Characterizing novel industrial chemical exposures during critical periods of development

Opportunities within the Environmental influences on Child Health Outcomes (ECHO) Program

Jessie P. Buckley, PhD, MPH
Assistant Professor, Environmental Health and Engineering & Epidemiology
Johns Hopkins University Bloomberg School of Public Health

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CHE Partnership Webinar
Critical periods of development

Santrock, 2009; pg. 74
Transgenerational propagation of health disparities

GESTATIONAL EXPOSURE

EXPOSURE → Mother (F₀)
Fetus (F₁)
Germ cells (F₂)

Health effects reported in the F₂ generation that was not directly exposed (transgenerational)

Health status

Better
Low exposure/vulnerability
High exposure/vulnerability

Worse

Disparities in exposure
Social vulnerability
Biological susceptibility

Source: NAP 2018. Gulf War and Health: Volume 11, Figure 3-3
Transgenerational propagation of health disparities

Source: NAP 2018. Gulf War and Health: Volume 11, Figure 3-3

Transgenerational exposure:
- **Mother** (F₀)
- **Fetus** (F₁)
- **Germ cells** (F₂)

Health effects reported in the F₂ generation that was not directly exposed (transgenerational)

Health status:
- Better
- Worse

Time

Low exposure/vulnerability
- Ongoing high exposure/vulnerability
- High exposure/vulnerability

Source: NAP 2018. Gulf War and Health: Volume 11, Figure 3-3
Chemicals are found in virtually all U.S. pregnant women

Pregnant women (n = 54; each vertical bar is one study participant)

No. of chemicals detected (out of 52 chemicals)

- Cotinine
- Metals
- OC pesticides
- PBDEs
- PAHs
- Phthalates

Woodruff et al. EHP 2011
Key Gap

➢ Only a fraction of chemicals have been measured in pregnant women or children

~350 chemicals biomonitorered in the U.S.

>40,000 chemicals approved for use in the U.S. (~8,000 high production volume)

>9.5 Trillion pounds of chemicals per year in the U.S. (~30,000 lbs/person)
Environmental influences on Child Health Outcomes (ECHO) Program

>55,000 children from 71 longitudinal cohorts across the US

Children’s race/ethnicity
- 45% Non-Hispanic White
- 25% Hispanic
- 13% Non-Hispanic Black
- 11% Non-Hispanic Other Race
- 6% Unknown/not reported/other
OBJECTIVE

Identify novel chemicals of importance to children’s health

- Pre-, peri- and postnatal
- Upper and lower airway
- Obesity
- Neuro-development
Identifying and prioritizing candidate chemicals

Review

Identifying and Prioritizing Chemicals with Uncertain Burden of Exposure: Opportunities for Biomonitoring and Health-Related Research

Edo D. Pellizzari, Tracey J. Woodruff, Rebecca R. Boyles, Kurunthachalam Kannan, Paloma I. Beamer, Jessie P. Buckley, Aolin Wang, Yeyi Zhu, and Deborah H. Bennett (Environmental influences on Child Health Outcomes)

1Fellow Program, RTI International, Research Triangle Park, North Carolina, USA
2Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, San Francisco, California, USA
3Biostatistics and Data Science, RTI International, Research Triangle Park, North Carolina, USA
4Wadsworth Center, New York State Department of Health, Albany, New York, USA
5Department of Community, Environment and Policy, Zuckerman College of Public Health, University of Arizona, Tucson, Arizona, USA
6Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA
7Northern California Division of Research, Kaiser Permanente, Oakland, California, USA
8Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA
9Department of Public Health Sciences, University of California, Davis, Davis, California, USA

BACKGROUND: The National Institutes of Health’s Environmental influences on Child Health Outcomes (ECHO) initiative aims to understand the impact of environmental factors on childhood disease. Over 40,000 chemicals are approved for commercial use. The challenge is to prioritize chemicals for biomonitoring that may present health risk concerns.

OBJECTIVES: Our aim was to prioritize chemicals that may elicit child health effects of interest to ECHO but that have not been biomonitored nationwide and to identify gaps needing additional research.

METHODS: We searched databases and the literature for chemicals in environmental media and in consumer products that were potentially toxic. We selected chemicals that were not measured in the National Health and Nutrition Examination Survey. From over 700 chemicals, we chose 155 chemicals and created eight chemical panels. For each chemical, we compiled biomonitoring and toxicity data, U.S. Environmental Protection Agency exposure predictions, and annual production usage. We also applied predictive modeling to estimate toxicity. Using these data, we recommended
Conducted a rigorous review of extant data to prioritize 155 chemicals in 8 classes

Chemical Classes
- Alternate flame retardants
- Alternative plasticizers
- Aromatic amines
- Environmental phenols
- Organophosphorus flame retardants
- Perfluoroalkyl substances
- Pesticides
- Quaternary ammonium compounds

USDA, FDA, EPA, NHANES Databases and literature
Drinking water, air, house dust, food, biofluids
Selected 45 Consumer Product Categories
EPA CPCat Database: 372 Product Categories; ~170K chemicals

- Chemicals Quantifiable in ≥20% of Samples
- Duplicates Removed
- Excluded inorganics

Group I: Measured in NHANES
Group II: Legacy chemicals
Group III: Measured in environmental media
Group IV: EPA predicted exposure
Group V: No EPA predicted exposure, sparse environmental media data

Conducted a rigorous review of extant data to prioritize 155 chemicals in 8 classes

Group I, Measured Nation-wide (NHANES)
Group II, legacy chemicals

Sorted into Chemical Groups I-V

GII (260), GIV (280), GV (219)
Total chemicals (759)

Remaining Chemicals (604)

Selected 155 Chemicals — Created 8 Panels: AFRs (23), APs (10), AAs (28), EPs (16), OFPRs (11), PFASs (8), PEs (43), QACs (16)

Chemical Prioritized as:
- recommended for biomonitoring
- deferred, insufficient data, or
- low priority for biomonitoring
Criteria for recommending chemical biomonitoring in ECHO

- Present in human biospecimens or environmental media?
  - Yes
  - Toxicity concern?
    - Yes
      - Available biomarker?
        - Yes
          - Candidate chemical for biomonitoring
        - No
          - Deferred pending biomarker development (or if not possible, use proxy-measure)
    - No
      - Insufficient information
        - Deferred pending further data
      - Monitored but not detected
        - Low priority for ECHO
      - Insufficient information
        - Deferred pending further data
      - Low/non-toxic
        - Low priority for ECHO
Example: organophosphorus-based flame retardants

<table>
<thead>
<tr>
<th>Name</th>
<th>Dermal Contact</th>
<th>Biofluids/hair/nails</th>
<th>Air/Indoor Dust</th>
<th>Food/Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2-Bis(chloromethyl) propane-1,3-diyltetrakis(2-chloroethyl) bisphosphate (V6)</td>
<td>[412]</td>
<td>[29, 404, 405]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Ethylhexyl diphenyl phosphate (EHDPP)</td>
<td>[407, 409]</td>
<td></td>
<td>[408, 410-413]</td>
<td>[27, 414]</td>
</tr>
<tr>
<td>Bis(2-ethylhexyl) phosphate (BEHP)</td>
<td>[417]</td>
<td></td>
<td>[410, 413]</td>
<td>[418]</td>
</tr>
<tr>
<td>Diquanidine hydrogen phosphate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triethyl phosphate (TEP)</td>
<td>[419-421]</td>
<td>[413]</td>
<td></td>
<td>[28]</td>
</tr>
<tr>
<td>Tris(2,3-dibromopropyl) phosphate (TBP)*</td>
<td>[424]</td>
<td></td>
<td>[411-413]</td>
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<tr>
<td>Tris(2,3-dichloropropyl) phosphate (TDCnPP)</td>
<td>[426]</td>
<td></td>
<td>[419, 427]</td>
<td>[428]</td>
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<tr>
<td>Tris(2-butoxyethyl) phosphate (TBOEP)</td>
<td>[407, 432-434]</td>
<td>[24, 155, 315, 407, 411, 415, 435, 436]</td>
<td>[27, 28]</td>
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<tr>
<td>Tris(2-chloro-iso-propyl) phosphate (TCIPP)</td>
<td>[108, 445]</td>
<td>[88, 89, 155, 315, 404, 407, 410, 412]</td>
<td></td>
<td>[28]</td>
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<tr>
<td>Tris(2-ethylhexyl) phosphate (TEHP)</td>
<td>[433]</td>
<td>[420, 425, 446]</td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>Tris(tribromoneopentyl) phosphate (TTBNPP)</td>
<td></td>
<td></td>
<td></td>
<td>[450, 451]</td>
</tr>
</tbody>
</table>

Present in human biospecimens or environmental media?

- Quantified in media/biofluids; qual. id in biofluids
- Qualitative id in media or dermal contact
- No or sparse data
Example: organophosphorus-based flame retardants

Toxicity concern?

<table>
<thead>
<tr>
<th>Name</th>
<th>Health Effects/Toxicity</th>
<th>In Vivo/In Vitro</th>
<th>HTP Assay</th>
<th>QSAR Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocrine</td>
<td>Developmental</td>
<td>Reproductive</td>
<td>Neurotoxicity</td>
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<tr>
<td>2,2-Bis(chloromethyl) propane-1,3-Diyttetraakis(2-chloroethyl) bisphosphate (V6)</td>
<td>[415]</td>
<td>[416]</td>
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<tr>
<td>2-Ethylhexyl diphenyl phosphate (EHDP)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bis(2-ethylhexyl) phosphate (BEHP)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Triethyl phosphate (TEP)</td>
<td>[415, 422]</td>
<td>[423]</td>
<td></td>
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<td>Tris(2,3-dichloropropyl) phosphate (TDcNP)</td>
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<tr>
<td>Tris(2-butoxyethyl) phosphate (TBOEP)</td>
<td>[437, 438]</td>
<td>[439, 440]</td>
<td>[441]</td>
<td>[442-444]</td>
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<td>Tris(2-chloro-iso-propyl) phosphate (TCIPP)</td>
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<td></td>
<td></td>
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<tr>
<td>Tris(2-ethylhexyl) phosphate (TEHP)</td>
<td>[447, 448]</td>
<td>[449]</td>
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<tr>
<td>Tris(tribromoneopentyl)phosphate (TTBNPP)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**In Vivo/In Vitro Studies**
- Human study, risk Assess.
- In vivo animal studies
- In vitro experiments
- No or sparse data

**QSAR Models**
- Toxicant-High reliability
- Toxicant-Medium reliability
- Toxicant-Low reliability
- Not likely a toxicant
- No prediction
Example: organophosphorus-based flame retardants

Available biomarker?

<table>
<thead>
<tr>
<th>Name</th>
<th>Plasma/Serum</th>
<th>Hair/Nails</th>
<th>Urine</th>
<th>Breast Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organophosphorus-based Flame Retardants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,2-Bis(chloromethyl) propane-1,3-Diyltetakis(2-chloroethyl) bisphosphate (V6)</td>
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<td></td>
<td></td>
<td>[433]</td>
<td></td>
</tr>
</tbody>
</table>

*Parent or metabolite
No or sparse data
## Recommended biomonitoring of novel chemicals in ECHO

<table>
<thead>
<tr>
<th>Panel name</th>
<th># Chemicals</th>
<th># Recommended for biomonitoring</th>
<th># Deferred</th>
<th># Low priority for biomonitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate flame retardants</td>
<td>23</td>
<td>4</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Alternative plasticizers</td>
<td>10</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Aromatic amines</td>
<td>28</td>
<td>3</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Environmental phenols</td>
<td>16</td>
<td>6</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Organophosphorus flame retardants</td>
<td>11</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Perfluoroalkyl substances</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Pesticides</td>
<td>43</td>
<td>12</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Quaternary ammonium compounds</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>155</strong></td>
<td><strong>36</strong></td>
<td><strong>108</strong></td>
<td><strong>11</strong></td>
</tr>
</tbody>
</table>
Assessing novel chemical exposures in ECHO

Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement
### Alternative Flame Retardant
- Melamine

### Environmental Phenols
- Bisphenol A diglycidyl ether
- Bisphenol AF
- Bisphenol B
- 3,3',5,5'-Tetrabromobisphenol A
- 2,2',6,6'-Tetrachlorobisphenol A
- 3,3',5-Trichlorobisphenol A
- 4-n-Nonylphenol
- Bisphenol A (2,3-dihydroxypropyl) glycidyl ether
- Bisphenol A bis[(2,3-dihydroxypropyl) glycidyl ether
- Bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether
- Bisphenol A bis(3-chloro-2-hydroxypropyl) glycidyl ether
- 4-n-Octylphenol
- 4,4'-[(1,4-Phenylenedisopropylidene)biphenol
- 4,4'-[(1-Phenylethylidene)biphenol
- 4,4'-[(1,2-Cyclohexylidene)biphenol
- 4,4'-[(1,3-Dihydroxyphenyl)methane
- bis(4-Hydroxyphenyl)propane
- 2,4,5-Trichlorophenol
- 2,3,4,5-Tetrachlorophenol
- 2,3,4,6-Tetrachlorophenol
- 2,3,5,6-Tetrachlorophenol
- Pentachlorophenol
- 4-Hydroxybenzoate
- 4-Hydroxybenzophenone
- Benzophenone-1
- Benzophenone-2
- Benzophenone-3
- Benzophenone-6
- Benzophenone-8
- Benzyl paraben
- Ethyl paraben
- Heptaparaben
- Hydroxy-ethyl paraben
- Hydroxy-methyl paraben
- Methyl paraben
- n-Butyl paraben
- n-Propyl paraben
- Triclocarban
- Triclosan

### Aromatic Amines
- 2-Methylaniline
- 2-Methoxyaniline
- 3,4-Dichloroaniline
- 2,4-Diaminotoluene
- 4,4'-Diaminodiphenylmethane

### Organophosphorus-based flame retardants
- 2,2-Bis(chloromethyl) propane-1,3-diyltetras(2-chloroethyl) bisphosphate
- 2-Ethylhexyl diphenyl phosphate
- Bis(2-ethylhexyl) phosphate
- Tris(2-ethylhexyl) phosphate
- Tris(2-butoxyethyl) phosphate
- Triethyl phosphate
- Bis(2-methylphenyl) phosphate
- Cresyl diphenyl phosphate
- Dibutyl phosphate
- Diphenyl phosphate
- Di-isobutyl phosphate
- Tri-isobutyl phosphate
- Tri-isopropyl phosphate
- Trimethyl phosphate
- Trimethylphenyl phosphate
- Tri-n-butyl phosphate
- Triphenyl phosphate
- Tris(2-chloroethyl) phosphate

### Pesticides
- Azoxystrobin
- Cyprodinil
- Metalaxyl
- Metsulfuron
- Propiconazole
- Pyrimethanil
- Tebuconazole
- Tetraconazole
- 6-Cloronicotinic acid
- Acetamiprid
- Atrazine
- Cyanauc acid
- Ammeline
- Clothianidin
- Dinotefuran
- Flonicamid
- Imidaclopid
- Imidacotiz
- N-desmethyhtiamethoxam
- N-desmethyacetamiprid
- Nitepyrain
- Sulfoxafiyr
- Triaciprid-amide
- Thiacephoxam

### Alternate Plasticizers
- mono-Ethyl phthalate
- mono-Butyl phthalate
- mono-Benzyl phthalate
- mono-(2-Ethylhexyl) phthalate
- mono-(2-Ethyl-5-hydroxyhexyl) phthalate
- mono-(2-Ethyl-5-oxohexyl) phthalate
- mono-Carboxy-iso-octyl phthalate
- mono-Carboxy-iso-nonyl phthalate
- mono-Ethyl terephthalate
- mono-Tert-butyl terephthalate
- mono-Benzyl-terephthalate
- mono-(2-Ethyl hexyl) terephthalate

102 urinary biomarkers in multi-class assay
Assessing novel chemical exposures in ECHO

Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement

Conduct a pilot study to measure novel chemicals in urine collected from pregnant women
Pilot study measuring novel chemicals among 175 pregnant women from 9 ECHO cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Location</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Hampshire Birth Cohort Study</td>
<td>NH</td>
<td>2009-present</td>
</tr>
<tr>
<td>Fair Start</td>
<td>NY</td>
<td>2013-present</td>
</tr>
<tr>
<td>Rochester</td>
<td>NY</td>
<td>2016-present</td>
</tr>
<tr>
<td>Atlanta ECHO Cohort of Emory</td>
<td>GA</td>
<td>2014-present</td>
</tr>
<tr>
<td>Illinois Kids Development Study</td>
<td>IL</td>
<td>2013-present</td>
</tr>
<tr>
<td>MARBLES</td>
<td>CA</td>
<td>2006-present</td>
</tr>
<tr>
<td>Chemicals in our Bodies</td>
<td>CA</td>
<td>2014-present</td>
</tr>
<tr>
<td>MADRES</td>
<td>CA</td>
<td>2016-present</td>
</tr>
<tr>
<td>ECHO in Puerto Rico</td>
<td>PR</td>
<td>2011-present</td>
</tr>
</tbody>
</table>

Includes women from across the U.S. to capture geographic, temporal, and sociodemographic diversity.
Assessing novel chemical exposures in ECHO

- Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement
- Conduct a pilot study to measure novel chemicals in urine collected from pregnant women
- Assess associations of prenatal novel chemical exposures with birth outcomes among >7500 children
Assessing novel chemical exposures in ECHO

- Develop and demonstrate feasibility of a method for multiple chemical extraction and measurement
- Conduct a pilot study to measure novel chemicals in urine collected from pregnant women
- Assess associations of prenatal novel chemical exposures with birth outcomes among >7500 children
- Perform future studies evaluating associations of novel chemicals with additional child health outcomes
Action and policy implications

- First study to assess exposures or health effects for majority of selected chemicals

- Chemical exposures can be reduced through a variety of programs, policies, and practices to protect children’s health

**EXPOSURE REDUCTION STRATEGIES**

- Individual behaviors
- Household maintenance and purchasing
- Consumer advocacy and corporate responsibility
- Regulatory action via state/federal policies

Zota et al. J Epidemiol Community Health 2017
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- ECHO Study participants

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