Pesticides, Chemicals, and Other Exposures Matter in Allergic Disorders

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We need to think about pesticides?
Pervasive use of pesticides—still

- Phase-out of organophosphates in US homes led to increased pyrethroid insecticides use, esp in residential settings for pest control

- Permethrin is most frequently detected pesticide in residential floor wipe samples

- Piperonyl butoxide (PBO) used as a synergist and is more volatile than permethrin
  - Better indicator of any pyrethroid exposure?
Potential health impact on children from long-term residential pyrethroid not understood

- Exposure to permethrin in occupational/agricultural settings associated with asthma and wheeze in farmers

- Little data available using airborne pyrethroid measures (vs surrogates like questionnaire)

Hoppin AJRCCM 2002, 20082
Salam EHP 2004
Heudorf and Angerer EHP 2001
Lu EHP 2006
Pyrethroids and childhood cough

• Airborne concentrations of cis-permethrin, but not trans-permethrin, measured during pregnancy was associated with cough by age 5.*

• New hypothesis: Prenatal and age 5-6 year measures of PBO and permethrins would be associated with cough at age 5-6 years.
  – Explore the associations between these pesticides measures and wheeze, asthma, seroatopy, and FeNO.

• Approach: PBO and permethrins measured in personal air during third trimester of pregnancy and indoor residential air at ages 5-6 years

*Reardon, JACI, 2009
<table>
<thead>
<tr>
<th>Exposure Assessment</th>
<th>Biomarkers of Exposure/Effect/Susceptibility</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Monitoring</td>
<td>PAH metabolites</td>
<td>Asthma</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>PAH-DNA adducts</td>
<td>Allergic sensitization</td>
</tr>
<tr>
<td>GIS</td>
<td>Cotinine</td>
<td>Eczema, rhinitis, cough</td>
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<tr>
<td></td>
<td>Pesticides</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Phthalate metabas</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>
<td></td>
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<tr>
<td></td>
<td>T cell proliferation</td>
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<td></td>
<td>SNPs</td>
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<tr>
<td></td>
<td>Chromosomal aberrations</td>
<td></td>
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<tr>
<td></td>
<td>DNA methylation</td>
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</tr>
</tbody>
</table>

Pregnancy through childhood: Repeat measures on women and children
N=727 Dominican and African American women
Est 1998
Prenatal PBO, but not permethrin, was associated with cough

![Graph showing ORs and 95% CI for cough, asthma, and wheeze over different periods and exposures.](image)

N=224

Liu Environment International 2012
Other household chemicals?
Butylbenzyl phthalate (BBzP)  

- High production chemicals
- Endocrine disruptor chemicals (EDCs); anti-androgens
- Phthalates:
  - plastics, household and automotive materials, cosmetics, personal care products, medical supplies, & food packaging

Bisphenol A (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$_1$ (male adults)
- MnBP in urine → reduced FEV$_1$ (male adults)

Jaakkola AJPH 1999
Hoppin EHP 2004
Bornehag EHP 2004
Just EHP 2012
Hypothesis (eczema)

- Prenatal BBzP would be associated with increased risk of eczema and elevated indoor allergen specific and total IgE.
Approach

• 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 (eczema)

- MBzP was measured in urine during third trimester of pregnancy >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 (asthma)

- 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
- Physician evaluation for asthma if any report of child wheeze, a cough ≥ 1 week, other breathing problems, and/or any report of asthma 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, other respiratory symptoms, and/or use of asthma medications.

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

Whyatt 2014, submitted
Prenatal phthalate metabolites were associated with current asthma

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

* \( p < 0.05 \)

Whyatt, submitted

Whyatt 2014, submitted
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 and asthma and increased FeNO in children.
Urinary BPA associated with asthma & wheeze

<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 (0.5-0.9)</td>
<td>1.4 (1.1-1.8)</td>
<td>1.3 (0.9-1.7)</td>
<td></td>
</tr>
<tr>
<td>Wheeze 6</td>
<td>0.8 (0.5-1.3)</td>
<td>1.4 (1.0-1.9)</td>
<td>0.8 (0.6-1.1)</td>
<td></td>
</tr>
<tr>
<td>Wheeze 7</td>
<td>0.8 (0.5-1.2)</td>
<td>1.2 (0.8-1.5)</td>
<td>1.2 (0.9-1.6)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.8 (0.5-1.1)</td>
<td>1.5 (1.1-2.0)</td>
<td>1.4 (1.0-1.9)</td>
<td>1.5 (1.0-2.1)</td>
</tr>
</tbody>
</table>

Odds Ratio (95% CI)
‘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

**Relative Risk of Asthma (95% CI)**

A. Prenatal MBzP predicting asthma  
B. Postnatal BPA predicting asthma

**Interaction p=0.007**  
**Interaction p=0.015**

Higher BPA  
Lower BPA

Higher MBzP  
Lower MBzP

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

• Prenatal PBO was associated with cough at age 5-6 years

• Eczema (nonatopic) by age 2 yr 52% more likely following prenatal exposure to BBzP
  – Mechanisms: IL-31, IL-8, PPAR γ
Conclusion

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

• 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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