Environmental Risk Factors for Autism Spectrum Disorders

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Learning Objectives

1. Describe scientific evidence implicating environmental contributions to ASD
2. Understand the challenges of identifying specific environmental risk factors for ASD
3. Discuss approaches for identifying environmental factors that influence ASD risk
4. Describe potential environmental risk factors for ASD
What is the evidence that environmental factors contribute to ASD risk?

Rise in Autism Prevalence v. Other Major Chronic Conditions in US

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Jousseren et al. In Panel B, data on immune disorders are derived from Siwarbrick et al., Dubois et al., Tuomilehto et al., and Pugliatti et al.
What is the evidence that environmental factors contribute to ASD risk? continued

How much of the increased prevalence of ASD represents an actual growth in numbers?

Increased awareness, improved detection and broadening of diagnostic criteria for ASD contribute to increased prevalence

e.g., Diagnostic substitution – labeling people autistic who previously would have been diagnosed with something else
However, Hertz-Picciotto and Delwiche (2009) Epidemiology 20: 84-90:

600% increases in cases:
- 24% due to earlier diagnosis
- 56% due to inclusion of milder cases
- 120% due to changes in diagnostic criteria

400% of increased cases cannot be attributed to diagnostic distribution
What is the evidence that environmental factors contribute to ASD risk? continued

1. Rapid increase in ASD prevalence
2. Genetic studies
   a. Incomplete monozygotic concordance
   b. Most genes associated with ASD are not major effect genes but rather create modest vulnerabilities
   c. In some cases, genes create major vulnerabilities but even in genetic syndromes highly associated with ASD, a significant presentation of carriers do NOT have ASD
   d. De novo gene mutations
   e. Some gene variants confer altered vulnerability to environmental stressors and environmental exposures
      i. Redox or methylation
      ii. Heavy metal metabolism
      iii. Metabolism of organophosphorus pesticides (OPs)
What is the evidence that environmental factors contribute to ASD risk? continued

Glutathione – endogenous antioxidant

What is the evidence that environmental factors contribute to ASD risk? continued

1. Rapid increase in ASD prevalence
2. Genetic studies
3. Clinical heterogeneity of ASD
What is the evidence that environmental factors contribute to ASD risk? continued

1. Rapid increase in ASD prevalence
2. Genetic studies
3. Clinical heterogeneity of aSD
4. Systemic and CNS pathophysiology

- Oxidative stress
- Immune dysfunction (including neuroinflammation)
- Mitochondrial dysfunction

These pathophysiological outcomes known to be exacerbated by environmental factors: air pollution, OPs, heavy metals
Environmental risk factors for ASD

- Rubella infection during the first trimester of pregnancy
- *In utero* exposure to thalidomide or valproic acid
- Paternal age
- Environmental chemicals (?)
  - Heavy metals (lead, methylmercury)
  - Pesticides
    - Organophosphorus pesticides (OPs), e.g., chlorpyrifos, diazinon
    - Organochlorine pesticides (OCs), e.g., DDT, dieldrin, lindane
  - Persistent organic pollutants (POPs)
    - Polychlorinated biphenyls (PCBs)
    - Polybrominated diphenyl ethers (PBDEs)
    - Polycyclic aromatic hydrocarbons (PAHs)

However, efforts to identify specific environmental risk factors for ASD have produced a number of candidates but few definitive hits

Focus during the reminder of this presentation will be on environmental chemicals, particularly chemical contaminants
Trends in U.S. Chemical Production, 1920–1980

(--·--) Synthetic organic chemicals, Scale A
(···--) All chemicals and allied products, Scale B

Pesticide use more than doubled between 1964 and 1982 (USDA)

Total synthetic organic chemicals production (excluding tar, tar crudes, and primary products from petroleum and natural gas). Total chemicals and allied products, annual value added.
The Challenge of Identifying Environmental Risk Factors for ASD

Of the 287 chemicals detected in umbilical cord blood:

• 180 cause cancer in humans or animals
• 217 are toxic to the brain and nervous system
• 208 cause birth defects or abnormal development in animal tests
• Nearly 200 have been banned from the market for years

www.bodyburden.org
The Challenge of Identifying Environmental Risk Factors for ASD, continued

Status of Developmental Toxicity Testing for the 2,863 Chemicals Produced Above 1 million pounds/year

- Some Data on Developmental Toxicity: 21.4%
- No Data on Developmental Toxicity: 78.2%
- 0.4% Tested for Neurodevelopmental Toxicity According to EPA Guidelines
- 20-30 Tested for Neurodevelopmental Toxicity

This testing is NOT REQUIRED.

To test these 2,863 chemicals in combinations of 3 would require 85 BILLION tests.

In Harm’s Way, www.preventingharm.org
A significant challenge, particularly for epidemiological studies:

The complexity of heritable factors contributing to ASD susceptibility creates a range of sensitivities to environmental factors.
The Challenge of Identifying Environmental Risk Factors for ASD, continued

- Genetic susceptibility
- Environmental Factors
- Timing

ASD risk, severity and treatment outcome
How do environmental chemicals interact with genetic mechanisms to increase ASD risk?

Largely unknown. Possibilities include:

- *De novo* mutations
- Epigenetic changes
- Some gene variants confer altered vulnerability to environmental stressors and environmental exposures
- Endocrine disruption
Mechanistic approach for identifying environmental factors that influence ASD risk

Alternative mechanism by which genes interact with environment to influence ASD risk, severity and/or treatment outcome:

Heritable genetic vulnerabilities amplify adverse effects triggered by environmental exposures if genes and environment converge to dysregulate the same signaling system at critical times of neural development.
### Genes associated with ASD susceptibility: Neuronal connectivity

<table>
<thead>
<tr>
<th>Genes</th>
<th>Chr</th>
<th>Function</th>
<th>Evidence</th>
<th>Disorder</th>
<th>Observation</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECP2</strong></td>
<td>Xq28</td>
<td>Methyl-binding protein</td>
<td>M</td>
<td>MR, Rett, ASD</td>
<td>Girls with autistic features, one male with ASD</td>
<td>[14]</td>
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<tr>
<td><strong>FMRP</strong></td>
<td>Xq28</td>
<td>RNA-binding protein</td>
<td>M</td>
<td>MR, FXS, ASD</td>
<td>20–40% of boys with FXS have ASD</td>
<td>[15,16,18]</td>
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<tr>
<td><strong>EN2</strong></td>
<td>7q36</td>
<td>Transcription factor</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[21–23]</td>
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<tr>
<td><strong>HOXA1</strong></td>
<td>7p15</td>
<td>Transcription factor</td>
<td>A</td>
<td>ASD</td>
<td></td>
<td>[25–27]</td>
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<td><strong>WNT2</strong></td>
<td>7q31</td>
<td>Transcription factor</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[24]</td>
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<tr>
<td><strong>TSC1/TSC2</strong></td>
<td>9q34/16p13</td>
<td>Inactivation of GTPase</td>
<td>M</td>
<td>TCS</td>
<td>ASD in 43–86% of TS patients</td>
<td>[6]</td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>17q11</td>
<td>Inactivation of GTPase</td>
<td>M</td>
<td>NF1</td>
<td>Learning disabilities in 30–45% of NF1 patients</td>
<td>[30]</td>
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<tr>
<td><strong>cAMP-GEF</strong></td>
<td>2q31</td>
<td>Activation of GTPase</td>
<td>L, A</td>
<td>ASD</td>
<td>Rare variants observed in ASD</td>
<td>[31]</td>
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<tr>
<td><strong>SHANK3</strong></td>
<td>22q13</td>
<td>Dendrite induction</td>
<td>CR</td>
<td>MR, ASD</td>
<td>Binding partner of NLGN</td>
<td>[32]</td>
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<tr>
<td><strong>Receptors and transporters</strong></td>
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<tr>
<td><strong>GRIN2A</strong></td>
<td>16p13</td>
<td>NMDA receptor subunit</td>
<td>L, A</td>
<td>ASD</td>
<td>Highly significant association</td>
<td>[46]</td>
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<tr>
<td><strong>GRIK2</strong></td>
<td>6q16–21</td>
<td>Kainate receptor subunit</td>
<td>L, A</td>
<td>ASD</td>
<td>Two independent studies</td>
<td>[47]</td>
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<tr>
<td><strong>GABAR</strong></td>
<td>15q12</td>
<td>GABA receptor subunit</td>
<td>CR</td>
<td>ASD</td>
<td>Duplication of 15q is the major CR in ASD</td>
<td>[45]</td>
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<tr>
<td><strong>SLC6A4</strong></td>
<td>17p11</td>
<td>Serotonin transporter</td>
<td>L, A, M</td>
<td>ASD</td>
<td>Evidence for allelic heterogeneity in ASD</td>
<td>[41]</td>
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<tr>
<td><strong>SLC25A13</strong></td>
<td>2q31</td>
<td>Aspartate–glutamate carrier</td>
<td>L, A</td>
<td>ASD</td>
<td>Two positive and one negative association</td>
<td>[48]</td>
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<tr>
<td><strong>OXTR</strong></td>
<td>3p25–26</td>
<td>Oxytocin receptor</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[49]</td>
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<tr>
<td><strong>AVPR1</strong></td>
<td>12q14</td>
<td>Vasopressin receptor</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[50]</td>
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<td><strong>Second-messenger systems</strong></td>
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<td><strong>PRKCB1</strong></td>
<td>16p11.2</td>
<td>Protein kinase</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[52]</td>
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<tr>
<td><strong>CACNA1C</strong></td>
<td>12p13.3</td>
<td>Ca^{2+} channel</td>
<td>M</td>
<td>TS, ASD</td>
<td>Multiorgan dysfunction</td>
<td>[55]</td>
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<tr>
<td><strong>NBEA</strong></td>
<td>13q13</td>
<td>PKA anchor protein</td>
<td>L, CR</td>
<td>ASD</td>
<td></td>
<td>[51]</td>
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<tr>
<td><strong>Cell adhesion molecules</strong></td>
<td></td>
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<tr>
<td><strong>NLGN4</strong></td>
<td>Xq23.3</td>
<td>Synapse formation</td>
<td>L, CR, M</td>
<td>MR, ASD</td>
<td>Typical autism, Asp</td>
<td>[61–65]</td>
</tr>
<tr>
<td><strong>NLGN3</strong></td>
<td>Xq13.1</td>
<td>Synapse formation</td>
<td>L, M</td>
<td>MR, ASD</td>
<td>Typical autism, Asp</td>
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<td><strong>NrCAM</strong></td>
<td>7q31</td>
<td>Neuronal migration</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[70]</td>
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<td><strong>Secreted proteins</strong></td>
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<tr>
<td><strong>RELN</strong></td>
<td>7q22</td>
<td>Neuronal migration</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[77]</td>
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<tr>
<td><strong>LAMB1</strong></td>
<td>7q31</td>
<td>Cell migration</td>
<td>L, A</td>
<td>ASD</td>
<td></td>
<td>[70]</td>
</tr>
</tbody>
</table>
ASD Pathology

*Autism reflects altered patterns of neuronal connectivity within the developing brain*

*Autism may also involve altered neuronal connectivity of the autonomic and sensory nervous system*
At least some forms of autism result from an imbalance in the ratio of excitatory and inhibitory circuits within the developing brain.

Autism reflects altered tone of the autonomic nervous system.
Neurodevelopmental processes likely to be altered in ASD

*Neurodevelopmental processes that determine NEURONAL CONNECTIVITY*

- Neuronal migration
- Interneuron development
- Axonal growth and branching
- Dendritic growth and plasticity
- Synaptogenesis and synaptic plasticity
Organophosphorus Pesticides (OPs) as ASD risk factors: Epidemiological evidence

- Human studies have reported behavioral and cognitive problems in school-aged children following chronic exposure to low-level OPs

  - One of these studies linked perinatal OP exposures to ASD (Eskenazi et al., 2007, EHP)

  - Other studies showed that susceptibility to ASD is influenced by polymorphisms in PON-1, a key enzyme in OP detoxification (D’Amelio et al., 2005, Mol Psych; Pasca et al., 2006; Life Sci)
OPs as ASD risk factors: Imaging data

Rauh et al., 2012, PNAS 109: 7871-7876
Do OPs alter neurodevelopmental processes that determine neuronal connectivity?
Organophosphorus pesticides (OPs): Mechanism of acute toxicity

OPs ↓ (−) AChE

ACh ← choline + acetate

↓↓ cholinergic receptors
AChE is an axonal morphogen (AChE promotes axon outgrowth)

- AChE is expressed by non-cholinergic neurons during periods of axon outgrowth and synaptogenesis
  - Pharmacological inhibitors of AChE inhibit axon outgrowth at concentrations that do not alter the catalytic activity of AChE
  - Genetic manipulations of AChE expression in cultured neurons alters axonal outgrowth
    - AChE overexpression increases axon outgrowth
    - Suppression of AChE decreases axon outgrowth
Hypothesis

OPs disrupt axonal growth by interfering with the morphogenic activity of AChE
Predictions

1. OPs will inhibit axon outgrowth even in the absence of acetylcholine
2. Inhibition of axon outgrowth will occur independent of OP effects on AChE catalytic activity
3. Axon outgrowth in neurons that do not express AChE will not be altered by OPs
Chlorpyrifos (CPF)

A phosphorothioniate pesticide used for crop protection and in flea dips and roach control sprays
In Vitro Model

Primary culture of sensory neurons derived from mouse Dorsal Root Ganglia (DRG)

- Axons and growth cones express AChE during axon outgrowth
- DRG respond to morphogenic activity of AChE
- DRG neurons can be cultured in the absence of serum

24 hr
CPF inhibits axon outgrowth in DRG neurons

Yang et al. 2008 TAAP 228: 32-41.
CPF and CPFO inhibit axon outgrowth

*TCP (0.001 – 10 µM) had no effect

Yang et al. 2008 TAAP 228: 32-41.
Axon inhibitory effect of CPF and CPFO occurs independent of effects on cell viability, AChE enzyme activity and protein synthesis

Yang et al. 2008 TAAP 228: 32-41.
Hypothesis: OPs disrupt axonal growth by interfering with the morphogenic activity of AChE
AChE KO mouse

derived by Oksana Lockridge, U. Nebraska Medical Center

12 day old littermates
CPF inhibits axon outgrowth in AChE WT DRG but not AChE KO DRG

Yang et al. 2008 TAAP 228: 32-41.
CPF inhibits axon outgrowth in AChE WT DRG but not AChE KO DRG

Yang et al. 2008 TAAP 228: 32-41.
Are the differential responses of $AChE^{-/-}$ vs. $AChE^{+/+}$ DRG neurons due to deletion of the $AChE$ gene or to off-target effects?
Expression of pAChE restores WT phenotype to \textit{AChE-/-} DRG neurons

\textit{AChE-/-} DRG Neuron transfected with pGFP

\begin{tabular}{|c|c|c|}
\hline
Vehicle & GFP & NF \\
\hline
CPF & GFP & NF \\
\hline
\end{tabular}

\textit{AChE-/-} DRG neuron transfected with pAChE

\begin{tabular}{|c|c|c|}
\hline
Vehicle & GFP & NF \\
\hline
CPF & GFP & NF \\
\hline
\end{tabular}

Yang et al. 2008 TAAP 228: 32-41.
Do OPs also interfere with dendritic growth?
Sympathetic neurons cultured from rat superior cervical ganglia (SCG)

24 hr → AChE → 3 to 5 days → BMPs
CPF inhibits axonal outgrowth but enhances dendritic growth in SCG neurons.

CPF inhibits axonal outgrowth but enhances dendritic growth in SCG neurons.

CPF inhibits axonal outgrowth in mature SCG cultures

CPF and CPFO but not TCP inhibit AChE at concentrations that enhance
These findings suggest that:

- CPF and CPFO but not TCP inhibit axonal outgrowth
  - requires AChE but occurs independent of inhibition of catalytic activity of AChE
  - mediated by inhibition of the morphogenic activity of AChE

- CPF, CPFO and TCP enhance dendritic growth
  - not mediated by inhibition of AChE
  - mechanisms are speculative
    - decreased cAMP?
    - increased pCREB?
    - activation of the ryanodine receptor?

- Axonal outgrowth is the more sensitive endpoint
Chlorpyrifos does not inhibit axonal growth in cultured hippocampal neurons
Structural and functional homology between AChE and neuroligins

Arg451Cys mutation in neuroligin linked to ASD

(Dean and Dresbach, 2006, *Trends Neurosci* 29:21-29)
Hypothesis

OPs alter neuronal connectivity by interfering with neuroligin-mediated synapse formation
CPF interferes with both excitatory and inhibitory synapse formation in primary cultures of rat hippocampal neurons

vGlut1 = vesicular glutamate transporter 1
vGAT = vesicular GABA transporter

**vGlut1 (excitatory) graph**

**vGAT (inhibitory) graph**
CPF alters the balance of excitatory and inhibitory synapses in cultured hippocampal neurons.
Intriguing possibility

OP exposures during critical periods of development amplify effects of ASD-related gene mutations in neuroligin on synapse formation

\[\downarrow\]

Altered patterns of neuronal connectivity associated with ASD
Polychlorinated biphenyls (PCBs): Environmental risk factors for ASD?

- Human epidemiological data suggest a negative association between developmental exposure to environmental PCBs and cognitive function in infancy or childhood
  - Decreased IQ, impaired learning and memory, attentional deficits, lowered reading comprehension, psychomotor problems

- Comparable cognitive and behavioral deficits observed in primate and rodent models following developmental PCB exposures
  - Developmental neurotoxic effects of PCBs have been observed at relatively low exposure levels corresponding to between 1 and 10x the background levels observed in humans
PCB developmental neurotoxicity mediated primarily by non-dioxin-like PCB congeners

Non-dioxin-like congeners

- Developmental Neurotoxicity: +++
- Carcinogenic: +/-
- Arylhydrocarbon Receptor (AhR): Low to no affinity

Dioxin-like congeners

- Developmental Neurotoxicity: +/-
- Carcinogenic: +++
- Arylhydrocarbon Receptor (AhR): High affinity
Non-dioxin-like PCB congeners increase intracellular levels of $\text{Ca}^{2+}$ in neurons via sensitization of the ryanodine receptor (RyR).
# Genes associated with ASD susceptibility: Ca^{2+}-dependent signaling

<table>
<thead>
<tr>
<th>Gene (map)</th>
<th>Function</th>
<th>Mutation (Dysfunction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CACNA1C (12p13.3)</td>
<td>L-type voltage-dependent Ca^{2+} channel (CaV1.2)</td>
<td>G406R-delayed inactivation (Timothy Syndrome)</td>
</tr>
<tr>
<td>CACNA1H (16p13.3)</td>
<td>T-type voltage-dependent Ca^{2+} channel (CaV3.2)</td>
<td>R212C; R902W,W962C, A1874V- altered activation (autism)</td>
</tr>
<tr>
<td>SLC25A12 (2q24)</td>
<td>Ca^{2+}-dependent mitochondrial aspartate/glutamate carrier</td>
<td>SNPs (autism)</td>
</tr>
<tr>
<td>KCNMA1 (10q22.3)</td>
<td>Ca^{2+}-activated K^+ channel (BK_{Ca}^{2+})</td>
<td>Balanced 9q23/10q22 translocation</td>
</tr>
<tr>
<td>PTEN (10q23.3)</td>
<td>Ca^{2+} regulated PI-3-phosphatase; regulates CaV1.2</td>
<td>H33R, D252G, F241S- (macrocephaly; autism)</td>
</tr>
<tr>
<td>MECP2 (Xq28)</td>
<td>DNA methylation (Ca^{2+}-dependent phosphorylation)</td>
<td>Down regulated/mutations-altered DNA methylation (autism, RETT syndrome)</td>
</tr>
<tr>
<td>MET (7q21.1)</td>
<td>Tyrosine receptor kinase for hepatocyte growth factor coupled to IP3 production</td>
<td>Polymorphism-down regulation (autism)</td>
</tr>
<tr>
<td>CADPS2 (7q31-q32)</td>
<td>Ca^{2+}-dependent activator protein for secretion</td>
<td>aberrant alternative splicing lacks exon 3 (autism)</td>
</tr>
<tr>
<td>NL-1; NL-3</td>
<td>Neuroligin- synapse formation /function EF-hands</td>
<td>NL-1 R476C (autism)</td>
</tr>
<tr>
<td>3q26.31; Xq13.1</td>
<td></td>
<td>NL-3 R471C (autism)</td>
</tr>
</tbody>
</table>

Genome wide association study identified RyR2 as an ASD candidate gene

Hypothesis:

Non-dioxin-like PCBs disrupt neuronal connectivity via RyR-mediated mechanisms that modulate $Ca^{2+}$-dependent signaling pathways linked to activity-dependent dendritic growth and plasticity.
PCB 95 alters dendritic growth in primary cultures of hippocampal neurons

Wayman et al. (2012) Environmental Health Perspectives 120:997-1002.
SAR and pharmacological RyR blockade suggest dendrite-promoting activity of PCBs is RyR-dependent.

Wayman et al. (2012) *Environmental Health Perspectives* 120:997-1002.
RyR activity required for PCB effects on dendrites

Wayman et al. (2012) Environmental Health Perspectives 120:997-1002.
Experimental approaches for investigating Ca\textsuperscript{2+}-dependent signaling pathways in PCB-induced dendritic growth.

Wayman et al. (2012) *Environmental Health Perspectives* 120:1003-1009.
PCB 95 increases Ca^{2+} in primary cultured hippocampal neurons

Wayman et al. (2012) Environmental Health Perspectives 120:1003-1009.
Experimental approaches for investigating Ca$^{2+}$-dependent signaling pathways in PCB-induced dendritic growth

Wayman et al. (2012) Environmental Health Perspectives 120:1003-1009.
PCB-induced dendritic growth requires CREB activation

Wayman et al. (2012) Environmental Health Perspectives 120:1003-1009.
Experimental approaches for investigating $\text{Ca}^{2+}$-dependent signaling pathways in PCB-induced dendritic growth

Wayman et al. (2012) *Environmental Health Perspectives* 120:1003-1009.
PCB-induced dendritic growth requires Wnt signaling

Wayman et al. (2012) Environmental Health Perspectives 120:1003-1009.
Exposure of rat pups to PCBs in the maternal diet throughout gestation and lactation interferes with normal patterns of dendritic growth in the hippocampus of weanling rats.

Wayman et al. (2012) *Environmental Health Perspectives* 120:997-1002.
Developmental exposure to PCB 95 in the maternal diet interferes with the topographic organization of the auditory cortex in rats

Fig. 1. Exposure to PCB95 alters A1 maps. (Upper Left) Tonotopic map from a typical control rat pup. (Upper Right, Lower Left, and Lower Right) Examples of maps from PCB95-exposed rat pups. ✗ indicates an unresponsive site. Color bar, CF (kilohertz).

Kenet et al. (2007) PNAS 104: 7646-7651
Relevance of these findings to ASD?

• Animal studies
  – Perinatal exposure to a mixture of the non-dioxin-like PCB 47 and dioxin-like PCB 77 shown to alter social behaviors in rats

• Human exposure studies
  – PCB 95 found in significantly higher levels in postmortem brains of children with a syndromic form of autism (maternal 15q11-q13 duplication or Dup15q), but not idiopathic autism as compared to neurotypical controls
    [Mitchell et al. (2012) Environmental and Molecular Mutagenesis 58:589-98]
PCBs as Environmental Risk Factors for ASD

Environmental exposures × Genetic susceptibility × Timing

(heritable defects in Ca$^{2+}$ signaling)

↓

ASD risk, severity and treatment outcome
What do these findings mean to parents and clinicians?

- Chemical exposures are more readily controlled than genetic factors to prevent or mitigate the expression of ASD-related traits.
- Chemical exposure both pre- and postnatal can influence clinical outcome (types and severity of behaviors, co-morbidities).

What do these findings mean to parents and clinicians?

• Minimizing or preventing exposure to chemical contaminants during pregnancy or early childhood may improve clinical outcome
  – Do not use OPs in the home/yard
  – Consume organically grown produce
  – Work with local agencies to minimize use of OPs in public places and/or increase notice to the public of OP spray schedules/locations
  – Keep dust levels as low as possible; wash stuffed toys routinely
  – Limit dietary consumption of fatty fish, meats (PCBs)
Acknowledgements

Cecile Pickart, Johns Hopkins University
Oksana Lockridge, University of Nebraska
Isaac Pessah, UC Davis
Gary Wayman, Washington State University

Lein Laboratory
Angela Howard
Bob Bucelli
Dongren Yang
Donald Bruun
Christopher Barnhart
Hao Chen

Funding Sources
CROET, OHSU
NIEHS
M.I.N.D. Institute, UC Davis