Environmental sources of polybrominated diphenyl ether (PBDE) and organophosphorus (OP) flame retardants and risk of breast cancer in young women: Early results from a population-based Ontario study

Occupational and Environmental Health (OEH) seminar series

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Review article

A review of the role of emerging environmental contaminants in the development of breast cancer in women

Shabana Siddique [a, *], Cariton Kubwabo [b], Shelley A. Harris [a, c, d]

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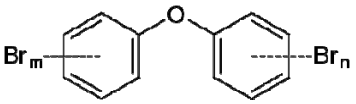
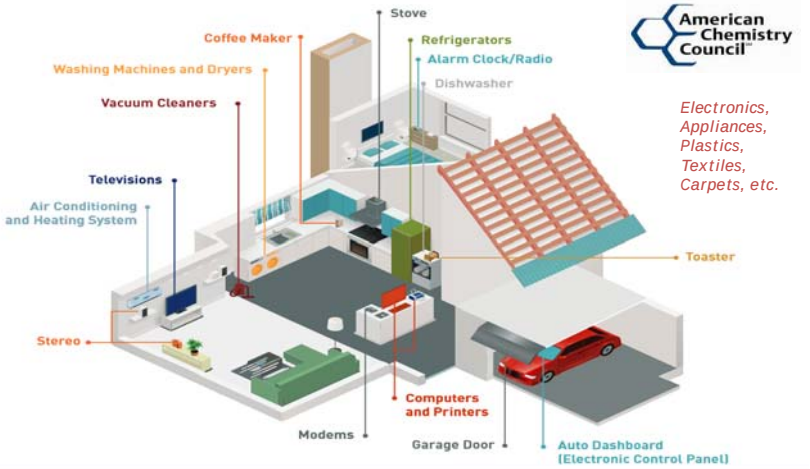
- *alkylphenols (APs)*
- *bisphenol A (BPA)*
- *parabens*
- *perfluoroalkyl substances (PFASs)*
- *phthalates*
- *synthtetic musks*
- *triclosan*
- *polybrominated diphenyl ethers (PBDEs)*

Polybrominated Diphenyl Ethers (PBDEs)



- Class of brominated flame retardants
- Used in a wide range of industrial and consumer products since 1970's to meet flammability standards for:
  - textiles, insulation, polyurethane foam, carpets, furniture, plastics, electrical appliances/equipment
- PBDEs can be released from products during manufacture, while in use and after disposal

Sources of Flame Retardants



https://flameretardants.americanchemistry.com/Electrical-Electronic-Equipment/Flame-Retardants-Fire-Safety-Tools-for-Electronics.pdf

4

Why focus on PBDEs?

- **Ubiquitous environmental pollutants**
  - Increasing levels in the environment, especially North America
  - Have contaminated the food chain
    - High concentrations found in fish (salmon, trout, mackerel)
    - **Premenopausal breast cancer** in women associated with consumption of **Great Lakes fish** (McElroy, 2004)
- **Endocrine disruptors**
  - Metabolites act as **pseudoestrogens**
- Classified as a "possible human carcinogen" by U.S. Environmental Protection Agency
- **Exposure through dust, air, dermal contact and diet**

PBDEs in human blood, milk, tissue (ng/g lipid)

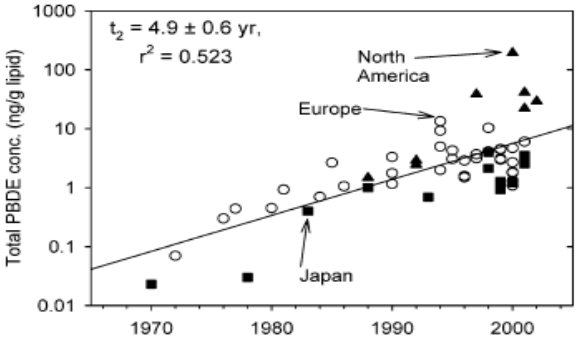


FIGURE 1. Total PBDE concentrations (∑PBDE) in human blood, milk, and tissue (in ng/g lipid) shown as a function of the year in which the samples were taken; see Table 2. The three symbol types indicate the location from which the samples were collected. The overall regression is shown.

Hites RA, 2004.
Environ Sci Technol 38, 945-956.

2003-2008 stopped new use in EU & North America

Organophosphorus Flame Retardants (OPFRs)

"With obvious advantages like environmental friendliness and safety, organophosphorus flame retardant is gradually substituting for halogen flame retardant ….in 2013 alone, the market volume of organophosphorus flame retardant reached some 620 kt, accounting for 30% of the global total."

http://www.researchinchina.com/Htmls/Report/2014/7904.html

Exposure to Emerging Environmental Contaminants and Risk of Breast Cancer in Young Women: A Case-Control Study using Biomarkers of Exposure. CCSRI, $842,000 2011-2017

http://oehs.ca/

OEHS – Case Control Study

Primary Objective:

1. To evaluate the associations between **lipid-adjusted serum concentrations of PBDEs** and the risk of **incident breast cancer** in young women, aged 18-44 years.

OEHS – Case Control Study

Secondary Objectives:

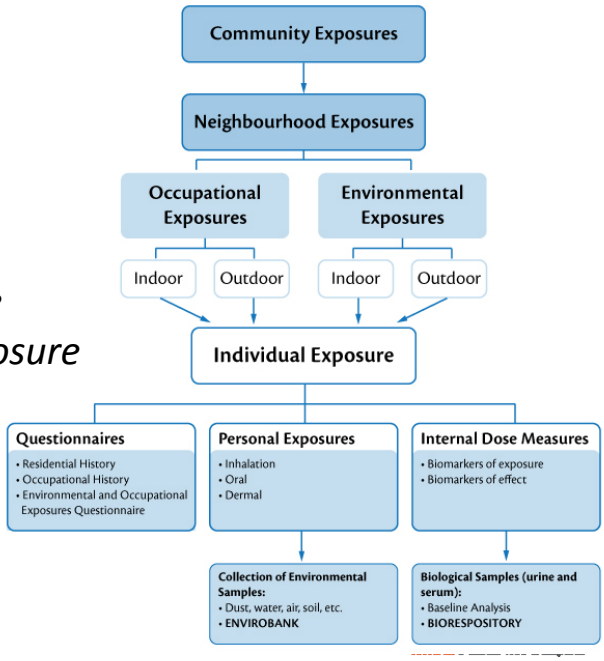
1. To evaluate the relative contribution of different sources to lipid-adjusted PBDE serum concentrations:
   - **Dietary exposures** (fish consumption, meat, poultry, dairy), **environmental** (household) and **occupational exposures**
2. To collect collect and store **serum** and **morning urine samples for future biomarker studies** of exposure, susceptibility or effect and the risk of breast cancer in premenopausal women (ie: Biobank)

OEHS – Case Control Study

- Cases: n=350
  - **Population-based**: identified from the **Ontario Cancer Registry** (OCR) 2013-2015
  - Aged **18-44 years**
  - Pathology-confirmed primary breast cancer diagnosis
- Controls: n=350
  - **Population-based:** identified using random-digit dialing (RDD) by the Institute for Social Research (ISR) at York University
  - Frequency-matched within 5-year age groups

OEHS Ontario Environment and Health Study

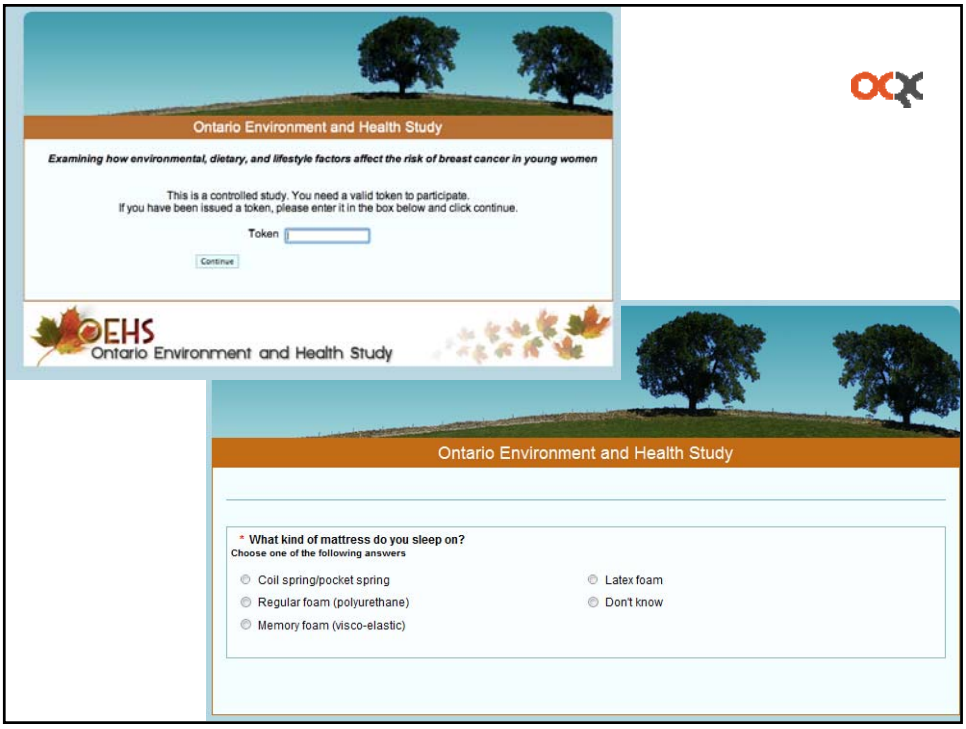
A comprehensive approach to exposure assessment



OEHS – Data Collection

Two web-based questionnaires:

1. **Environmental Questionnaire**
   - Lifetime residential history: age /type of home, type of **heating**, **ventilation**, renovations
     - Cleaning: frequency of **vacuuming**, **dusting**, carpet cleaning
     - **Furniture types**: age/type of mattress, presence of foam pillows, other foam furniture
   - **Occupational history**: computer repair, recycling facilities, hours spent on a computer
   - Transportation: vehicle use, airplane travel
   - A typical day: hours spent on work/home/travel/sleep
2. **Diet Questionnaire**



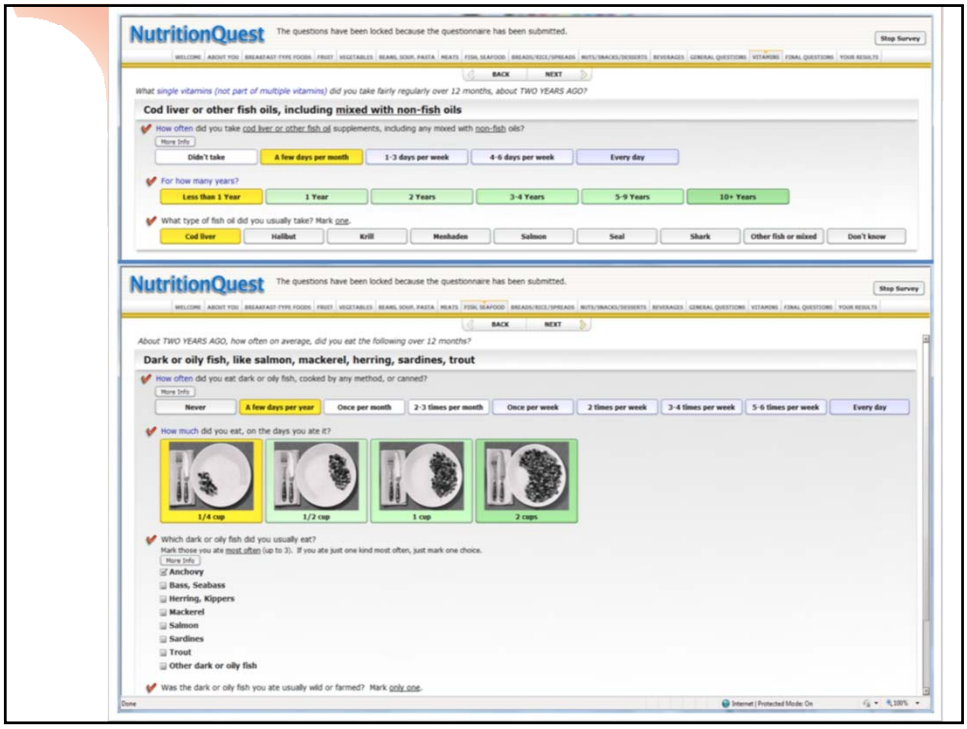
OEHS – Data Collection

Two web-based questionnaires:

1. **Environmental Questionnaire**
2. **Diet Questionnaire**
   - Modified full-diet Block 2005 FFQ to estimate **usual food and supplement intake** over 12 months about **2 years ago**
   - Modifications geared towards improved PBDE assessment:
     - Reviewed all animal foods
     - Modified questions and nutrient database to distinguish **meat** and **chicken** or **turkey sources**, **oily fish**, and **fish oil supplements**

OEHS – Data Collection

2. **Diet Questionnaire:** examples of modifications
   - New items and sub-questions added
     1. **Fish:** ready-to-eat vs. white/lean vs. dark/oily
        - Different fish types (i.e. wild vs farmed)
     2. **Meat products and liver:** poultry vs. animal
        - Different types of products (i.e. hot dogs, white vs. dark chicken, fried liver vs. paté)
     3. **Fish oil supplements vs. non-fish Omega3s**
        - 8 different types of fish oil supplements



Journal of Food Composition and Analysis

Available online 11 December 2017

In Press, Accepted Manuscript

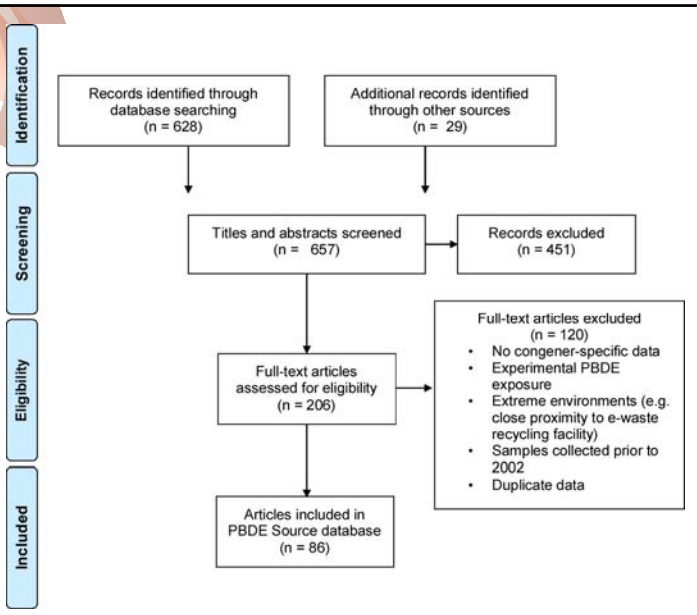
Original research article

A global database of polybrominated diphenyl ether flame retardant congeners in foods and supplements

Beatrice A. Boucher [a, b] [1] ✉, Julie K. Ennis [a, b, 1], Dina Tsirlin [a], Shelley A. Harris [a, c, d]

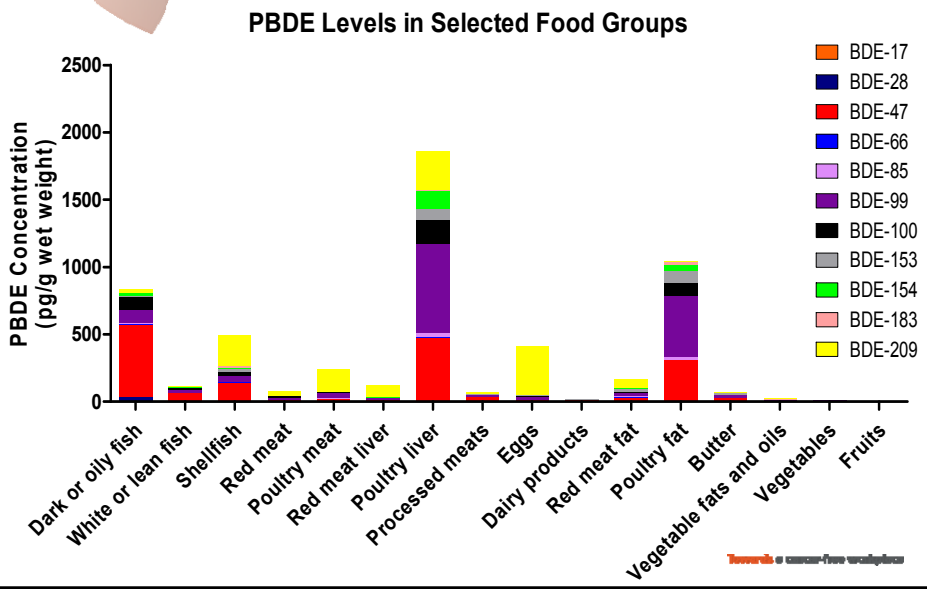
Search Strategy:

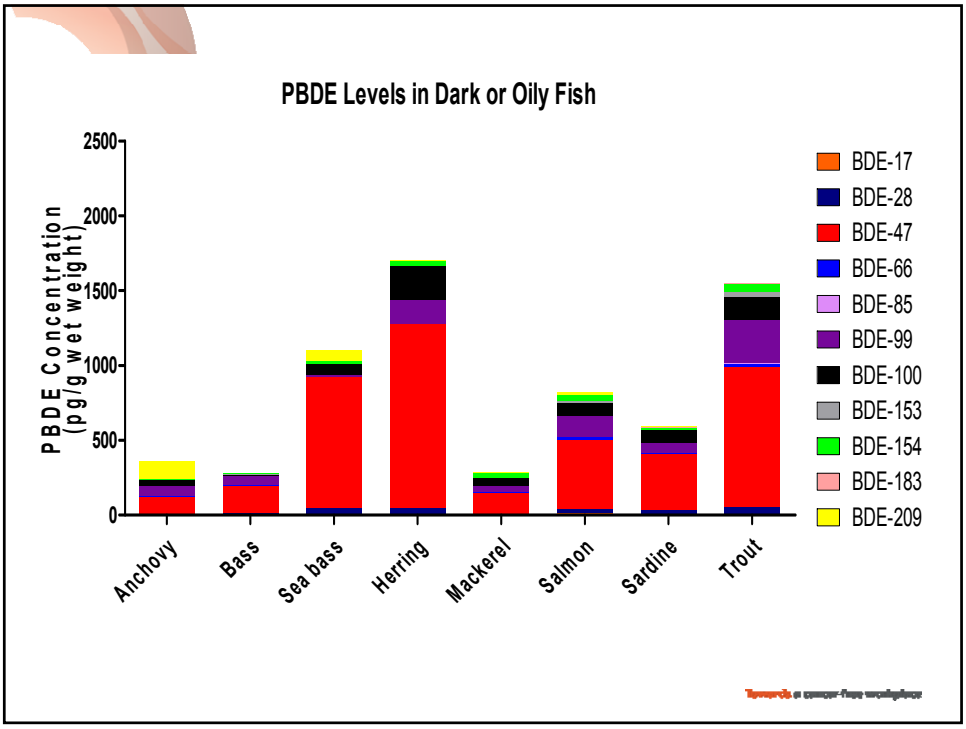
- Medline 1996 – April 2015
- MeSH terms and keywords: (flame retardants/an [Analysis]; OR halogenated diphenyl ethers/an, ch [Analysis, Chemistry]; OR hydrocarbons, brominated/an, ch [Analysis, Chemistry]; OR pbde) AND (food: OR diet: OR dietary supplements OR fish oils)



86 reports - 1358 database entries

Results: PBDE database





Results: PBDE database

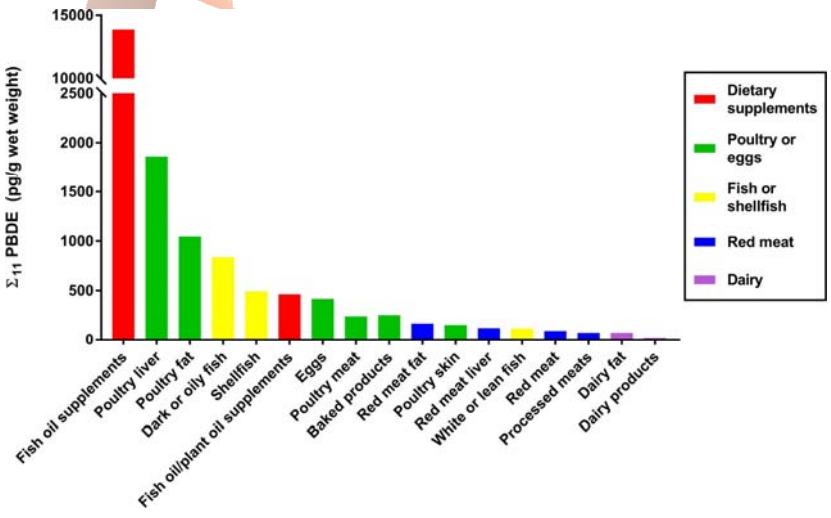
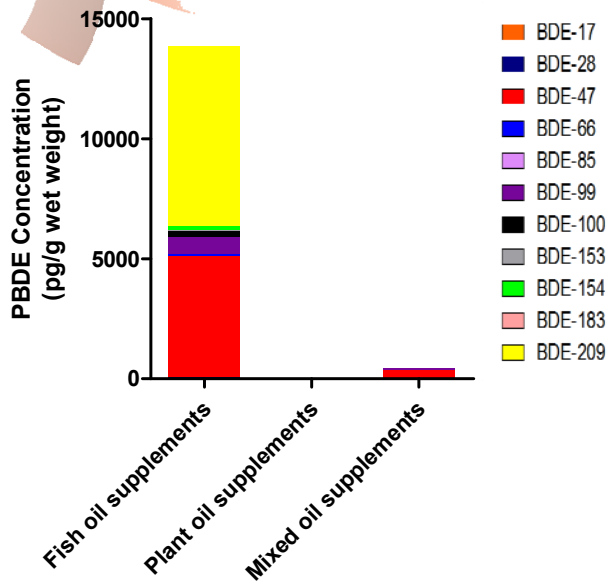


Figure ∑11Polybrominated diphenyl ether (PBDE) in the top 10 contaminated groups and additional animal groups (pg/g wet weight).

PBDE Levels in Selected Dietary Supplements



OEHS – Data Collection

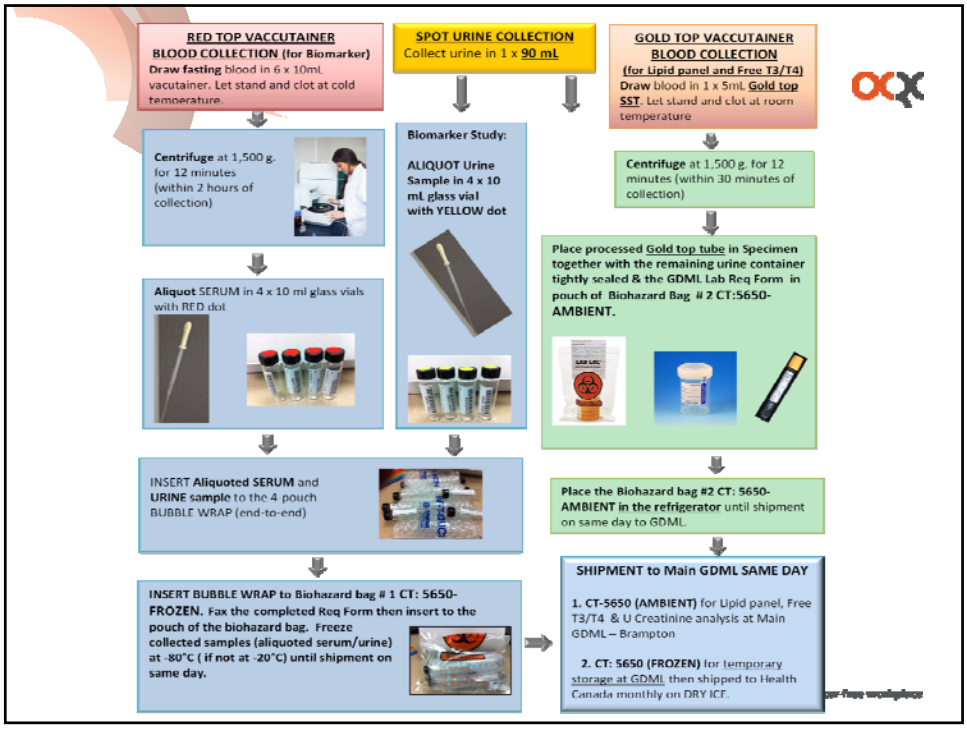
3. Biological sample collection

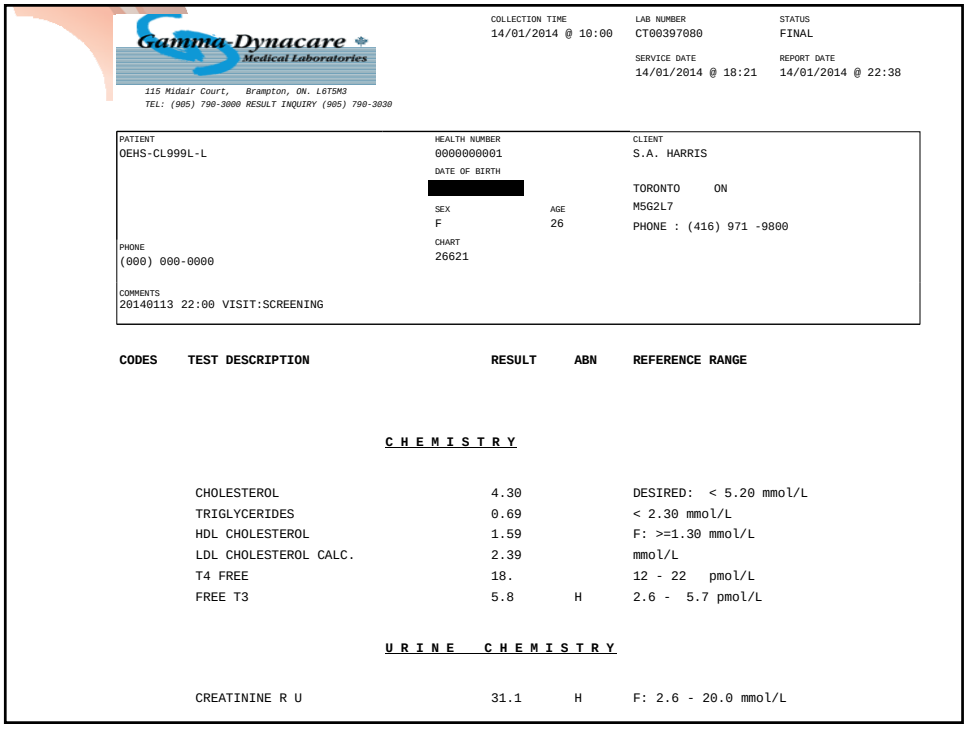
- After consent, cases and controls were mailed a **BioKit** containing:
  1. Test tubes, pipettes and containers for sample collection
  2. Participant instructions, a Google maps print out of the 5 closest GDML locations to their home
  3. A set of laboratory instructions

- Collect **60mL of fasting blood** and **90mL of urine**
- Location: **Gamma Dynacare Medical Laboratory (GDML)**

OEHS BioKit

- GDCML: Collection, processing, analysis, shipment, short term storage





Gamma-Dynacare Medical Laboratories

115 Midair Court, Brampton, ON. L6T5M3
TEL: (905) 790-3000 RESULT INQUIRY (905) 790-3030

COLLECTION TIME	LAB NUMBER	STATUS
14/01/2014 @ 10:00	CT00397080	FINAL
	SERVICE DATE	REPORT DATE
	14/01/2014 @ 18:21	14/01/2014 @ 22:38

PATIENT	HEALTH NUMBER	CLIENT
OEHS-CL999L-L	0000000001	S.A. HARRIS
	DATE OF BIRTH [redacted]	TORONTO ON
	SEX F / AGE 26	M5G2L7
	CHART 26621	PHONE : (416) 971 -9800
PHONE (000) 000-0000		
COMMENTS 20140113 22:00 VISIT:SCREENING		

CODES	TEST DESCRIPTION	RESULT	ABN	REFERENCE RANGE
	C H E M I S T R Y			
	CHOLESTEROL	4.30		DESIRED: < 5.20 mmol/L
	TRIGLYCERIDES	0.69		< 2.30 mmol/L
	HDL CHOLESTEROL	1.59		F: >=1.30 mmol/L
	LDL CHOLESTEROL CALC.	2.39		mmol/L
	T4 FREE	18.		12 - 22 pmol/L
	FREE T3	5.8	H	2.6 - 5.7 pmol/L
	U R I N E C H E M I S T R Y			
	CREATININE R U	31.1	H	F: 2.6 - 20.0 mmol/L

RESIDUES AND TRACE ELEMENTS

Challenges Associated with Sample Preparation for the Analysis of PBDEs in Human Serum

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1) GC/electron ionization-tandem MS method develop to quantify 8 PBDE congeners in human serum: BDE-28 BDE-47 BDE-85 BDE-99 BDE-100 BDE-153 BDE-154 BDE-183

2) Subset of 120 subjects (60 cases and 60 age-matched controls) assessed for OPFR exposures via urinary metabolites: BDCIPP, DPHP, BBOEP, DoCP & DpCP, TCIPPOH, BCIPP, BCEP, Desbutyl TBOEP

Results: demographic and health-related characteristics of OEHS participants

Characteristic	Cases (n=305) N	(%)	Controls (n=144) N	(%)
Age (years)				
Mean (SD)	39.70	(4.41)	38.33	(4.54)
20 years and younger	0	-	1	(0.69)
>20 to 30 years	12	(3.93)	6	(4.17)
>30 to 40 years	130	(42.62)	85	(59.03)
>40 to 45 years	163	(53.44)	52	(36.11)
Education				
Elementary School	0	(0.0)	1	(0.7)
High School	33	(10.8)	8	(5.6)
Trade or technical school	11	(3.6)	2	(1.4)
Non-university diploma	71	(23.3)	47	(32.6)
University, below Bachelor's	6	(2.0)	6	(4.2)
Bachelor's degree	123	(40.3)	55	(38.2)
Graduate degree	61	(20.0)	25	(17.4)
Marital Status				
Married or living with partner	246	(80.7)	120	(83.3)
Divorced	10	(3.3)	6	(4.2)
Widowed	1	(0.3)	0	(0.0)
Separated	6	(2.0)	4	(2.8)
Single or never married	42	(13.8)	14	(9.7)

Associations with selected characteristics, all models adjusted for age

Characteristic	Cases (n=305)	Controls (n=144)	OR	(95% CI)
Body mass index (BMI) - 2 years ago				
Mean (SD)	24.73	26.29	0.95	(0.92, 0.98)
Normal: 18.5 to <25	181	66	1.00	
Below 18.5	15	2	2.88	(0.63, 13.04)
35 to <30	70	41	0.61	(0.37, 0.98)
30 and above	39	34	0.40	(0.23, 0.69)
Smoking status				
Never (<100 cigarettes)	197	101	1.00	
Ever	106	38	1.38	(0.88, 2.15)
Dietary alcohol intake (grams)				
Mean (SD)	9.08	5.86	1.02	(1.00, 1.04)
≤Q1	60	35	1.00	
Q1 to Q2	60	35	1.11	(0.61, 2.03)
Q2 to Q3	70	34	1.22	(0.68, 2.20)
Q3≥	105	34	1.81	(1.02, 3.22)
Parity: number of live births				
None	92	20	1.00	
1	52	18	0.47	(0.22, 1.00)
2	111	66	0.27	(0.14, 0.50)
3 or more	50	40	0.18	(0.09, 0.37)

OEHS Data Collection, Part 4
HOME Study -Diamond Laboratory, University of Toronto/Environment Canada

NEW FUNDING:

Monitoring and modeling of residential indoor semi volatile organic compounds. Harris, S.A. (PI) and Diamond, M. (PI)

Health Canada, Water, Air and Climate Change Bureau, CARA project funds.

2014 - 2017, Amount: $497,100

Monitoring organophosphorus flame retardants in Canadian homes.

Harris, S.A., (PI) Diamond, M. (PI) and Jantunen, L. (Co-I)

Health Canada, CMP Monitoring and Surveillance Fund.

2014 to 2017, Amount: $100,000

SVOCs?

- SVOCs include: halogenated (bromine and chlorine) organic compounds, phthalates, and phosphorus-containing (OP) flame retardants (FRs)
- The concentration of SVOCs in indoor air is influenced by a number of poorly characterized emission sources:
  - Personal care products
  - Building and decorator materials (wallpaper, flooring type)
  - Electronic equipment, furniture
  - Indoor sinks (carpets, dust)

HOME Study Objectives

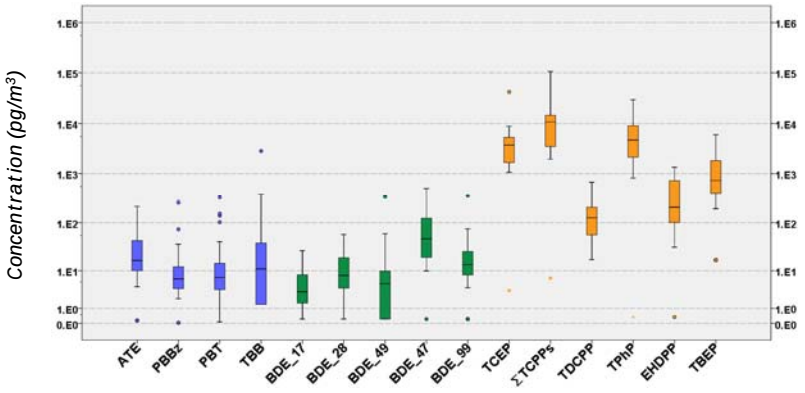
- Evaluate association between SVOCs, as measured in a variety of media (air, dust, hand wipes…)
  - serum PBDE levels of individuals residing in the household
  - urinary OPFRs
- Investigate whether housing characteristics are predictive of measured SVOCs

Methods OEHS Home Study

Figure 2. Equipment set-up in a participant's home

Figure 1. Study process and timeline

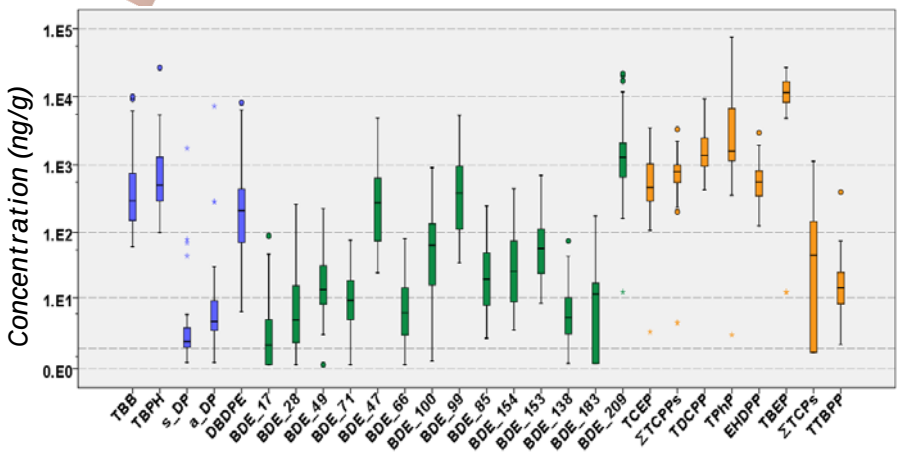
BROMINATED AND ORGANOPHOSPHATE FLAME RETARDANTS (BFRS AND OPES) IN HOUSEHOLD AIR IN ONTARIO, CANADA



- *OPFRs > NBFRs & PBDEs by ~ 2-3 orders of magnitude (PUF passive)*

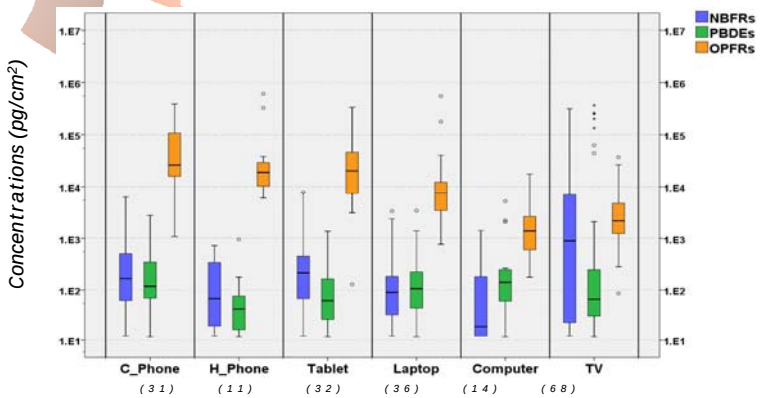
Yang et al., BFR 2016

Dust Concentrations



➢ OPFRs ~ 10 times higher than NBFRs & PBDEs

Handheld *Non-Handheld*



- *OPFRs Handheld > non-handheld*
- *BFRs Handheld ≈ Non-handheld*
- *Handheld newer than non-handheld?*

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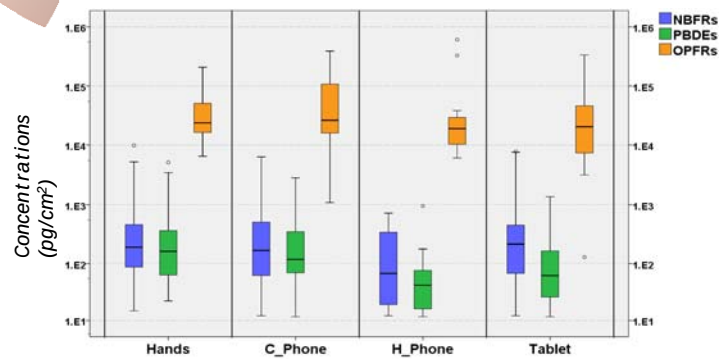
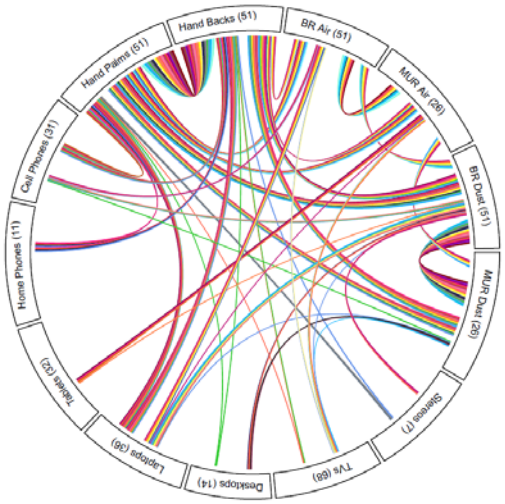
Hands vs Handheld Devices



- *Hands ≈ Handheld devices*
  - *Handheld devices as sources to hands or vice versa?*

Exposome Globe BFRs, Yang et al., in prep



Cold tone/blueish ribbons represent NBFRs, and warm tone/redish ribbons represent PBDEs.

05

Conclusions

- **associations for PBDE exposures** and premenopausal breast cancer risk …..
- elevated breast cancer risk observed in relation to urinary concentrations of **OP flame retardants** ….
- **diet** may be an important contributor to serum PBDE concentrations
- **OPFRs more frequently detected** and in higher concentrations that PBDE congeners in biological samples
- OPFR concentrations far **higher in indoor environments** than PBDEs

OEHS Future Directions

- **Diet analysis**
  - PBDEs in foods/supplements
  - Organic foods
- **OEHS Home Study** – predictive modelling of serum (PBDEs) and urinary (OPs) biomarkers
- **Additional analyses funded**:
  - Multimedia Exposure to Replacement Chemicals of Emerging Concern and Selected CMP3 Chemicals (Awarded); PI: Kubwabo, C, Mandy Fisher (Co-PI), Dr. Pat Rasmussen (Co-PI), Harris, S.A. (Co-I) et al. Chemical Management Plan, Health Canada 2017- 2021, Amount: $600,000.

Investigators and Collaborators

OEHS:

- **Shelley Harris** (PI), Beatrice Boucher, Cariton Kubwabo, Michelle Cotterchio, Julia Knight, Len Ritter, Paul Villeneuve
- Grad Student/Post Doc/RAs: **Linda Kachuri, Lidija Latifovic**, Gil Valencia, Brooke Filsinger

Health Canada Biomonitoring Team:

- **Cariton Kubwabo, Shabana Siddique** Kaela Lalonde, Ivana Kosarac

PBDE database team:

- **Beatrice Boucher**, Julie Ennis, Dina Tsirlin

OEHS Home Study Team:

- **Miriam Diamond**, Liisa Jantunen, Congqiao Yang, Jospeh Okeme, Dina Tsirlin, Lidija Latofivic, Regina De La Campa; Hung You, Ryan Kulka, Bruce Fraser