What Have We Observed About the Effects of Xenoestrogens on the Development of Childhood and Adult Asthma and Allergy?

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Butylbenzyl phthalate (BBzP)  Bisphenol A (BPA)

- High production chemicals
- Endocrine disruptor chemicals (EDCs); anti-androgens
- Phthalates:
  - plastics, household and automotive materials, cosmetics, personal care products, medical supplies, & food packaging
- BPA:
  - manufacture of polycarbonate plastic and epoxy resins
  - toys, dental sealants, water pipes, food, beverage containers and cans
Phthalates associated with eczema and asthma (Cross-sectional studies)

Vinyl flooring → bronchial obstruction in children
Vinyl flooring → incident asthma in children
BBzP in dust → eczema in children
DEHP in dust → asthma in children
MEP in urine → reduced FEV\textsubscript{1} (male adults)
MnBP in urine → reduced FEV\textsubscript{1} (male adults)

Jaakkola  AJPH 1999
Hoppin  EHP 2004
Bornehag EHP 2004
Just  EHP 2012
Hypothesis

• Prenatal BBzP would be associated with increased risk of eczema and elevated indoor allergen specific and total IgE.
Columbia Center for Children’s Environmental Health (CCCEH) cohort

<table>
<thead>
<tr>
<th>Exposure Assessment</th>
<th>Biomarkers of Exposure/Effect/Susceptibility</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>PAH metabolites</td>
<td>Asthma</td>
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<tr>
<td>Questionnaire</td>
<td>PAH-DNA adducts</td>
<td>Allergic sensitization</td>
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<tr>
<td>GIS</td>
<td>Cotinine</td>
<td>Eczema, rhinitis, cough</td>
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<td></td>
<td>Pesticides</td>
<td>Obesity</td>
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<tr>
<td></td>
<td>Phthalate metabolbs</td>
<td>Growth &amp; neurobehavioral development</td>
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<tr>
<td></td>
<td>BPA</td>
<td>Cancer risk</td>
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<tr>
<td></td>
<td>IgE, cytokines</td>
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<td></td>
<td>T cell proliferation</td>
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<td></td>
<td>Genetic polymorphisms</td>
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<td></td>
<td>Chromosomal aberrations</td>
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<td></td>
<td>DNA methylation</td>
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</tbody>
</table>

Pregnancy through childhood: Repeat measures on women and children
N=727 Dominican and African American women
Est 1998
Approach (eczema)

- Prenatal urinary phthalate metabolites (3rd trimester)
- Questionnaire child age 3-60 months: “has your doctor ever said that your child has eczema?”
- Early eczema: First report on any questionnaire through 24 mo
- Late onset eczema: First report of eczema btw 24-60 mo
- Total, allergen-specific IgE level by Immunocap
Results

• MBzP was measured in urine during third trimester of pregnancy from >99% 
  (Geometric mean = 13.6; interquartile range 5.7-31.1 ng/ml)

• By 24 month, 30% of children developed eczema, with proportion higher among African Americans (48%) than Dominicans (21%)
MBzP concentration was associated with early onset eczema

\[ n = 376 \]
Hypothesis

- Phthalate metabolites of DEHP, DEP, and DnBP, BBzP, measured prenatally would be associated with current asthma.

Metabolites:
MEHHP, MEP, MnBP, MzBP
Approach

• CCCEH mothers and their children ages 5-11 yrs
• Urinary phthalate metabolites: 3rd trimester; child age 3, 5, and 7 years
• Repeated respiratory questionnaire ages 5-11 yrs
• Referred for physician evaluation for asthma if any report of child wheeze, a cough ≥ 1 week, other breathing problems, and/or any report of asthma rescue or controller med use
• Standardized diagnosis of current asthma using pre-specified criteria of children
Results

- History of asthma-like symptoms
  n=157 (54%)
- Diagnosis: current asthma
  n= 93 (32%)
- Diagnosis: not current asthma: AHR?
  n= 64 (22%)
- No history of asthma-like symptoms (non-asthmatic)
  n=134 (46%)
Prenatal phthalate metabolites were associated with child wheeze, respiratory symptoms, and/or use of asthma medications.

On repeat questionnaires administered between child ages 5-11 years; n=267

Whyatt, 2014, submitted

*p<0.05
Prenatal phthalate metabolite concentrations were associated with current asthma.

On standardized MD evaluation for current asthma between child ages 5-11 years; n=211.

*\(p<0.05\)
Association between FeNO and urinary concentrations of three phthalate metabolites

Concentration of FeNO

$\text{Concentration of FeNO, ppb}$

$n=373$ observations from 280 children

- MEP
- MnBP
- MBzP
MBzP and FeNO association stronger among kids who wheeze

Interaction p-value = 0.038
BPA

• Mouse models suggest exposure to BPA may increase allergic inflammation.

• Hypothesis: BPA exposure, assessed from urinary BPA concentrations, would be associated with increased odds of wheeze, asthma, IgE in children.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prenatal</th>
<th>3 years</th>
<th>5 years</th>
<th>7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze 5</td>
<td>0.7</td>
<td>1.4</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.5-0.9)</td>
<td>(1.1-1.8)</td>
<td>(0.9-1.7)</td>
<td></td>
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<tr>
<td>Wheeze 6</td>
<td>0.8</td>
<td>1.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.5-1.3)</td>
<td>(1.0-1.9)</td>
<td>(0.6-1.1)</td>
<td></td>
</tr>
<tr>
<td>Wheeze 7</td>
<td>0.8</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>(0.5-1.2)</td>
<td>(0.8-1.5)</td>
<td>(0.9-1.6)</td>
<td>(1.0-1.9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.8</td>
<td>1.5</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(0.5-1.1)</td>
<td>(1.1-2.0)</td>
<td>(1.0-1.9)</td>
<td>(1.0-2.1)</td>
</tr>
</tbody>
</table>

Odds Ratio (95% CI)
But not IgE

<table>
<thead>
<tr>
<th>Urinary BPA</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>(0.8 to 1.6)</td>
</tr>
<tr>
<td>Age 3 Years</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>(0.9 to 1.6)</td>
</tr>
<tr>
<td>Age 5 Years</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(0.7 to 1.2)</td>
</tr>
<tr>
<td>Age 7 Years</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(0.8 to 1.4)</td>
</tr>
</tbody>
</table>
‘Two hit paradigm’ for asthma?

- Sequential high exposures to multiple toxins (allergens, endotoxin, viruses, pollution, cig smoke) have been implicated in the development of asthma.

- ‘Multiple-hit hypothesis’ apply to chemical exposures?

- Hypothesis: BPA and MBzP may act synergistically to increase asthma risk.
Interaction between prenatal phthalate and postnatal BPA on risk of child asthma

by strata of the other chemical (above and below median)
n=211
*p<0.05, ***p<0.001
And risk of persistent wheeze and emergency care visits

A. Prenatal MBzP predicting persistent wheeze

B. Postnatal BPA predicting persistent wheeze

A. Prenatal MBzP predicting emergency care visits

B. Postnatal BPA predicting emergency care visits
Conclusion

- Eczema (nonatopic) by age 2 yr 52% more likely following prenatal exposure to BBzP
  - Mechanisms: IL-31, IL-8, PPAR $\gamma$

- Prenatal MBzP concentrations were associated with childhood asthma and maybe airway hyperreactivity
  - Mechanisms: Th2 adjuvant, epigenetic, hormonal
Conclusion

• Higher prenatal exposures to MBzP may render the child more susceptible to the effects of early childhood exposure to BPA in a novel ‘two-hit model’ of childhood asthma.
  – Mechanisms: hormonal or epigenetic regulation
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Any questions?