Perinatal Exposure to Flame Retardant Chemicals and Impacts on Children's Growth and Development

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Flame Retardant Chemicals

Chemicals added to many consumer products to comply with fire safety regulations.

Use has increased dramatically over the last few decades.

Common classes of FRs:

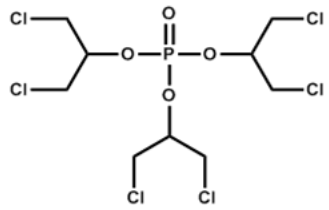
- Brominated flame retardants
  - Polybrominated diphenyl ethers (PBDEs)
  - 2,3,4,5-tetrabromo-ethylhexylbenzoate (TBB)
- Organophosphate flame retardants
  - Tris(1,3-dichloro-2-propyl)phosphate (TDCIPP)
  - Triphenyl phosphate (TPHP)

Types of Products Treated with FRs

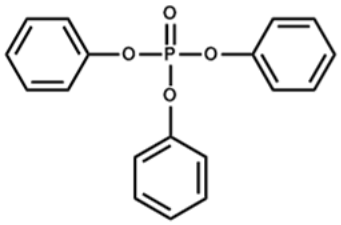




Organophosphate Flame Retardants (PFRs)



tris(1,3-dichloro-2-propyl) phosphate (TDCIPP)



triphenyl phosphate (TPHP)

- Like many flame retardants, PFRs migrate out of products over time.
- PFRs are commonly detected in dust and air samples from homes, office, schools and cars.
- Human exposure is widespread, as evidenced by urinary metabolite concentrations.

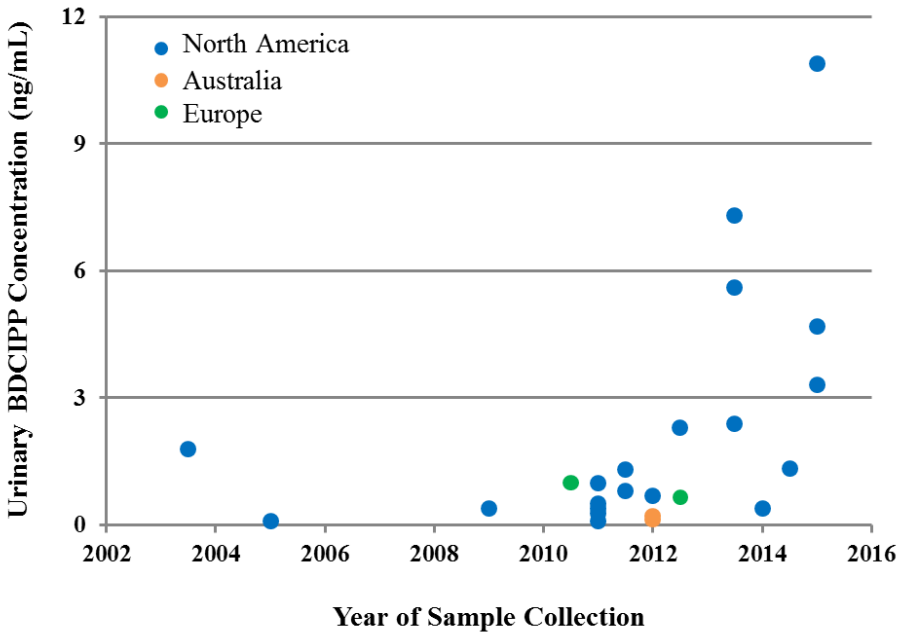
PFR Metabolites

Parent Compound		Urinary Metabolite
Tris(1,3-dichloro-2-propyl) phosphate **TDCIPP**	→	**BDCIPP**
Triphenyl phosphate **TPHP**	→	**DPHP**
Isopropylated triaryl phosphates **ITPs**	→	**ip-PPP**

Human PFR Exposure

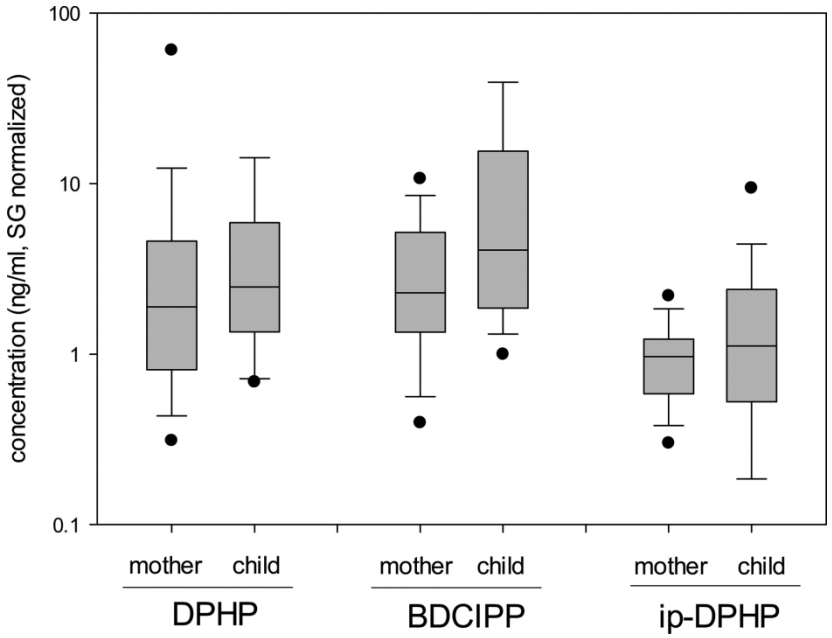
- PFR metabolites are detected in >90% of urine samples provided by the general population.
- Levels tend to be higher in samples from children, particularly infants.
- Levels of some PFRs appear to be increasing over time, reflecting potential increases in exposure.
  - BDCIPP increased 16X 2002-2015

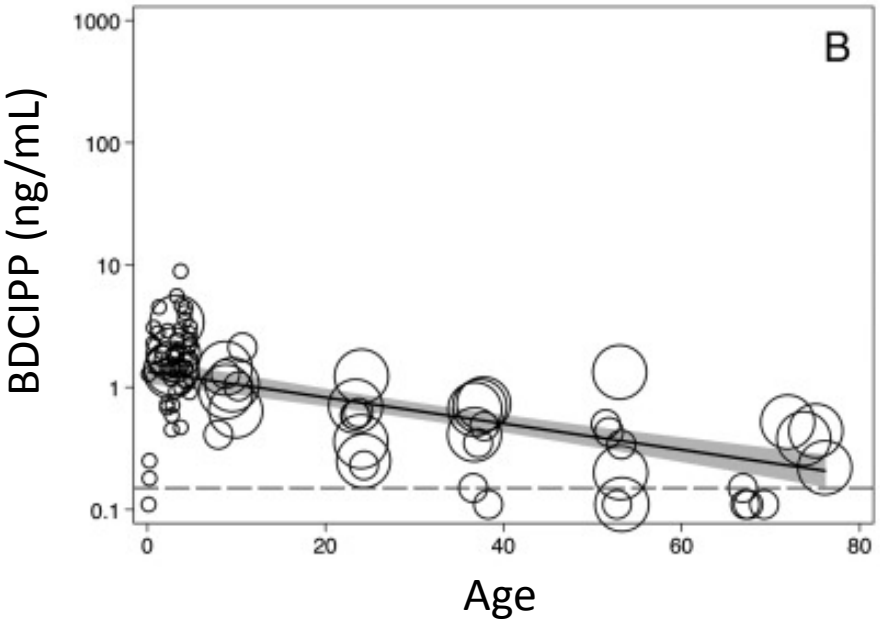
Published geometric mean (or median) BDCIPP concentration from 21 cohorts



Butt, 2014; Butt, 2016; Carignan, 2013; Carignan, 2016; Cequier, 2015; Cooper, 2011; Dodson, 2014; Fromme, 2014; Hammel, 2016; Hoffman, 2015a, 2017, 2014, 2015b, Kosarac, 2016; Meeker, 2013; Mendelsohn 2016; Preston, 2017; Soubry, 2017; Su, 2015; Van den Eede, 2013; Van den Eede, 2015.

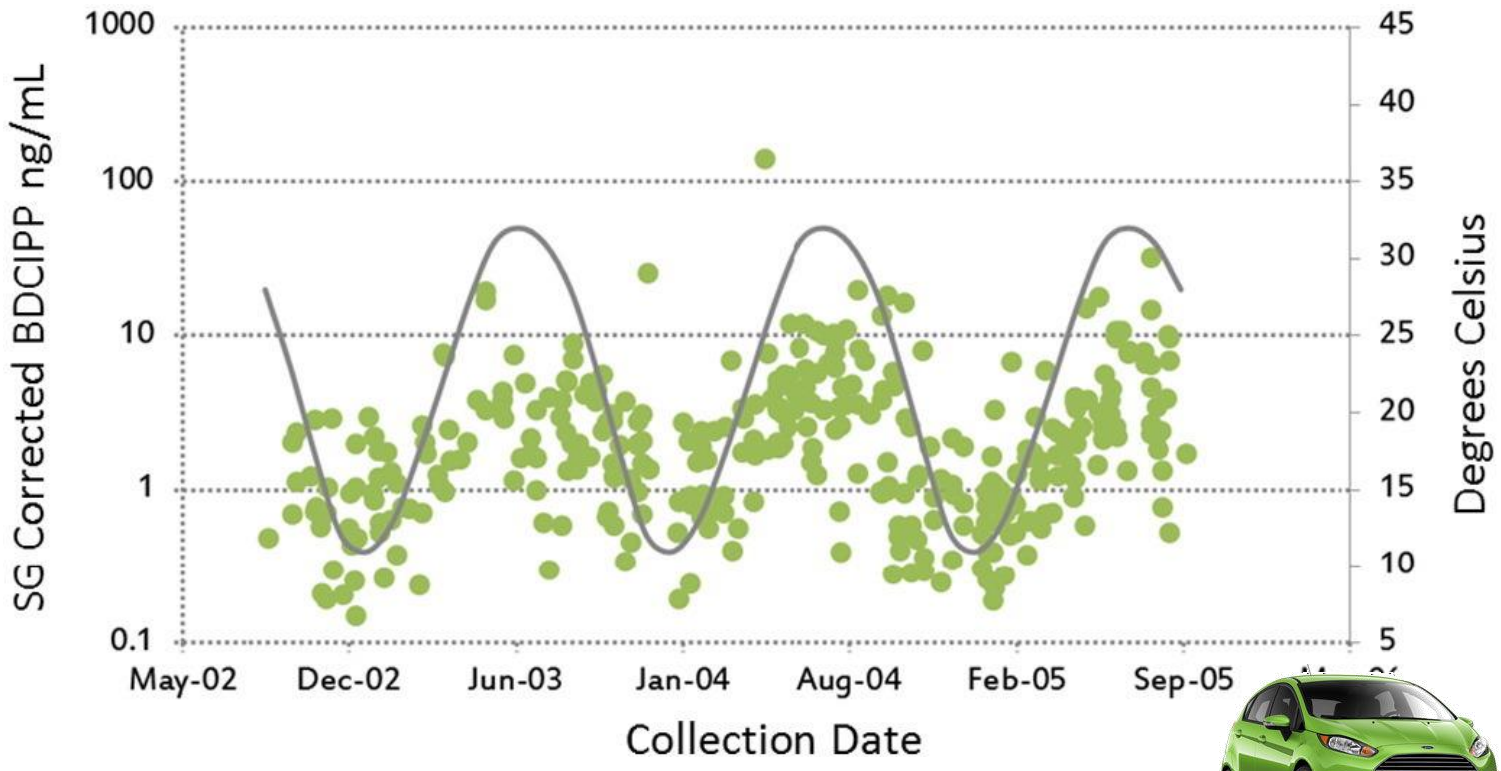
PFR metabolite levels decrease with age.





Van den Eede et al., 2015; Butt et al., 2014

Urinary metabolite levels of several PFRs are higher in the summer.



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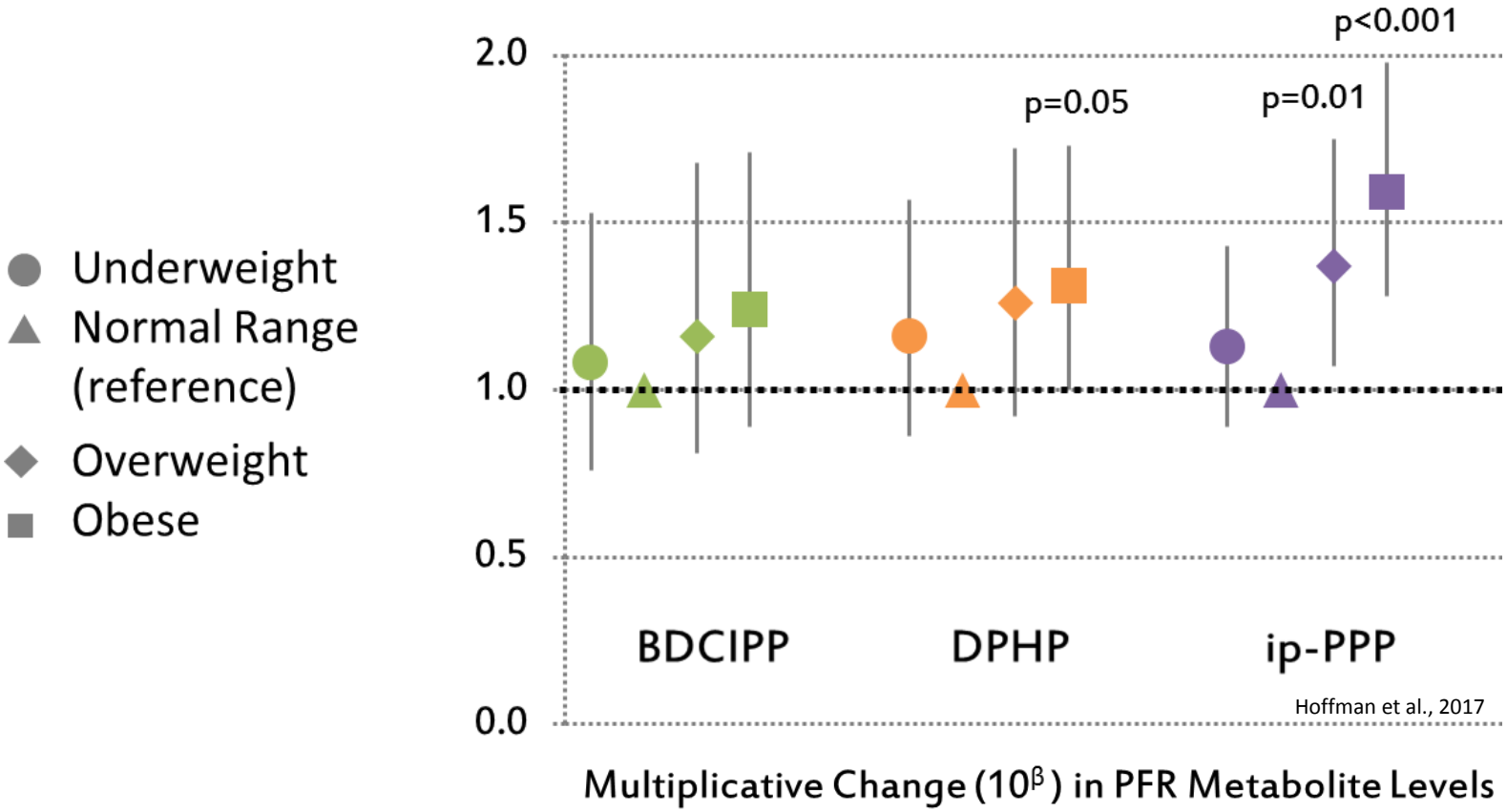
Hoffman et al., 2017

PFR metabolite levels tend to be higher for overweight and obese individuals.



Health Impacts of PFR Exposure

- Some PFRs are considered probable human carcinogens (e.g. TDCIPP under CA Prop 65).
- Data suggest that PFR exposure could impact endocrine function.
  - Higher levels of TDCIPP in dust associated with lower levels of T_4 in men and adverse reproductive endpoints
  - Higher urinary DPHP associated with higher TT_4 among men and women

Meeker et al. 2010; Preston et al. 2017

Health Impacts of PFR Exposure (Snap Shot)

Animals

- PFR exposure has been associated with thyroid hormone levels in a number of species
  - Zebrafish: reduced T_3 and T_4
  - Chicken embryos: reduced T_4
  - Rats: no change in T_3 or T_4

- Fetal growth
  - Chicken embryos: decreased in weight at hatching
  - Rodents: lower pup weights following prenatal exposure

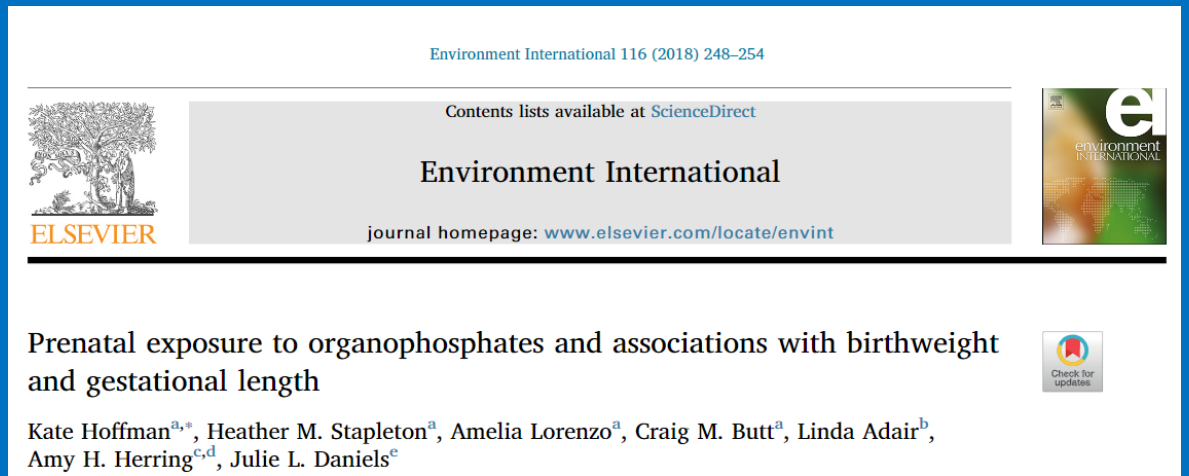
- Postnatal growth
  - Rats: perinatal Firemaster® 550 exposure associated with later obesity

Wang et al., 2013; Wang et al., 2015; Farhat et al., 2013; Fernie et al., 2015; Moser et al., 2015; Farhat et al. 2013; NRC, 2000; Patisaul et al. 2013.

Animal data suggest that exposure to PFRs could impact growth, particularly during early life.

Based on these data, we hypothesize that prenatal PFR exposure could alter fetal growth and impact the risk for obesity in early childhood.

Additionally, we hypothesize that prenatal PFRs could alter gestational duration and the risk of preterm birth.



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Prenatal exposure to organophosphates and associations with birthweight and gestational length

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Low Birthweight (LBW) and Preterm Birth (PTB)

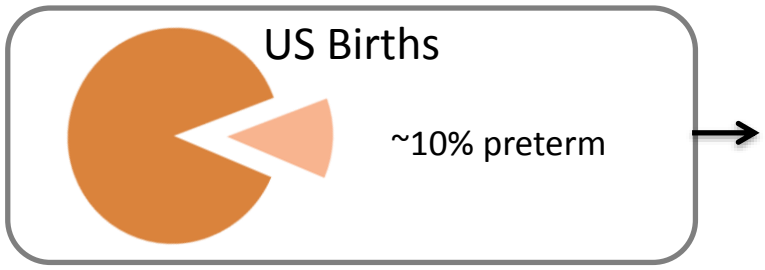
A baby is born weighing less than 5.5 pounds is considered “low birthweight”.

~1 in 12 US babies is born with LBW.

Proximal causes include preterm birth and fetal growth restriction.

A preterm birth is a birth that happens too early, before 37 weeks of pregnancy.

15 million PTBs per year
1 million deaths related to PTB



Estimated cost: $26.2 billion per year (2005)

$16.9 billion in medical and health care costs for the baby
$1.9 billion in labor and delivery costs for mom

(Institute of Medicine 2007; March of Dimes 2015)

Pregnancy Infection and Nutrition Study (PIN)

Pregnant NC Women

- 2002 to 2005
- Recruited from UNC prenatal care clinics
- Provided a urine sample (~27 weeks gestation)
- Completed demographic surveys
- Birth outcomes recorded in medical records
- Follow-up through age 3, including measurements of height and weight

Study Population Characteristics (n=349)

- Age range: 17-46 years
- Highly educated cohort
  ~70% had graduated from college before pregnancy
- Little racial or ethnic diversity among participants
  ~80% white

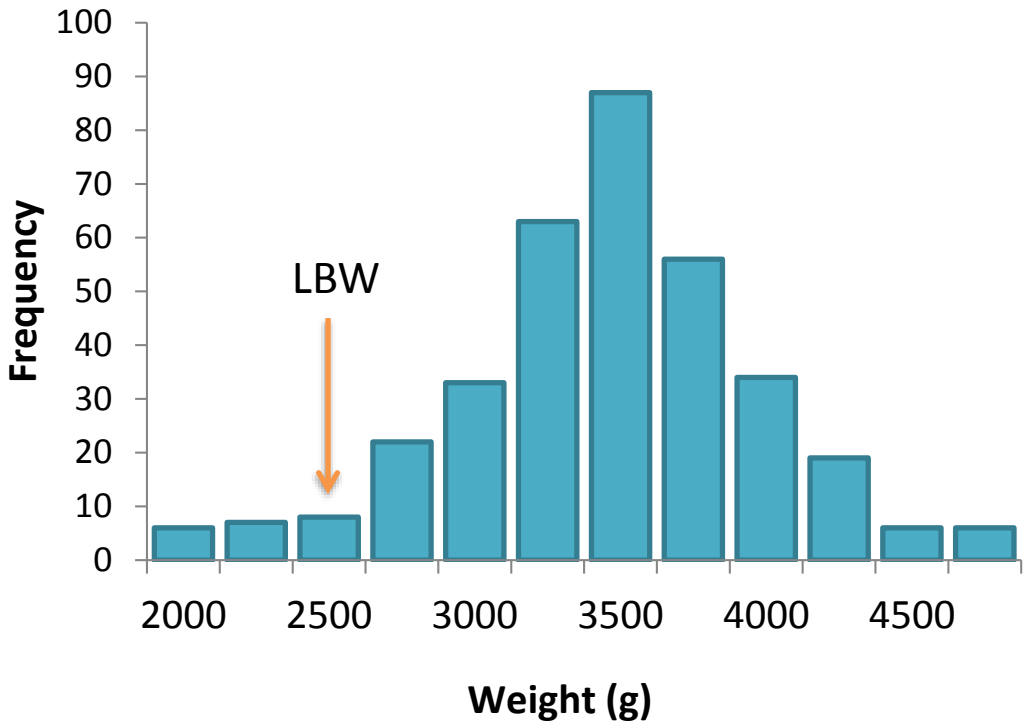
Age	N	%
≤25	76	21.8
26-30	126	36.1
31-35	107	30.7
≥36	40	11.5
Education (years)		
≤15	106	30.4
≥16	243	69.6
Parity		
0	166	47.6
≥1	183	52.4
Pre-pregnancy BMI		
Underweight	46	13.2
Normal range	194	55.6
Overweight	42	12.0
Obese	67	19.2

Urinary PFR Metabolite Levels (ng/mL)

Metabolite	% Detect	GM[a]	Maximum
BDCIPP	93	1.8	140
DPHP	84	1.4	112
ip-PPP	99	6.8	69

[a] GM: geometric mean

Birthweight (n=347)



- All children in the sample were born between 1400 and 4800 g.
- Mean BW = 3326 g (7.25 pounds)
- 23 infants were born with low birthweight (6.9%).

PFR Exposure and Birthweight

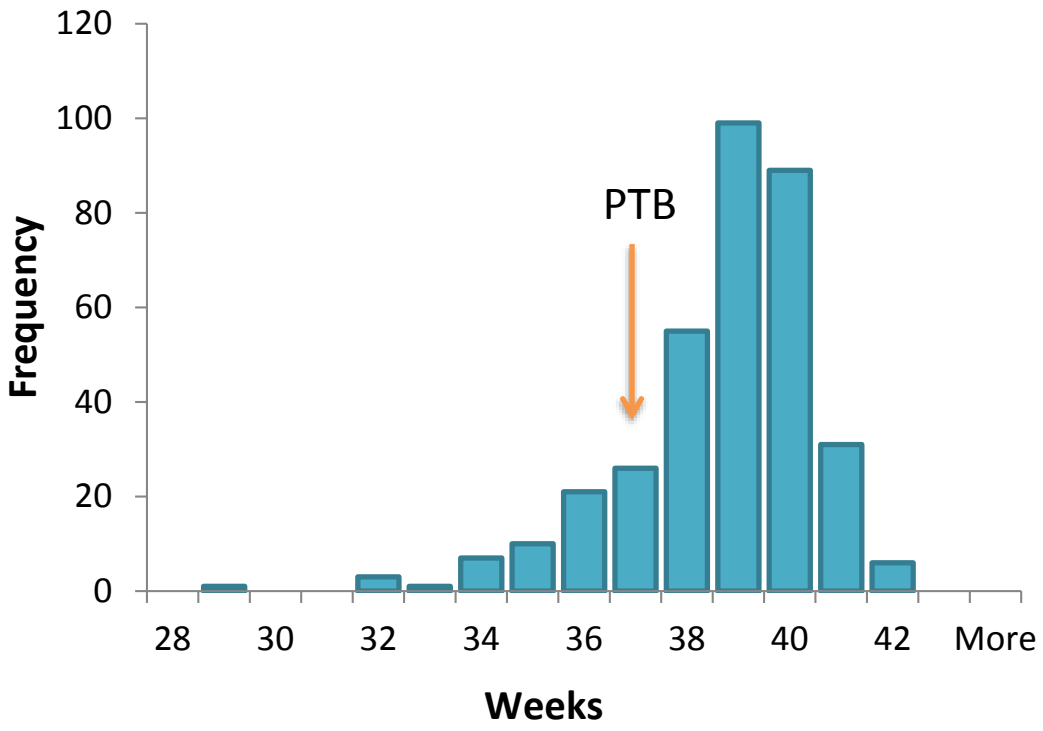
Baby girls with the highest levels of prenatal exposure to **ip-PPP** were born an average of **331 g smaller** than baby girls with the lowest levels of exposure.

Given the limited number of LBW infants, we did not evaluate exposure and dichotomous birthweight.

		Female Infants	Male Infants
PFR Metabolite		Mean Difference (g) (95% CI)	Mean Difference (g) (95% CI)
BDCIPP	Q1	Reference	Reference
	Q2	119 (-121, 359)	-127 (-356, 102)
	Q3	-13 (-274, 249)	-73 (-311, 166)
	Q4	51 (-224, 326)	-66 (-318, 186)
DPHP	Q1	Reference	Reference
	Q2	-88 (-343, 166)	44 (-174, 262)
	Q3	-93 (-346, 161)	89 (-122, 300)
	Q4	-159 (-414, 95)	117 (-107, 341)
ip-PPP	Q1	Reference	Reference
	Q2	-71 (-325, 183)	-100 (-314, 113)
	Q3	-248 (-495, -2)	44 (-173, 261)
	Q4	-331 (-587, -75)	21 (-211, 252)

Adjusted for maternal age, education, parity, race, pre-pregnancy BMI and season.

Gestational Age (n=349)



- All children in the study were born between 29 and 42 weeks.
- Mean GA = 39 weeks
- 43 infants were born preterm (12.3%).

Odds Ratios for Preterm Birth in the High Exposure Group

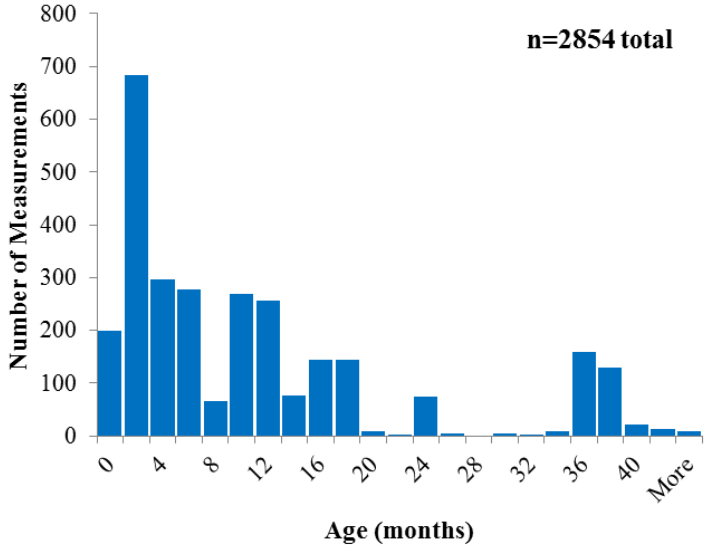
Baby girls with the highest levels of prenatal exposure to **ip-PPP** and **BDCIPP** were **4 times** as likely to be PTBs.

Baby boys with the highest levels of **ip-PPP** exposure were **0.2 times** as likely to be PTBs.

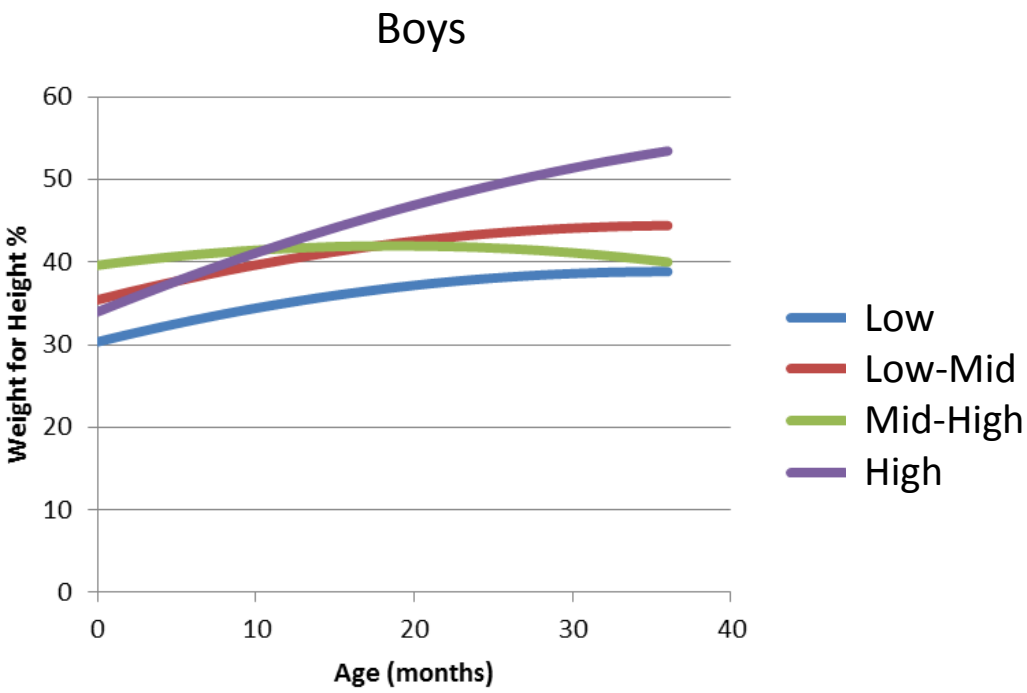
	Females	Males
	OR (95% CI)	OR (95% CI)
BDCIPP	3.99 (1.08, 14.8)	0.76 (0.25, 2.32)
DPHP	1.11 (0.37, 3.35)	0.46 (0.17, 1.25)
ip-PPP	4.58 (1.23, 17.1)	0.21 (0.06, 0.68)

Do the impacts of prenatal PFR exposure persist into early childhood?

- Children's height and weight were recorded at every well-baby doctor's visit from birth through age 36 months.
- Age and sex specific BMI percentiles were calculated.



Do the impacts of prenatal PFR exposure persist in early childhood?



Boys with higher levels of prenatal ip-PPP exposure appear to grow more rapidly and become bigger than their peers by age 2-3 years.

Girls appear to catch up with their peers, but their weights are not significantly different at age 1-3 years.

Are early-life exposures more important in children's growth?

Environmental Science & Technology

Article

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High Exposure to Organophosphate Flame Retardants in Infants: Associations with Baby Products

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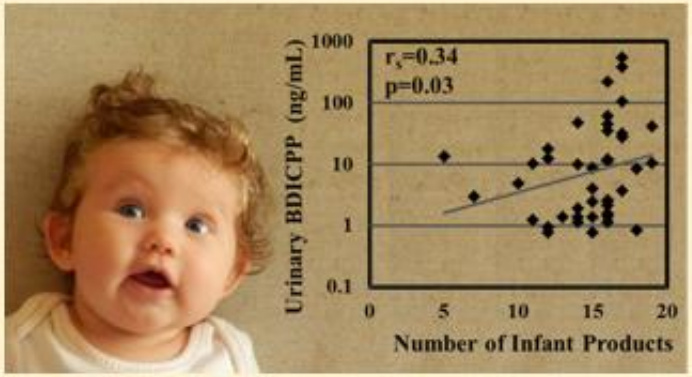
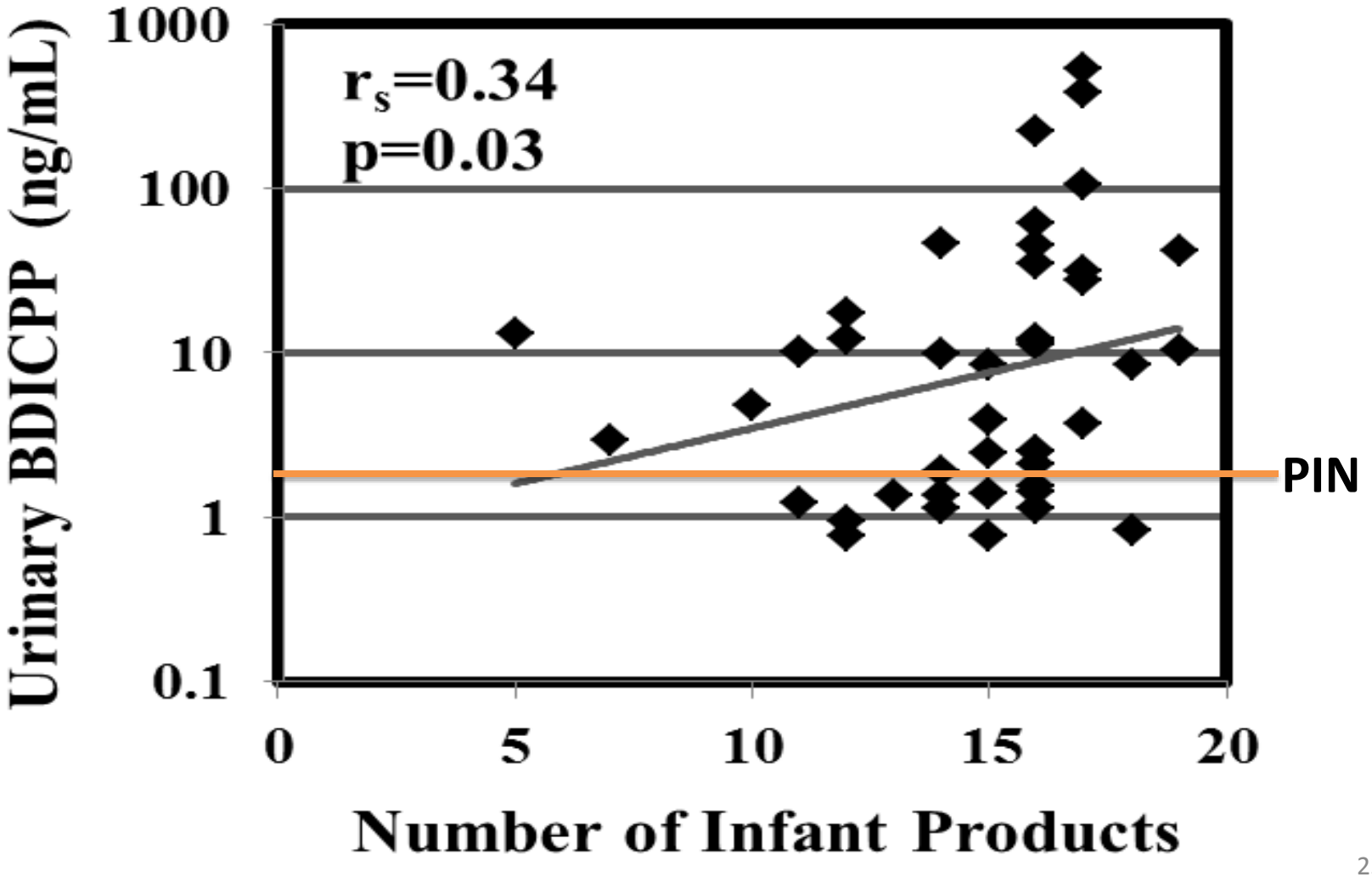
ABSTRACT: Infant products containing polyurethane foam are commonly treated with organophosphate flame retardants (PFRs), including tris(1,3-dichloro-2-propyl)phosphate (TDCIPP) and triphenyl phosphate (TPHP). Infants may have greater exposure due to greater contact with these products, yet little is known about levels of exposure or the factors contributing to higher exposure. We recruited children age 2–18 months from North Carolina to investigate PFR exposure (n = 43; recruited 2014–2015). Parents provided information on potential sources and modifiers of exposure, and reported whether they owned common infant products. We measured five PFR metabolites in urine samples collected



Are early-life exposures more important in children's growth?



Toddler's Exposure to Semi-volatile Chemicals in the Indoor Environment

- Children of mothers participating in the Newborn Epigenetic STudy (NEST), a NC pregnancy cohort
- Children were age 3-6 years at the time of TESIE enrollment
- Children's height and weight were measured
- Children provided 3 urine samples over a 48 hour period which were pooled for the measurement of FR metabolites.

PFRs and BMI Percentile

PFR	Mean Difference	95% CI	p-value
ip-PPP Low	Reference	---	---
ip-PPP Mid	2.13	-10.30, 14.55	0.74
ip-PPP High	14.79	2.21, 27.37	0.02

Children with higher levels of urinary ip-PPP had BMI percentiles that were **14% higher** on average than those with the lowest levels of exposure.

The direction of association is unclear, but these results could suggest that early childhood exposure to ITPs is associated with increased BMI.

Other PFRs = no association

Conclusions

- Exposure to PFRs is common and variable.
- A limited number of factors associated with increased levels of exposure have been identified.
- Prenatal exposure has been linked to lower birthweight in animals.
- Prenatal BDCIPP and ip-PPP may be associated with shorter gestation among girls. DPHP and ip-PPP may increase gestation duration in boys.
- The long-term impacts of perinatal exposure remain unclear, but data suggest that early childhood exposures are correlated with children's BMI.

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