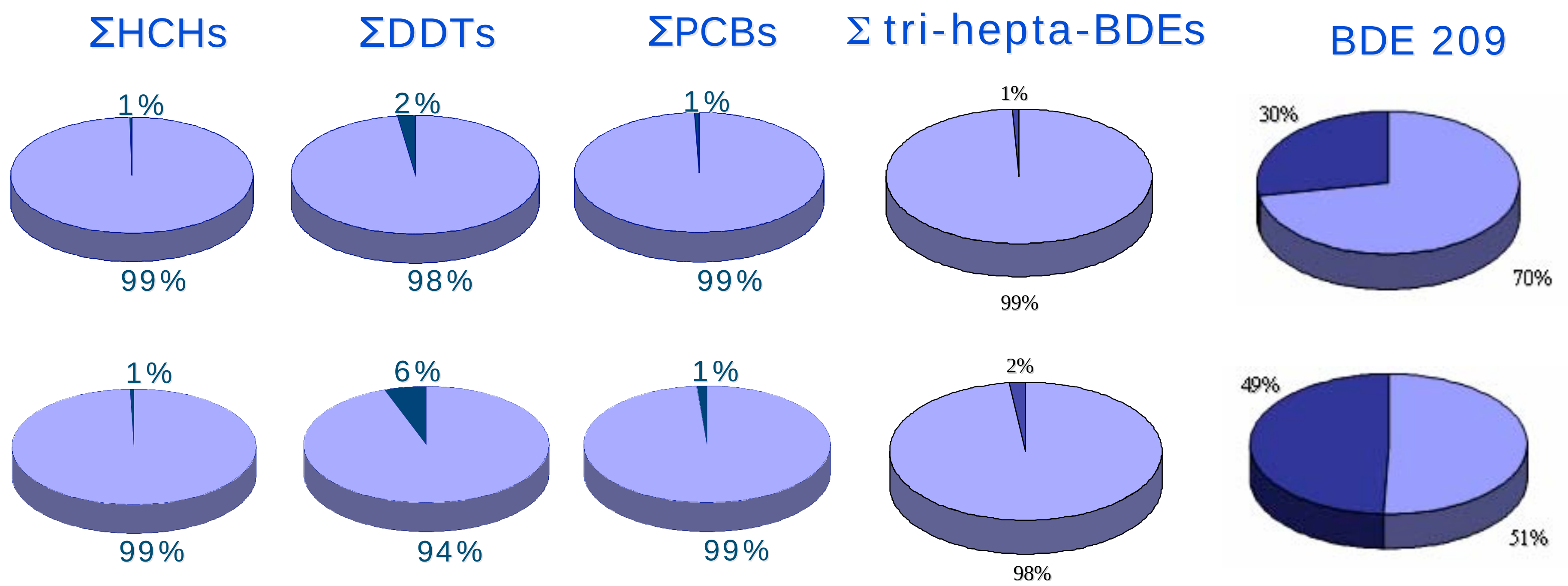
▪ selective bioavailability?

RECENT STUDY - Romania

ADULTS

Food

Dust



Average dust intake

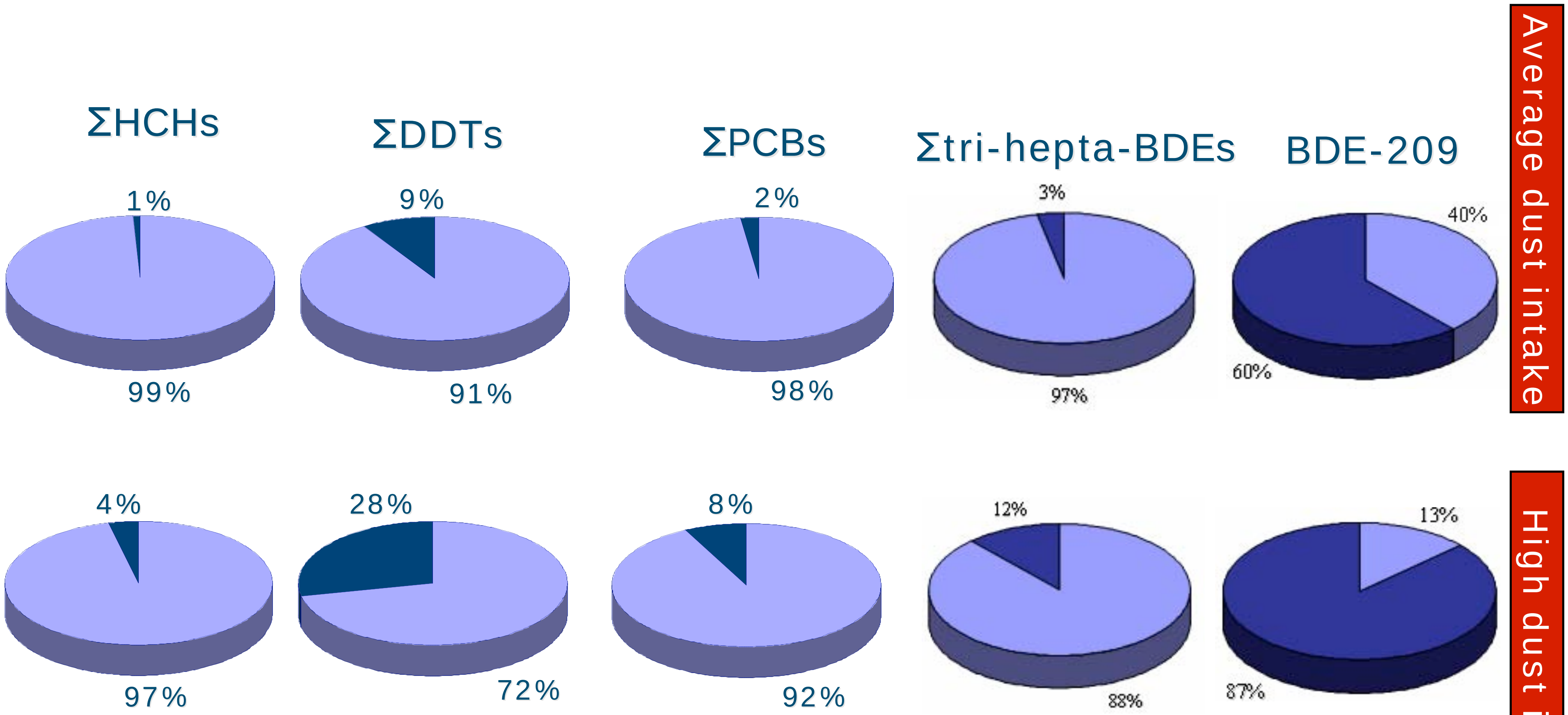
High dust intake

Universiteit Antwerpen

(Dirtu and Covaci, Organohalogen Compd 2008)

TODDLERS

Food
Dust



Universiteit Antwerpen

(Dirtu and Covaci, Organohalogen Compd 2008)

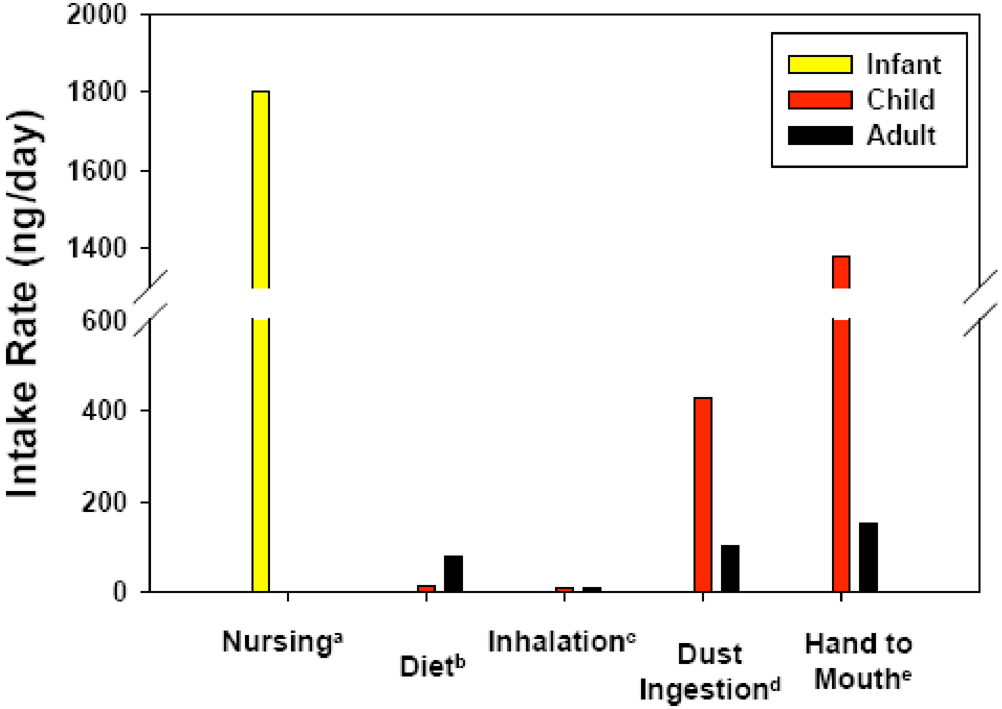
Exposure of infants/children

- Prenatal – via placenta and cord blood
- **Postnatal – via mother's milk and dust**

MEDIAN EXPOSURES
- **mother milk** (800 g per day) = 2 ng/g ww penta-BDE (in the US)
  - intake 1600 ng/day
  - 160 ng/kg bw/day (for 10 kg infant)

- **dust** (200 mg/day) from 4000 ng/day penta-BDE (in the US)
  - intake 800 ng/day
  - 80 ng/kg bw/day (for 10 kg infant)

Estimates of Median PBDE Intake by Source In U.S. Population



a-assuming an infant weighs 5 kg and ingests 800 mL of breast milk/day (Schecter et al., 2005).
b-assuming adult weighs 65 kg and a child weighs 13 kg (Schecter et al., 2006).
c-assuming an inhalation rate of 20 m^3/day (Allen et al., 2007).
d-assuming that children ingest 100 mg of dust/day and an adult 20 mg dust/day (Stapleton et al., 2005).
e- Using model parameters estimates on previous slide and median BDE levels of 130 ng on hands.

Stapleton, 2008

Risk levels

Agency for Toxic Substances and Disease Registry (ATSDR) + U.S. EPA

Minimum Risk Level (MRL) - estimate of the daily human exposure likely to be without appreciable risk of adverse health effects over a specified duration of exposure.

Penta-BDEs	oral: 7 µg/kg/day (490 µg/day) - adult
BDE-209	oral: 10 mg/kg/day (700 mg/day) - adult

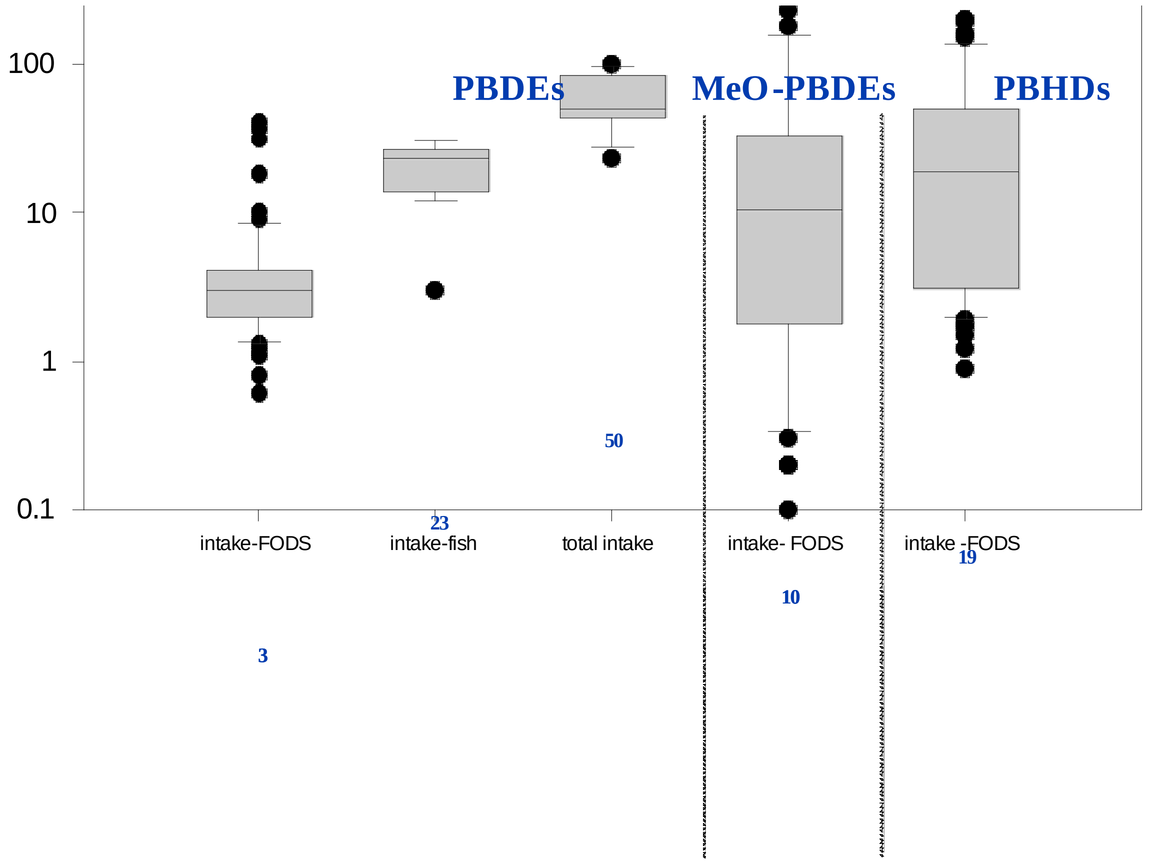
Median exposures: food + dust (literature)

Penta-BDEs	< 1 µg
BDE-209	< 10 µg

- Extreme values are not taken into account
- Synergism with other POPs??
- Children are more sensitive

Spikes in exposure

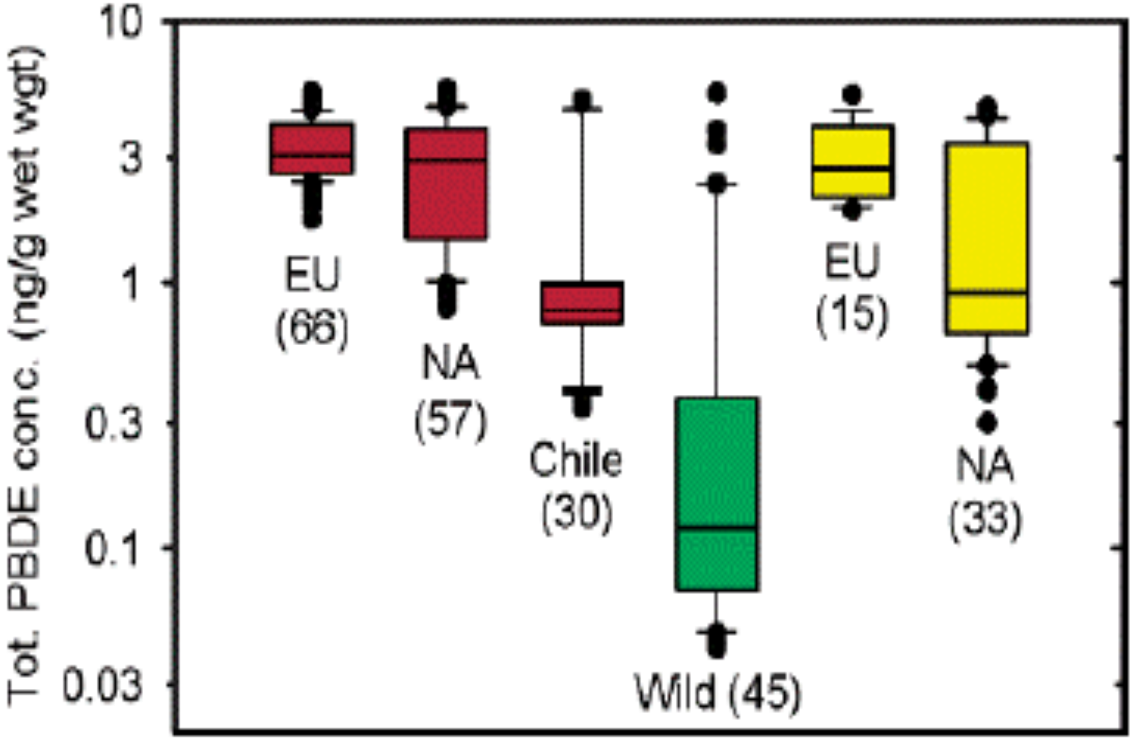
- 70 oils marketed as dietary supplements rich in omega-3 fatty acids



Universiteit Antwerpen

Covaci et al, ES&T 2007

Spikes in exposure



Large variation between levels in fish

Hites et al., ES&T 2004

Spikes in exposure

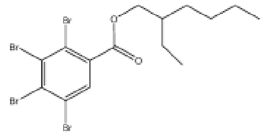
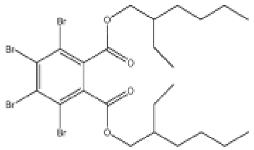
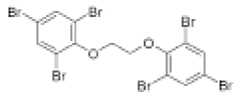
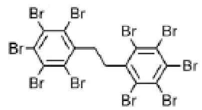
Dust extreme levels:

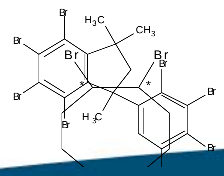
- HBCD: up to 140 µg/g dw

- BDE-209: up to 1-2.5 mg/g dw

Air levels in occupational settings!

Alternate BFRs

Short name	Chemical name	Technical name	Structure	Potential substitute for
NEW BFRs				
TBB + TBPH	TBB: 2 -ethylhexyl 2,3,4,5 - tetrabromobenzoate TBPH: 2 -ethylhexyl) tetrabromophthalate	FR550	 	Penta -BDE
BTBPE	1,2-bis(2,4,6 -tribromophenoxy) ethane	FR680		Octa -BDE
OBIND	Octabromotrimethyl -phenylindane			Octa -BDE
DBDPE	Decabrominated diphenyl ethane	SAYTEX 8010		Deca -BDE
TBCO	1,2,5,6 -tetrabromocyclooctane			HBCD



Alternate BFRs

In which matrices are other BFRs found?

- Sewage sludge - occasionally - domestic use
- Sediments - occasionally
- Air - mostly particle-associated - occasionally
- Biota - very occasionally
- Dust - occasionally

- Human food – no reports
- Human levels – very rare

- Levels of alternate BFRs are MUCH LOWER than “classical” BFRs

Quo Vadis?

Alternate BFRs
- Potential for human exposure
- Yet, no idea of current exposure…..
- So is there a problem?
- VERY LIMITED TOXICOLOGICAL DATABASE.…

Other FRs
-Organophosphorus (OPPs)
-Organochlorinated (PCAs)

Not sure if these are better alternatives

KEEP ON LOOKING FOR BETTER ALTERNATIVES

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University of Birmingham, UK

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Thank you!