Early Life Exposure to Replacement Flame Retardants and Child Respiratory Outcomes

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Outline

Background

Preliminary Data

- Single flame retardants and subsequent respiratory symptoms
- Mixtures of flame retardants and adverse respiratory outcomes

Future Directions

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Background on Flame Retardants

- Chemicals ***added*** to household products to reduce flammability and risk of fire
- Added not bound products, therefore can leach and ***accumulate in house dust***
- Children also exposed through ***baby products*** containing flame retardants (**eg.** toys, pillows, sleep positioners) and ***in-utero*** from pregnant mothers exposed to chemicals due to ability to cross placental barrier


Electronics


Furnitures


Building insulation


Textiles


Mattresses


Car seats

- Polybrominated diphenyl esters (PBDEs) previously used as flame retardants were ***phased out*** starting 2004, due to environmental and health concerns and ***substituted with organophosphate (OPFRs) and replacement brominated flame retardants (RBFRs)***
- Flame retardants are ***under consideration for regulation by EPA***

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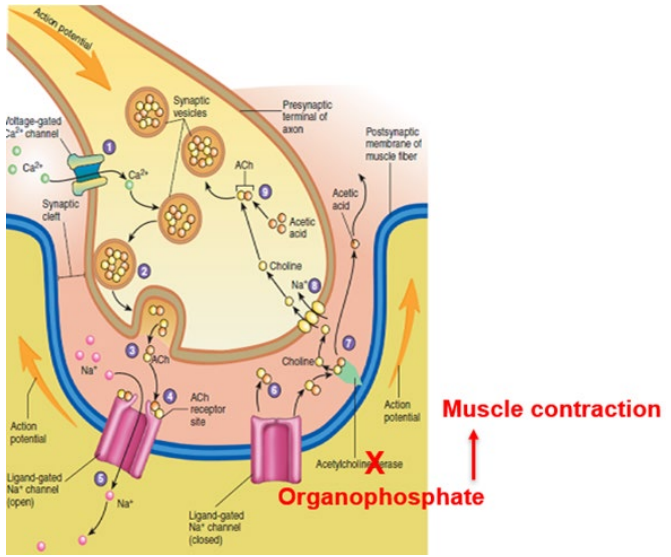
Relevance of OPFRs & RBFRs for Respiratory Health?

- ***Inhalation as a major exposure route*** raises concerns for respiratory health
- Additional mechanisms for concerns:
  1) ***Irritation*** of skin by certain OPFRs and possibly of airways when inhaled
  2) Stimulation of ***oxidative stress***-related gene expression by RBFRs
  3) OPFRs may cause ***bronchoconstriction***:
     - inhibition of acetylcholinesterase → airway hyperreactivity
     - Effect on M3 muscarinic receptor (smooth muscle)



Effect of organophosphates on Neuromuscular Junction

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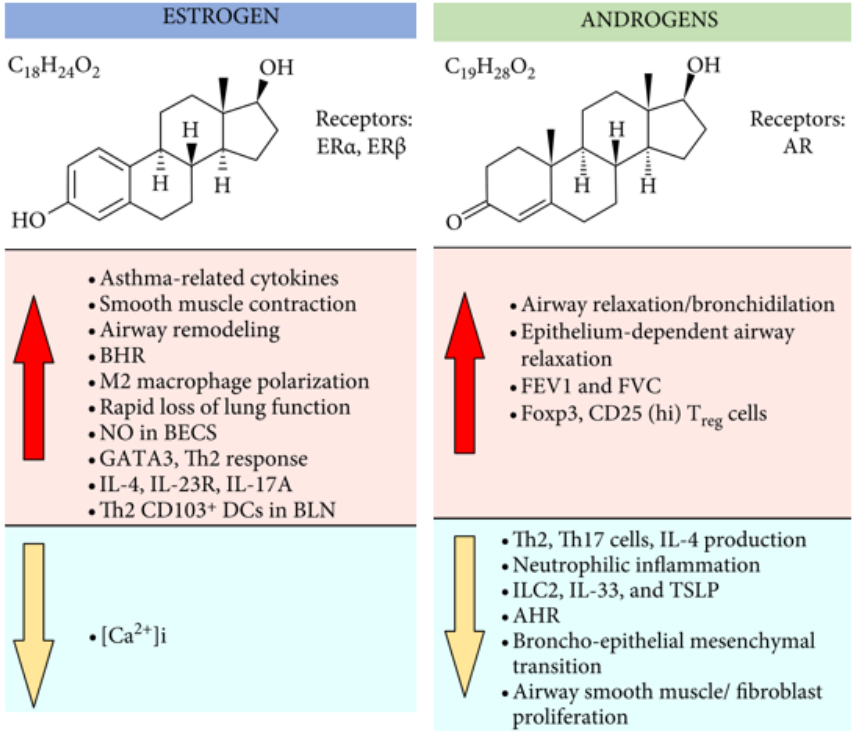
Relevance of OPFRs & RBFRs for Respiratory Health?

4) ***Endocrine disruption*** (xenoestrogen and antiandrogenic)
- Activate ERs in immunomodulatory cells and promote Th2 responses
- In utero, xenoestrogen interferes with lung surfactant and alveolar development

5) ***Epigenetic changes*** in Bdnf and Tnfa genes by PBDEs (lung innervation and inflammation)

Children vulnerability to chemicals in dust and respiratory conditions in childhood may lead to diseases in adulthood such as COPD, obesity, type 2 diabetes, hypertension, cardiovascular diseases



Effects of sex hormones on respiratory system
(Wasti et al. Oxid Med Cell Longev. 2021:7097797)

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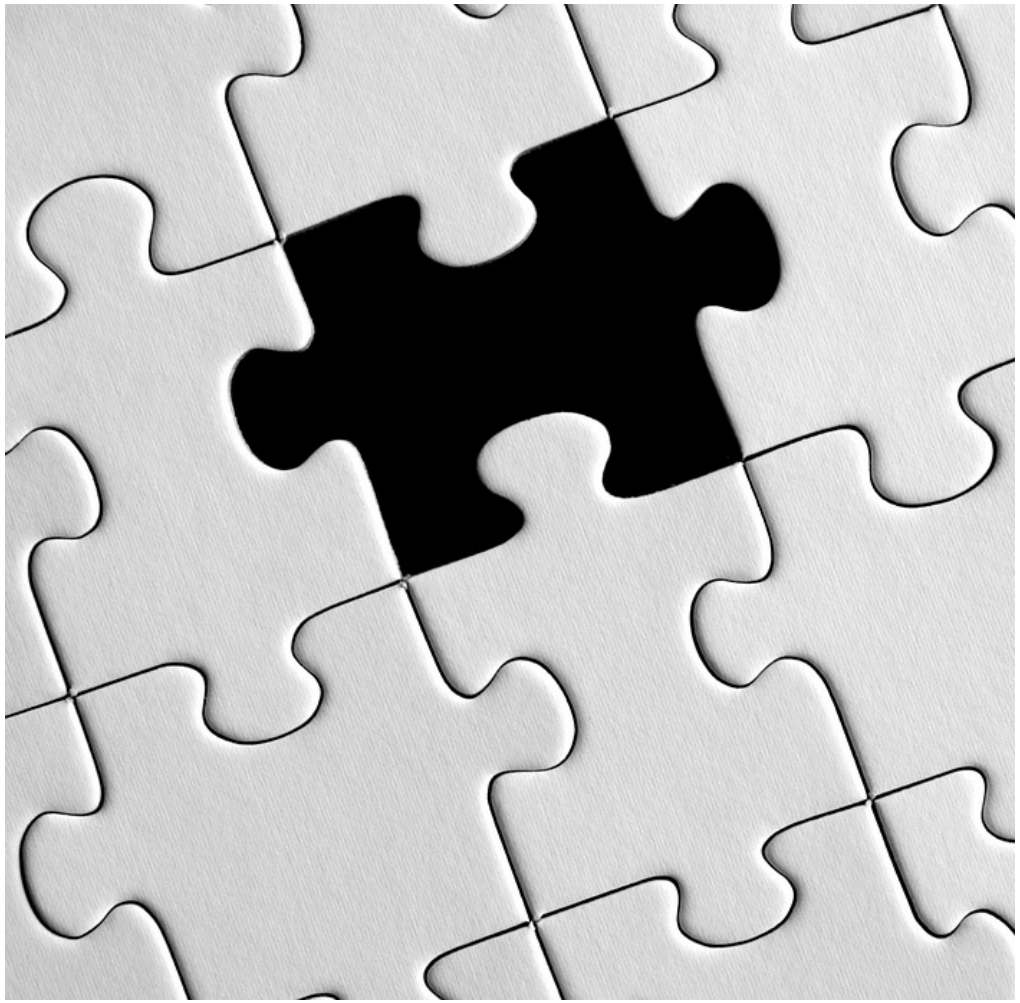

Research gap

- ***No study on RBFRs and respiratory outcomes***
- Research on OPFRs and respiratory outcomes ***scarce with no evidence of temporality***
  - 4 cross-sectional and 1 case-control studies
  - ***No*** prospective study
  - ***No*** study with lung function
  - ***No*** study of prenatal exposure
  - ***No*** study with repeated exposure measures
    (Cross-sectional study using urinary levels of toxicants with short half-live in a *single* spot urine)

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Hypothesis & Specific Aims

- **Hypothesis**: ***In utero and early childhood exposures to OPFRs & RBFRs alone or in mixtures are associated with respiratory symptoms and impaired lung function in children mediated by DNA methylation alterations***

- **Aims**
  1. Determine the association of early childhood and in utero exposure to ***single*** OPFRs and RBFRs with adverse respiratory outcomes
  2. Determine the association of ***mixtures*** of exposures to OPFRs and RBFRs occurring prenatally and postnatally with adverse respiratory outcomes
  3. Determine prenatal OPFRs and RBFRs related ***cord blood DNA methylation alteration*** associated with children's respiratory outcomes

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Preliminary data

Concentration of replacement flame retardants in house dust sampled at age 1 year and subsequent respiratory symptoms

Association between ***single exposures*** and outcomes

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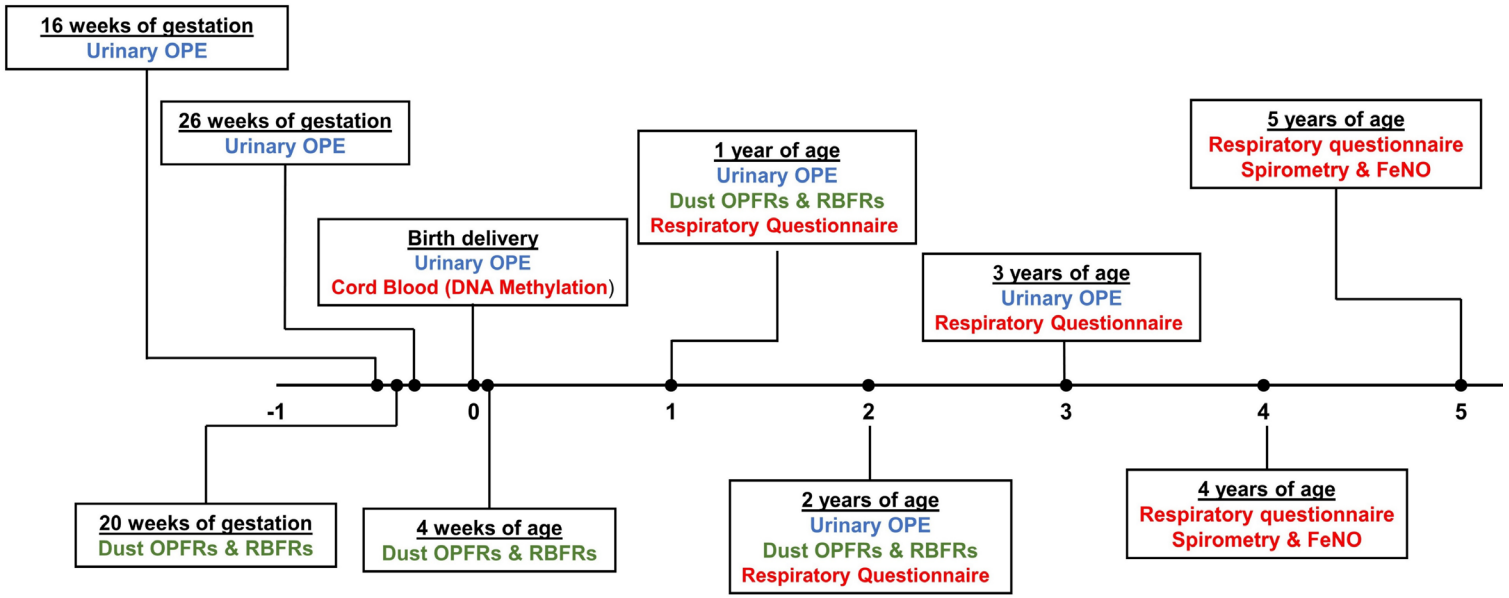
Methods

- **Cohort**: Health Outcomes and Measures of the Environment (HOME) Study, pregnancy and birth cohort study including pregnant women from Cincinnati, OH Metro recruited from 2003 to 2006
- **Exposure**: Dust concentration of OPFRs and RBFRs at child age 1 (Additionally: *Dust OPFRs and RBFRs at 20 weeks gestation and at delivery (prenatally) and postnatally at child age 1 and 2 years; urinary OPE at 16- and 26-weeks gestation and at delivery (prenatally) and postnatally every year, until child age 3*)
- **Respiratory**: wheeze, respiratory infection, hay fever/allergies assessed every 6 months until 5 years, PEF at age 5 (Additional measurement: *FEV1 measured at age 5 years*)
- **Covariates:** Child sex, child race/ethnicity, birth weight, gestational age, household income, breastfeeding duration, serum cotinine during pregnancy, total dust weight, and parental allergy
- **Statistical Analysis**: descriptive statistics and generalized estimating equations (GEE) adjusted for covariates with unstructured matrix for exposure-outcome associations. GEE with binomial distribution with logit link due to the longitudinal and binary nature of outcomes



Timeline of the HOME Study

Characteristics of participants included in analysis (N=234)

Characteristics	N (%)
Female sex	134 (57.3)
Race/ethnicity	
Non-Hispanic White	155 (66.2)
Non-Hispanic Black	65 (27.8)
Other	14 (6.0)
Household income	
< $50,000	104 (44.4)
$50,000 to $74,999	35 (15.0)
≥ $75,000	95 (40.6)
Maternal serum cotinine	
< 0.1 ng/mL	168 (71.8)
0.1 to <10 ng/mL	48 (20.5)
≥ 10 ng/mL	18 (7.7)
Paternal allergy	73 (31.2)
Maternal allergy	105 (44.9)
Breastfed	200 (85.5)
Preterm birth	22 (9.4)
Low birth weight	12 (5.1)
High birth weight	36 (15.4)

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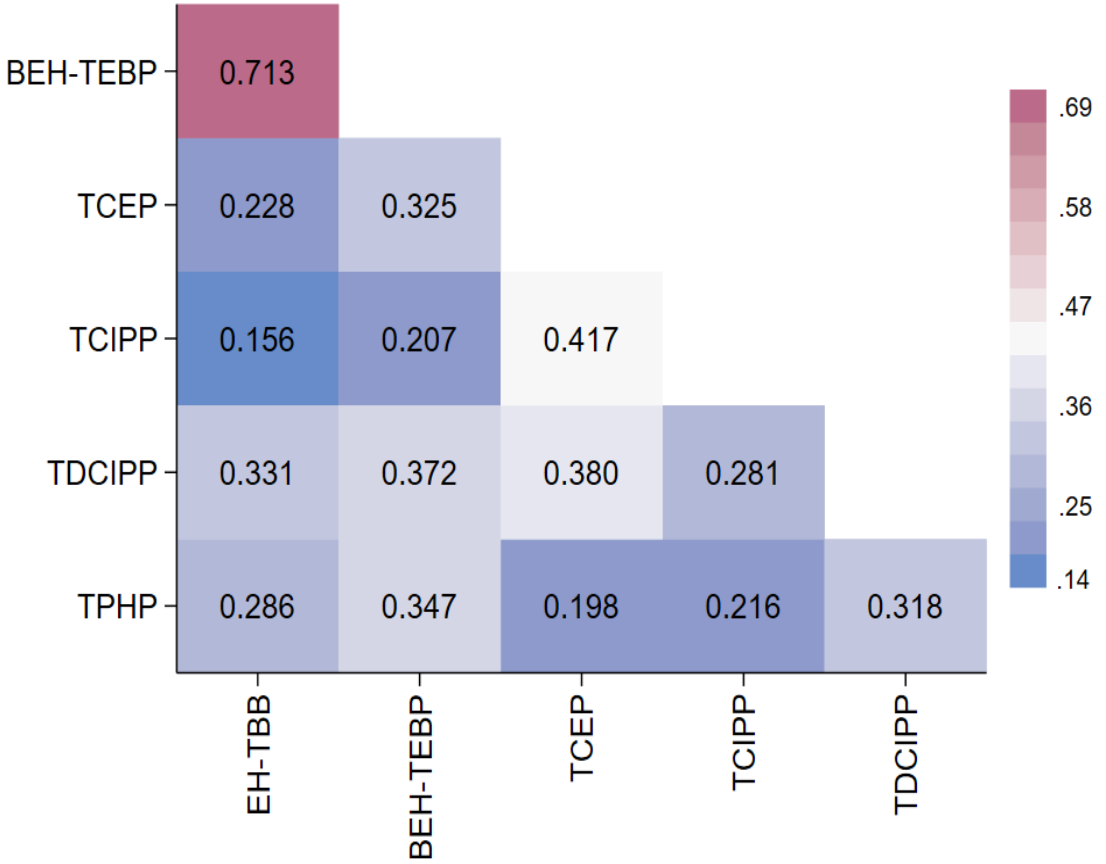
OPFRs and RBFRs per µg/g of house dust at children's age of 1-year old

Exposure	Median	Interquartile	Range
OPFRs			
∑OPFR	9.84	6.08, 17.87	0.5, 104.16
TCEP	1.09	0.53, 2.05	0.05, 39.27
TCIPP	2.04	1.06, 5.06	0.01, 96.75
TDCIPP	2.14	1.25, 3.84	0.05, 75.36
TPHP	1.80	1.00, 3.24	0.03, 52.47
RBFRs			
∑RBFR	0.46	0.24, 0.87	0.02, 38.24
EH-TBB	0.14	0.06, 0.34	0.01, 27.14
BEH-TEBP	0.28	0.14, 0.57	0.01, 11.10



Heatmap for intercorrelation between dust OPFRs and RBFRs concentrations

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Factors associated with OPFRs and RBFRs concentration in house dust samples, HOME Study

	OPFRs								RBFRs							
	TCEP		TCIPP		TDCIPP		TPHP		BEH-TEBP		EH-TBB		∑OPFRs		∑RBFRs	
	CR	95% CI	CR	95% CI	CR	95% CI	CR	95% CI	CR	95% CI	CR	95% CI	CR	95% CI	CR	95% CI
Household size	1.09	0.92–1.30	1.13	0.98–1.31	1.14	1.00–1.31	1.13	0.98–1.31	**1.20**	**1.08–1.34**	1.10	0.96–1.26	1.13	1.00–1.28	**1.19**	**1.06–1.34**
Race																
White	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Non-white	**0.59**	**0.35–0.98**	**0.47**	**0.30–0.72**	0.72	0.48–1.08	1.01	0.66–1.56	**0.56**	**0.39–0.78**	0.70	0.46–1.05	**0.65**	**0.45–0.95**	0.71	0.50–1.02
Education																
HS or less	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Some college	1.09	0.59–2.01	1.03	0.62–1.72	1.19	0.73–1.93	1.32	0.79–2.21	**1.74**	**1.16–2.60**	1.03	0.62–1.69	1.13	0.72–1.76	1.47	0.96–2.26
Bachelor's Degree	**2.71**	**1.30–5.62**	1.70	0.92–3.14	1.21	0.68–2.16	1.25	0.68–2.32	**1.66**	**1.02–2.71**	0.98	0.54–1.81	1.57	0.92–2.65	1.34	0.80–2.23
Some graduate school	**2.22**	**1.03–4.82**	1.36	0.71–2.61	1.47	0.80–2.72	1.61	0.85–3.06	**1.82**	**1.10–3.03**	1.14	0.60–2.15	1.35	0.77–2.34	1.54	0.90–2.65
Year																
2003	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2004	0.79	0.35–1.77	0.76	0.38–1.51	1.30	0.68–2.48	1.10	0.57–2.14	1.58	0.90–2.77	1.52	0.72–3.21	0.95	0.53–1.72	1.63	0.89–3.00
2005	0.60	0.26–1.38	0.86	0.43–1.73	1.21	0.63–2.34	1.53	0.78–3.00	**1.96**	**1.10–3.49**	1.98	0.93–4.23	0.99	0.54–1.81	**1.90**	**1.02–3.54**
2006	0.60	0.24–1.48	0.75	0.35–1.60	1.46	0.71–2.98	1.27	0.61–2.65	**2.74**	**1.48–5.05**	**3.01**	**1.36–6.67**	0.94	0.49–1.80	**2.92**	**1.51–5.64**
Floor type																
Carpet	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Hard floor	1.72	0.88–3.36	1.12	0.64–1.96	**1.99**	**1.17–3.38**	**2.11**	**1.21–3.67**	0.82	0.53–1.26	1.00	0.59–1.68	**1.97**	**1.23–3.18**	0.85	0.53–1.35
Visible Cleanliness																
Clean	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Less clean	0.69	0.44–1.07	0.79	0.54–1.14	0.83	0.58–1.18	0.90	0.62–1.31	0.88	0.66–1.18	0.94	0.67–1.32	0.78	0.57–1.08	0.86	0.63–1.15

Percy et al. *Chemosphere*. 2020;239:124701.

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Adjusted association of dust OPFRs and RBFRs as at age 1 year with subsequent respiratory symptoms up to age 5 years

Exposure	Wheeze		Respiratory infection		Hay fever or allergies	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
∑OPFR	**2.09 (1.37, 3.18)**	**< 0.001**	**4.85 (1.99, 11.88)**	**< 0.001**	**1.36 (1.00, 1.84)**	**0.049**
TCEP	1.26 (0.99, 1.61)	0.06	**1.91 (1.22, 2.99)**	**0.005**	**1.25 (1.00, 1.57)**	**0.049**
TCIPP	**1.44 (1.07, 1.94)**	**0.017**	1.10 (0.53, 2.29)	0.79	1.23 (0.99, 1.54)	0.06
TDCIPP	**1.63 (1.15, 2.31)**	**0.006**	**2.46 (1.16, 5.21)**	**0.019**	1.05 (0.81, 1.37)	0.72
TPHP	1.16 (0.83, 1.62)	0.39	1.26 (0.60, 2.67)	0.54	1.18 (0.91, 1.53)	0.22
∑BFR	1.28 (0.98, 1.66)	0.07	1.42 (0.90, 2.24)	0.13	0.89 (0.70, 1.12)	0.31
EH-TBB	1.02 (0.81, 1.29)	0.85	1.43 (0.97, 2.10)	0.07	0.95 (0.78, 1.16)	0.62
BEH-TEBP	**1.40 (1.04, 1.87)**	**0.02**	1.40 (0.88, 2.23)	0.15	0.87 (0.68, 1.10)	0.25

Bold indicates significance. Abbreviations: OR: odds ratio; CI: confidence interval. Models adjusted for child sex, race/ethnicity, serum cotinine, birth weight, gestational age, household income, breastfeeding duration, and maternal and paternal allergy, and total dust weight

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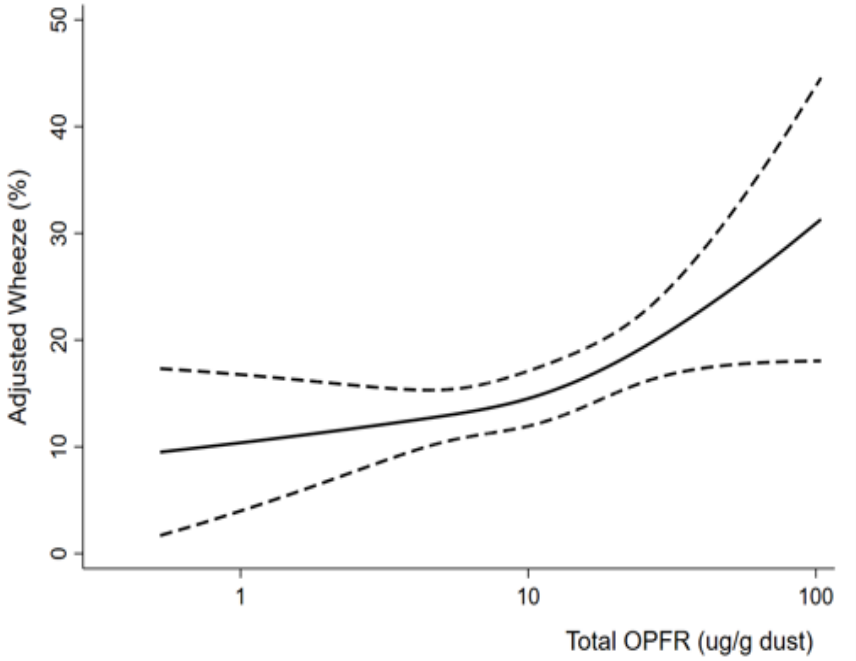
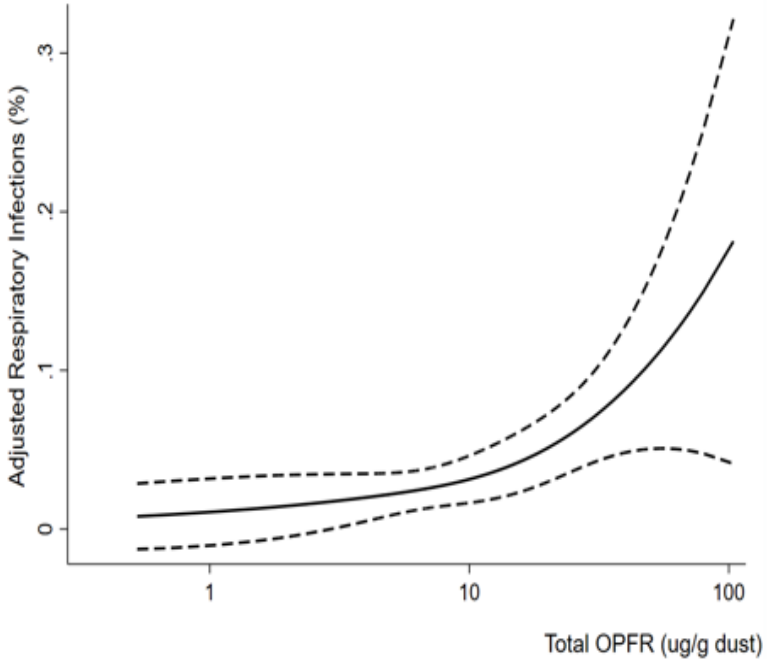
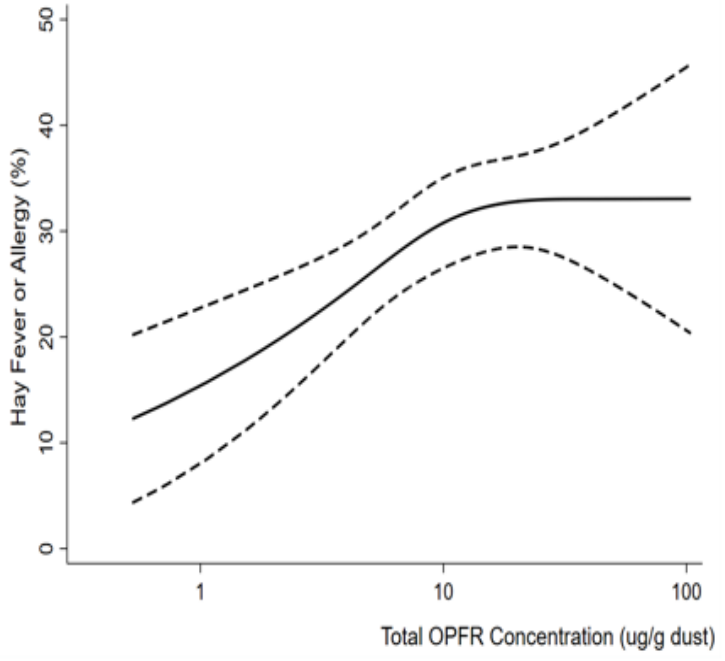
OR: 2.09, 95% CI: 1.37, 3.18) ***



OR: 4.85, 95% CI: 1.99, 11.88) *



OR: 1.36, 95% CI: 1.00, 1.84) *



Restricted cubic splines for associations of total OPFRs measured at age 1 with subsequent respiratory symptoms

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Preliminary data

Concentration of replacement flame retardants in house dust sampled at age 1 year and PEF at age 5

Association between ***exposure mixtures*** and outcomes

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Flame Retardants Mixtures

Rationale

- People simultaneously exposed to multitude toxicants
- Mixtures of flame-retardants common, since compounds often share same source
- In preliminary results, strong correlation between TBB and TBPH (Firemaster 550®)
- ***Often, co-exposures have toxicities not predictable by evaluating individual effects***

Approach: Bayesian Kernel Machine Regression (BKMR)

- Allows to flexibly evaluate exposure mixtures, ***allowing for nonlinear and non-additive effects and differential directions***
- ***Identifies importance of individual flame retardants*** to overall mixture by calculating their posterior inclusion probabilities (PIPs)

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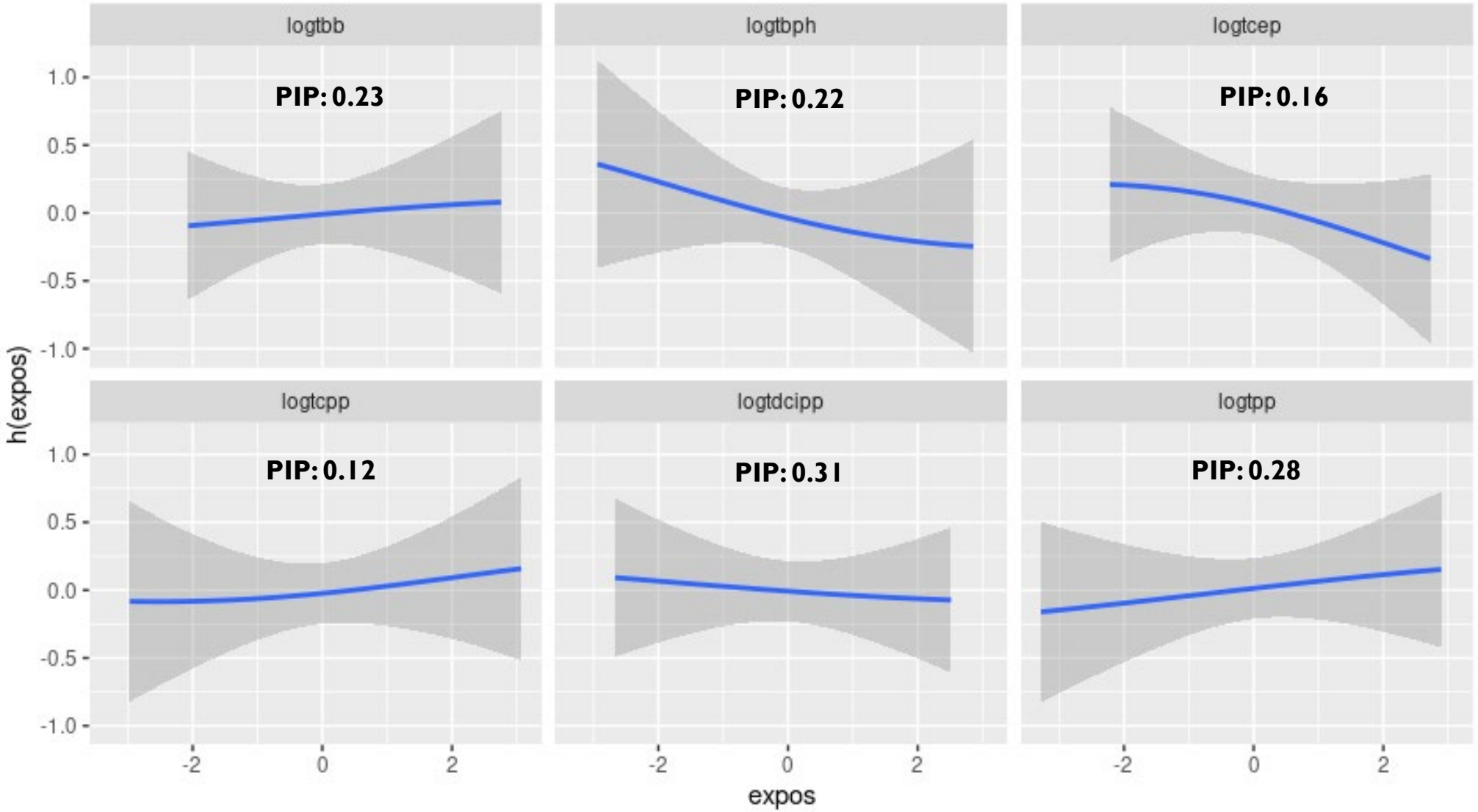

Dose-response relationships for each flame retardant and PEF when the other chemicals fixed at their median levels

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Summary of Findings

Single Exposure to flame retardants in house dust of at children age 1

- OPFRs associated with wheeze, respiratory infection, and hay fever/allergies
  - TCEP associated with respiratory infection and hay fever
    - Reported to cause ***oxidative stress*** and to be ***estrogenic*** in animal models (Sutha et al. *Comp Biochem Physiol C Toxicol Pharmacol*. 2022;254:109263)
  - TCIPP associated with wheeze
    - Reported to be ***antiandrogenic*** (Bello et al. *Environ Int*. 2018;113:55-65)
  - TDCIPP associated with wheeze and respiratory infection
    - Reported to be ***irritative & antiandrogenic*** (Bello et al. *Environ Int*. 2018;113:55-65)
- TBPH associated with wheeze
  - Found to be a ***estrogenic*** (Bello et al. *Environ Int*. 2018;113:55-65)

Exposure Mixtures

- TCEP & TBPH ***possibly*** associated with lower PEF within mixtures of flame retardants

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Future directions

- Determine association of OPFRs and RBFRs ***dust concentrations and loadings*** as well as ***urinary OPE*** with respiratory symptoms and impaired lung function (PEF and FEV1) for ***prenatal*** and ***early childhood repeated exposures***

- Identify ***windows of susceptibility*** in associations for single exposures (***multiple informant modeling***) and exposure mixtures (***lagged Kernel machine regression [LKMR]***)

- Identify ***epigenetic alterations mediating exposure-outcome associations***
  - Epigenome wide association Study (EWAS) for prenatal exposure and cord blood DNA methylation
  - Structural Equation Modeling (SEM) for mediation analysis
    - Identify CpGs and DMRs related to prenatal exposures are mediate association with adverse respiratory outcomes and to what extent

Acknowledgments

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Questions ?

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