



Update: Center for Children's Environmental Health and Disease Prevention

UNIVERSITY OF CALIFORNIA, DAVIS

UC Davis M.I.N.D. Institute

Isaac N. Pessah, Ph.D.



UC Davis Center for Children's Environmental Health and Disease Prevention

Isaac N. Pessah, Ph.D. - Director

Irva Hertz-Picciotto, Ph.D. - Associate Director

- **Established in 2001 Competitive NIH/EPA Peer review**
- **Competitive renewal granted 2006**

Funded by NIEHS P01ES011269 & EPA R833292/R829388

UC Davis M.I.N.D. Institute



Goal:

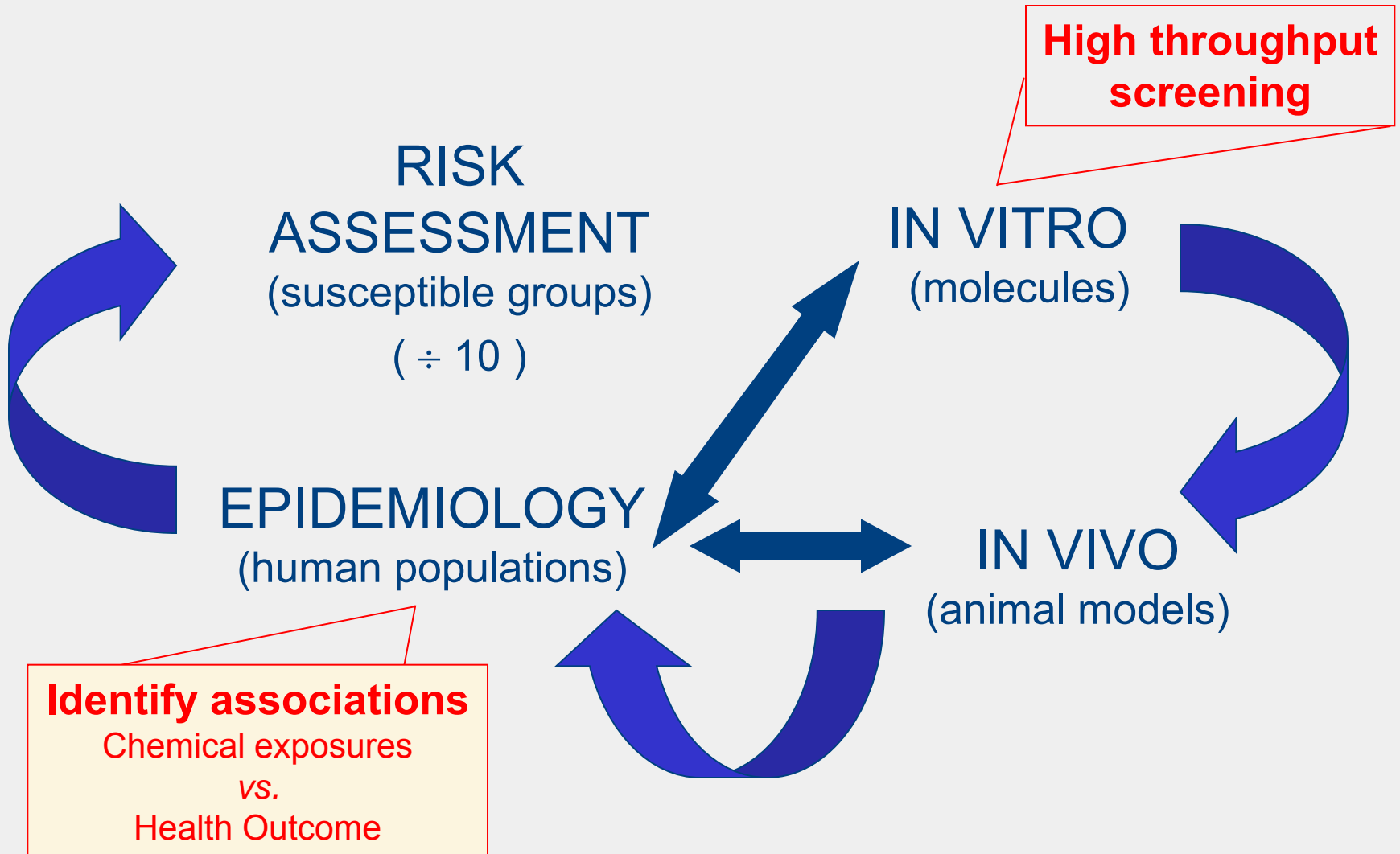
- To advance scientific knowledge in the field of Autism
- *evaluate environmental factors contributing to autism risk*
 - *evaluate gene x environment factors contributing to autism susceptibility*
 - *identify xenobiotic mechanisms of developmental neurotoxicity relevant to ASD*



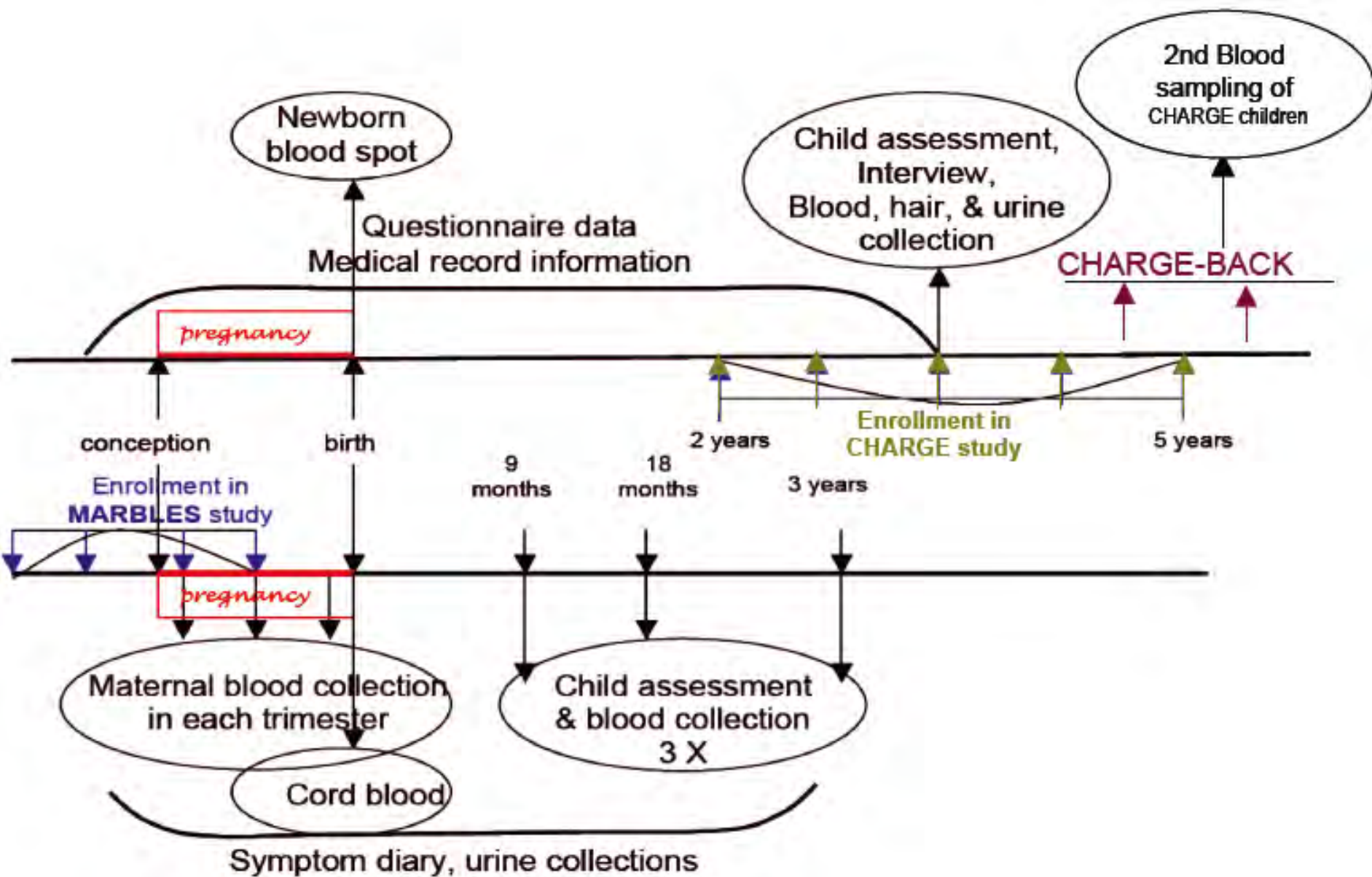
Integrated multidisciplinary approach

- **Epidemiology**
(Project 1/COTC: CHARGE, CHARGE-BACK, MARBLES)
- **Clinical and cellular immunology**
(Project 2: autoantibodies, cytokines, PBDEs)
- **Cellular & mechanism → mouse models**
(Project 3: autoantibodies, mercury, PCBs, PBDEs)
- **Analytical chemistry**
(Core 3: Mercury, PBDEs, pesticides, oxylipids, vitamin D)
- **Molecular genomics**
(Core 4: transcription arrays, CNV, epigenetics)
- **Statistics Core**
- **Administrative Core**

EXTRAPOLATION OF EXPOSURE RISK



UC DAVIS Center for Children's Environmental Health and Disease Prevention





Mechanism of thimerosal immunotoxicity

Project 3; Core 4

Environmental Health Perspectives 114(7), 1083-91 (2006)



Uncoupling of ATP-Mediated Ca²⁺ Signaling and Dysregulated IL-6 Secretion in Dendritic Cells by Nanomolar Thimerosal

Samuel Goth, Ruth Chu, Jeffery Gregg, Gennady Cherednichenko, Isaac N. Pessah

Project 3

Journal of Immunological Methods 308, 179-191 (2006)



Oxygen tension regulates the in vitro maturation of GM-CSF expanded murine bone marrow dendritic cells by modulating class II MHC expression

Samuel Goth, Ruth Chu, Isaac N. Pessah



Mercury and autism susceptibility

Project 3; Cores 1,3

Toxicological Sciences 101(2), 294-309 (2008)

Low-Level Neonatal Thimerosal Exposure: Further Evaluation of Altered Neurotoxic Potential in SJL Mice

Robert F. Berman, Isaac N. Pessah, Peter R. Mouton, Deepak Mav, Jean Harry





Mercury and autism susceptibility

Projects 1,3; Cores 1,2,3

***Environmental Health Perspectives* 118(1), 161-166 (2010)**



Blood Mercury Concentrations in CHARGE Study Children with and without Autism

Irva Hertz-Picciotto, Peter G. Green, Lora Delwiche, Robin Hansen, Cheryl Walker, Isaac N. Pessah

Projects 1,2,3; Cores 1,2,3,4

Neurotoxicology Research in press (2010)



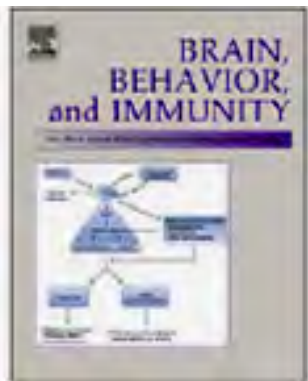
Correlations of Gene Expression and Mercury Levels in Blood of Boys with Autism Compared to Typically Developing Controls

Boryana Stamova, Peter G Green, Yingfang Tian, Irva Hertz-Picciotto, Isaac N Pessah, Robin Hansen, Xiaowei Yang, Jennifer Teng, Jeffrey P Gregg, Paul Ashwood, Judy Van de Water, Frank R Sharp



Immunological Factors and Autism Risk

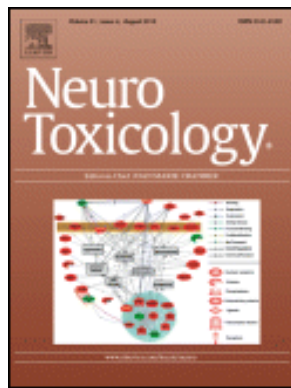
Projects 1,2,3; Cores 1,2,4 *Brain, Behavior, and Immunity* 23(1):124-33 (2009)



Altered gene expression and function of peripheral Blood natural killer cells in children with autism

Amanda Enstrom, Lisa Lit, Charity Onore, Jeff Gregg, Robin Hansen, Isaac Pessah, Irva Hertz-Picciotto, Judy Van de Water, Frank Sharp, Paul Ashwood

Projects 1,2,3; Cores 1,2 *NeuroToxicology* 118(1), 161-166 (2010)



Autism: Maternally derived antibodies specific for fetal brain proteins

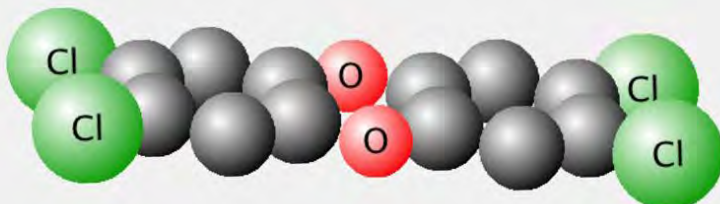
Daniel Braunschweig, Paul Ashwood, Paula Krakowiak, Irva Hertz-Picciotto, Hansen, Lisa Croen, Isaac Pessah, Judy Van de Water



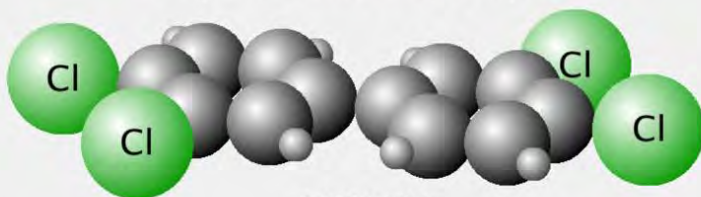
Autism: Maternal IgG from mothers at risk can affect brain development and produce behavioral syndrome in a mouse model (Projects 2,3; Cores 1,2,5)

Non-dioxin-Like Compounds Under the regulatory radar screen?

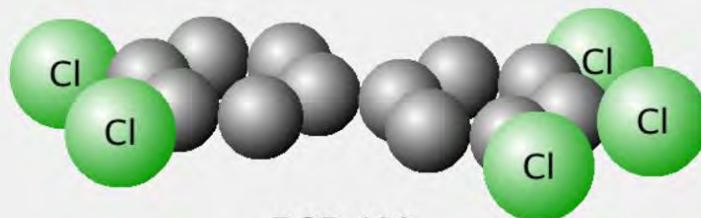
Dioxin
2,3,7,8-tetrachlorodibenzo-*p*-dioxin



Dioxin-like
Polychlorinated biphenyls

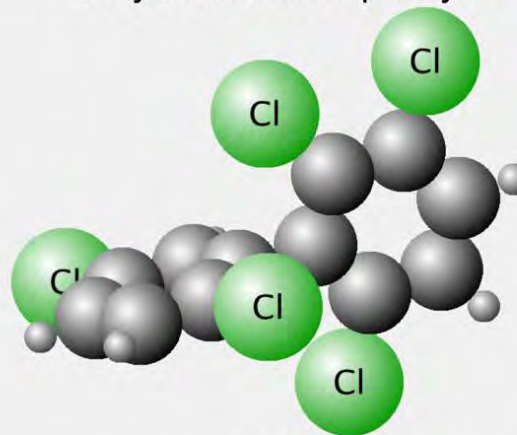


PCB 77
3,3',4,4'-tetrachlorobiphenyl

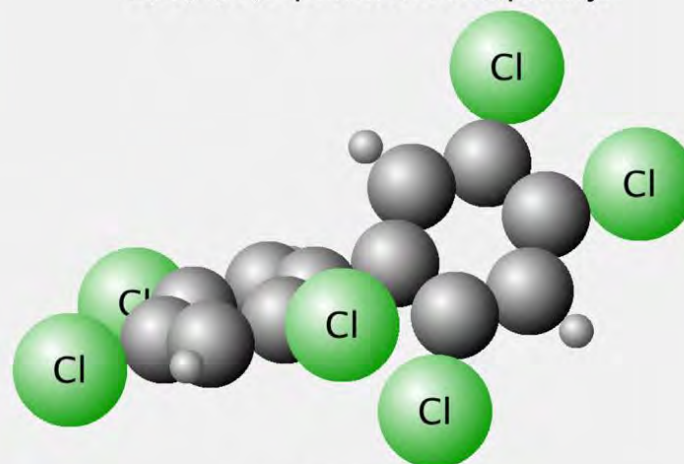


PCB 126
3,3',4,4',5-pentachlorobiphenyl

Non-Dioxin-like
Polychlorinated biphenyls



PCB 95
2,2',3,5',6-pentachlorobiphenyl



PCB 153
2,2',4,4',5,5'-hexachlorobiphenyl



Non-dioxin-Like Compounds Under the radar screen?

Project 3; Core 3

Toxicology and Applied Pharmacology 237(2):168-77 (2009).

Excitatory and inhibitory synaptic transmission is differentially influenced by two *ortho*-substituted polychlorinated biphenyls in the hippocampal slice preparation

Kyung Ho Kim ^a, Salim Yalcin Inan ^{b,1}, Robert F. Berman ^b, Isaac N. Pessah ^{a,*}

Project 3 and new investigator (Lein)

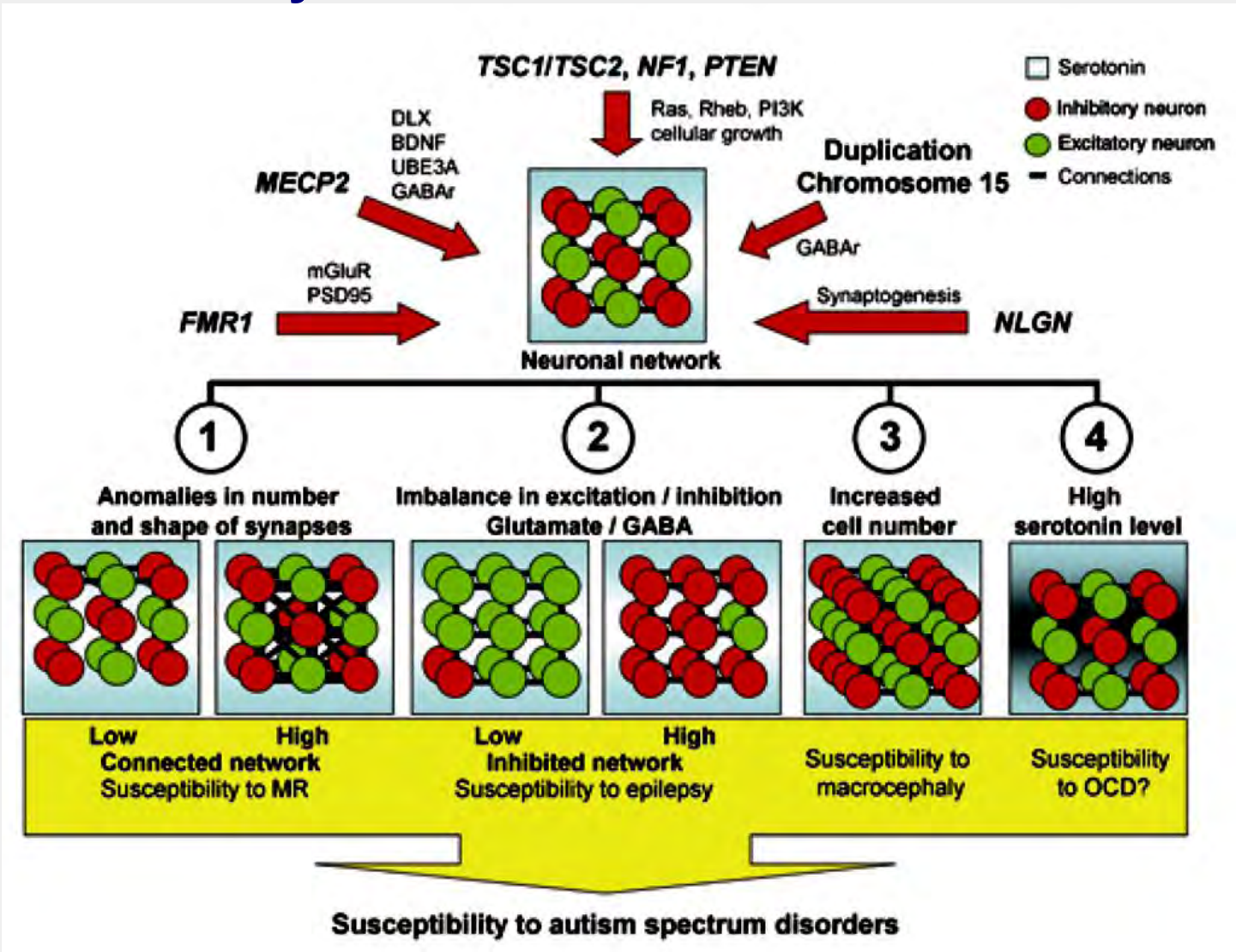
Environmental Health Perspectives 117(3):426-35 (2009)



Developmental Exposure to Polychlorinated Biphenyls Interferes with Experience-Dependent Dendritic Plasticity and Ryanodine Receptor Expression in Weanling Rats

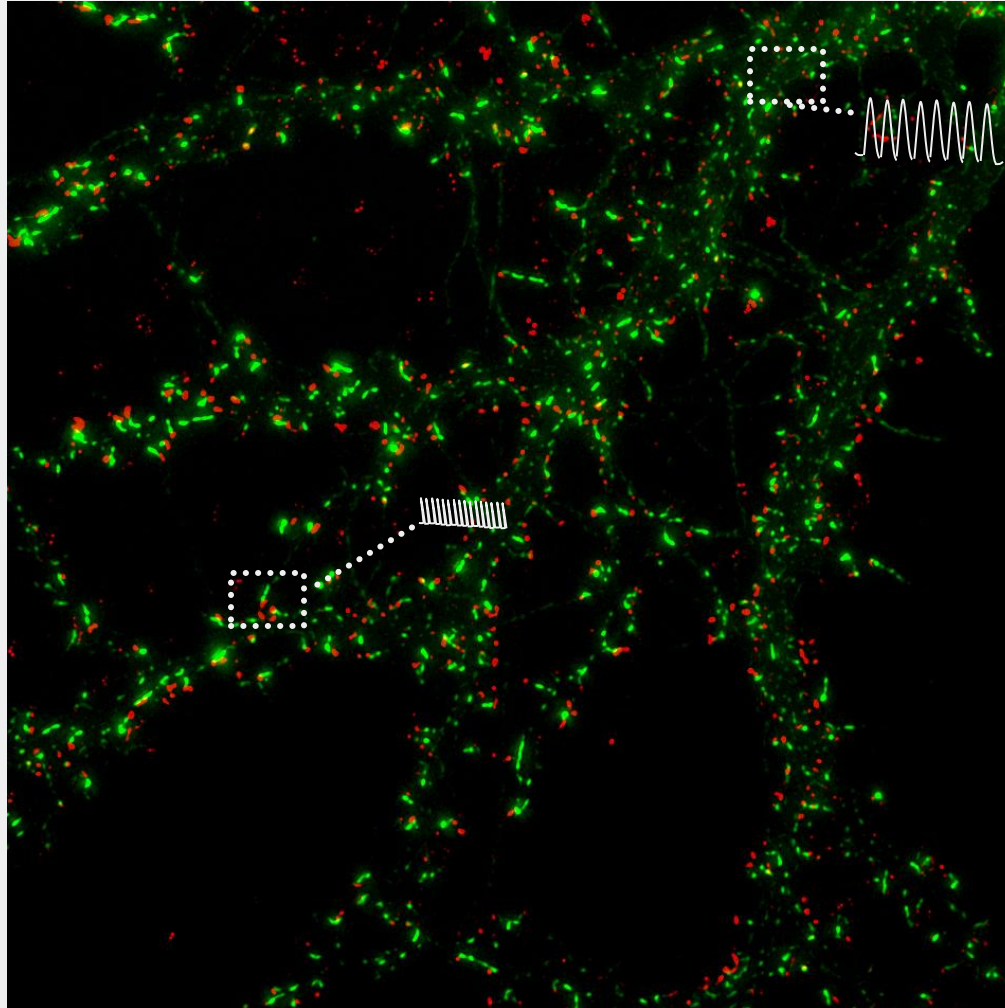
Dongren Yang,^{1*} Kyung Ho Kim,^{2*} Andrew Phimister,² Adam D. Bachstetter,³ Thomas R. Ward,⁴ Robert W. Stackman,⁵ Ronald F. Mervis,³ Amy B. Wisniewski,⁶ Sabra L. Klein,⁷ Prasada Rao S. Kodavanti,⁴ Kim A. Anderson,⁸ Gary Wayman,⁹ Isaac N. Pessah,² and Pamela J. Lein^{1, 2, 10}

Common pesticide exposures could further influence already abnormal ratios of excitatory/inhibitory neurons and impact the networks they form



Ca²⁺: A Common Currency of Cell Signaling

All cells utilize spatially and temporally discrete changes in [Ca²⁺]_i to regulate ongoing functions



signal transduction

metabolism

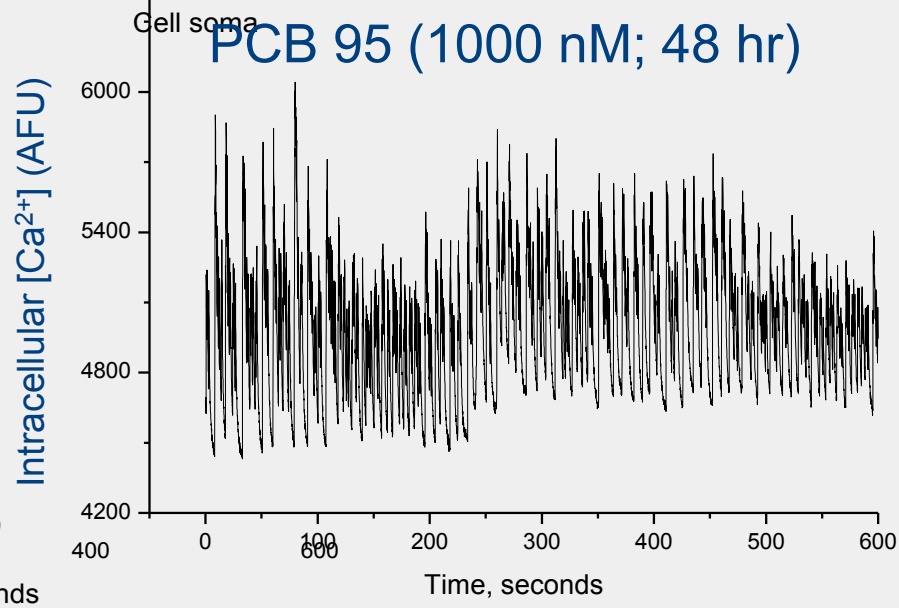
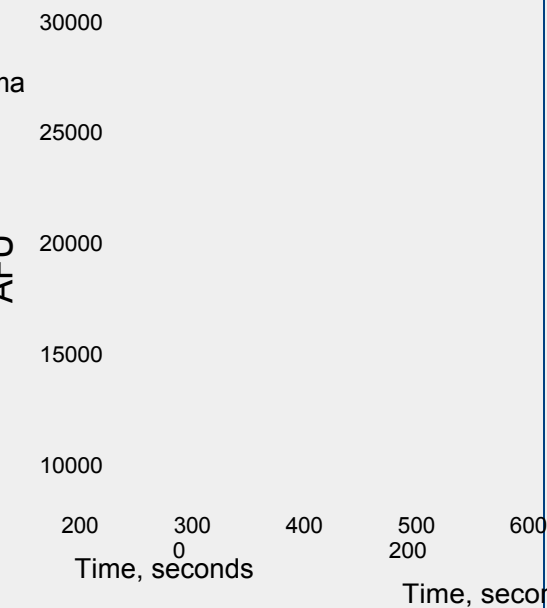
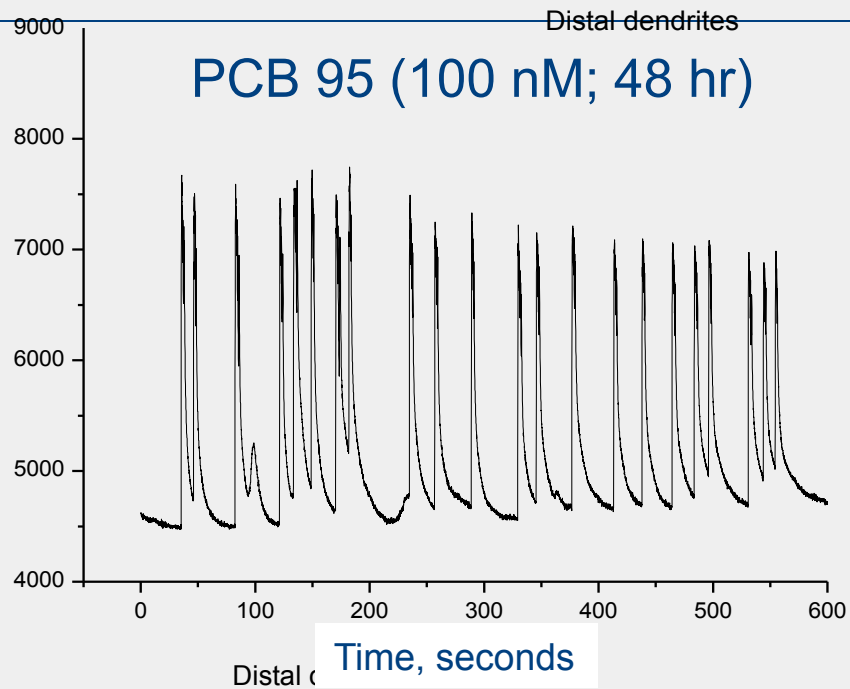
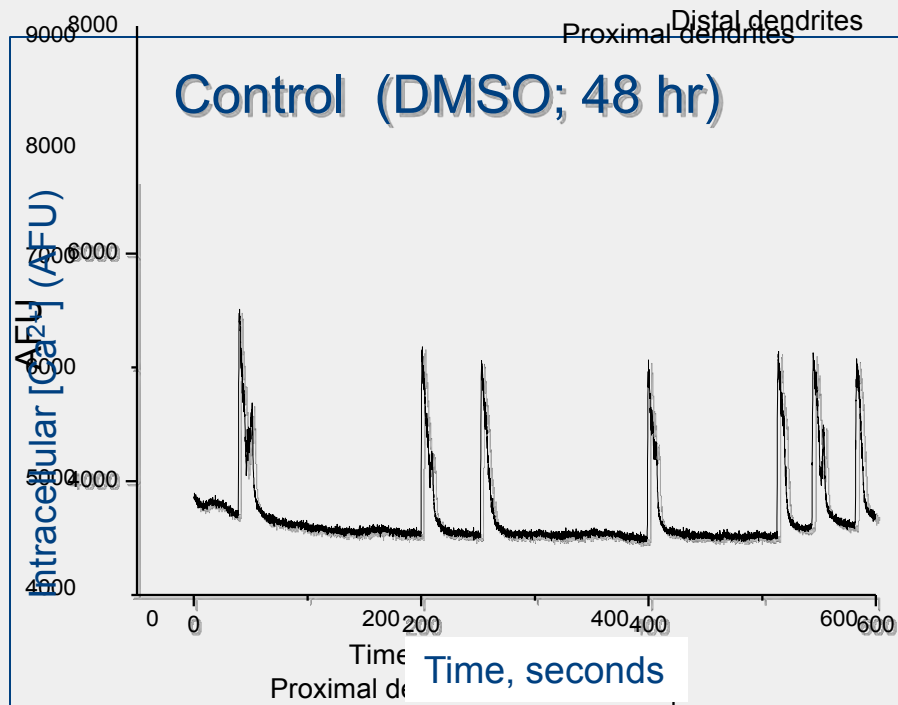
gene transcription

growth

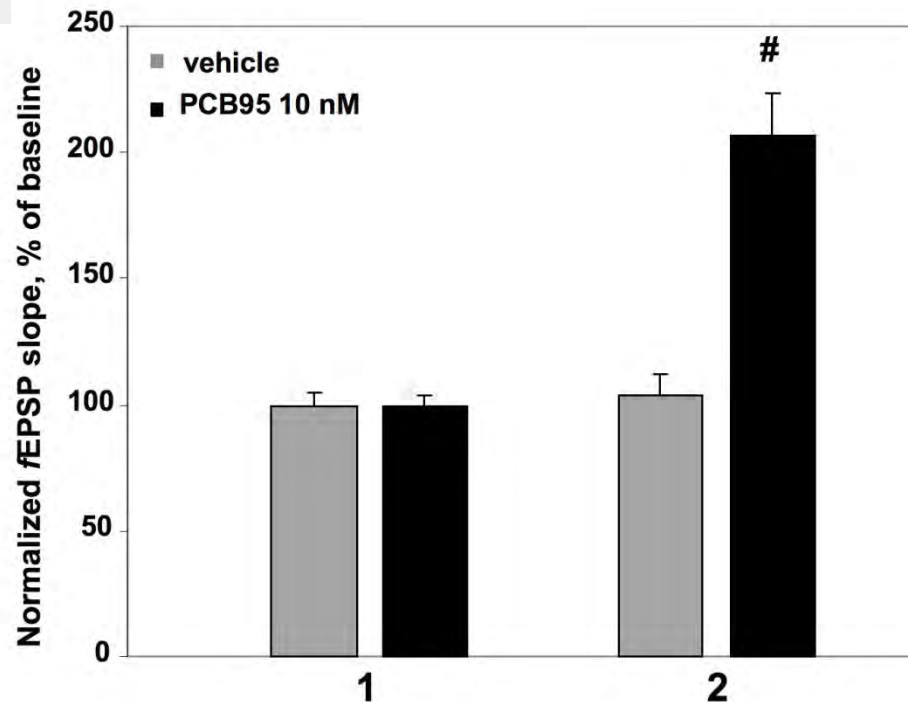
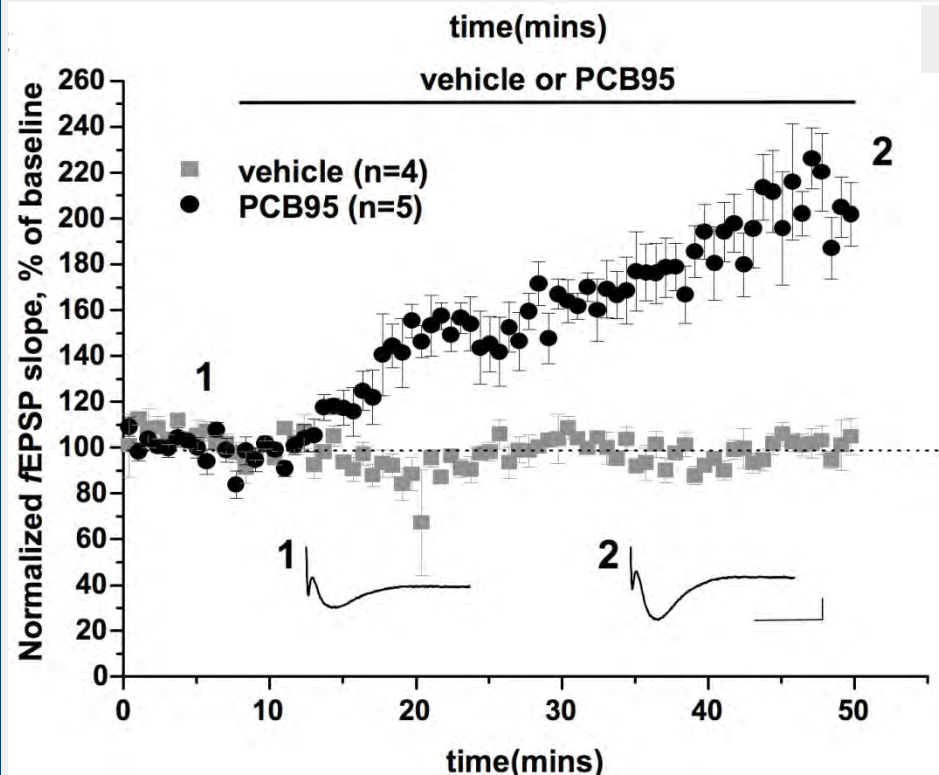
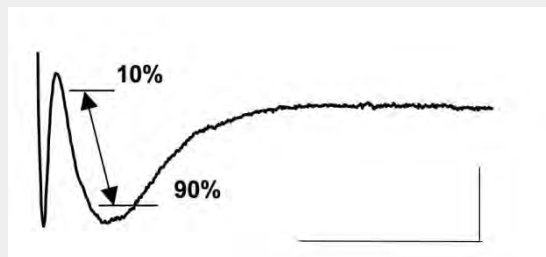
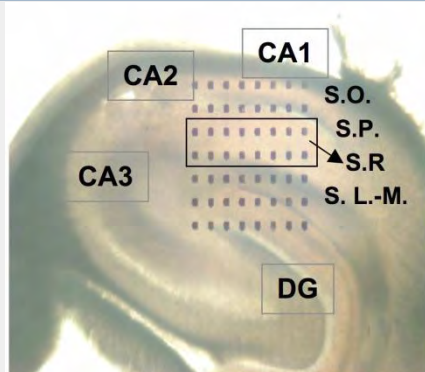
migration

apoptosis

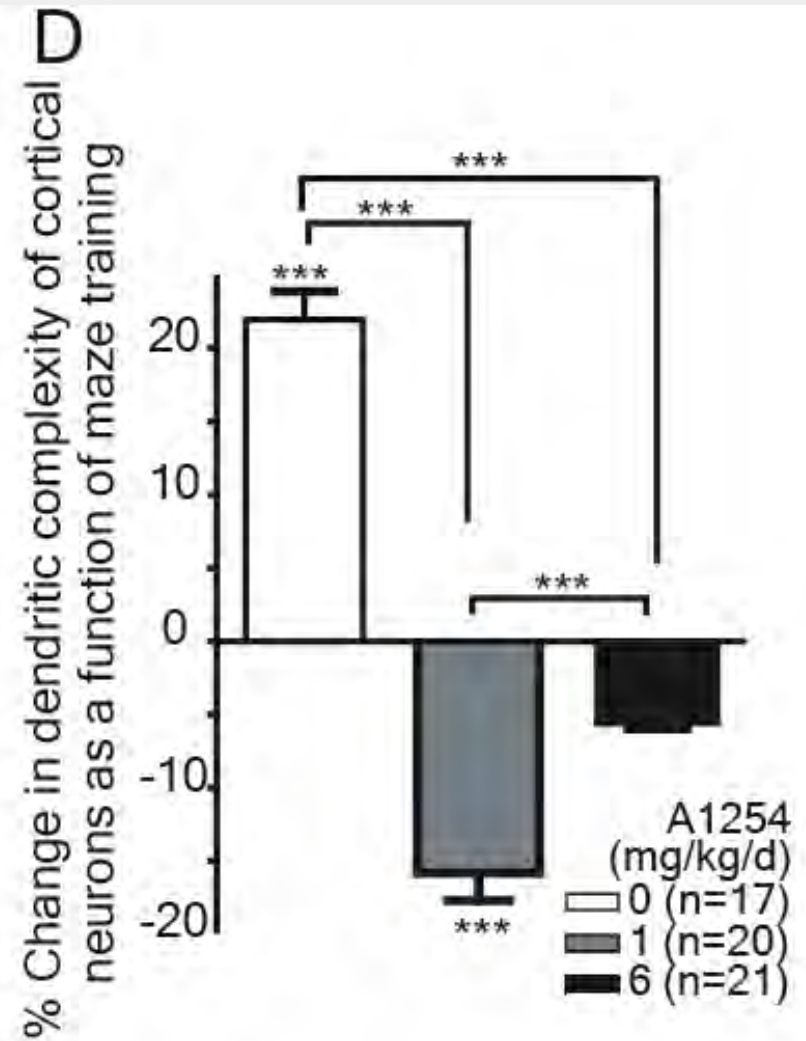
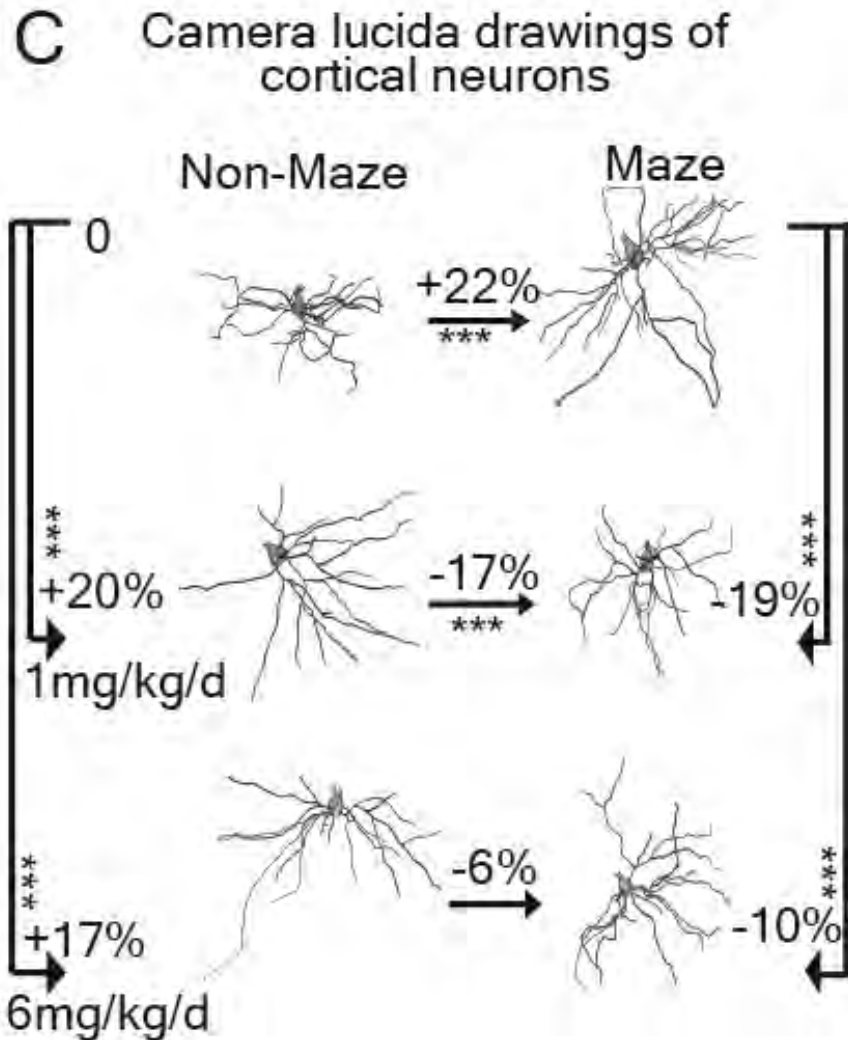
 Alexa 488-phalloidin  Alexa 568-shank



Nanomolar non-coplanar PCB 95 enhances hippocampal excitability *in vitro*



PCBs alters activity dependent dendritic growth *In vivo*



- Do PCB-like effects extend to other nondioxin-like compounds of concern to human health?

ehp

ehponline.org

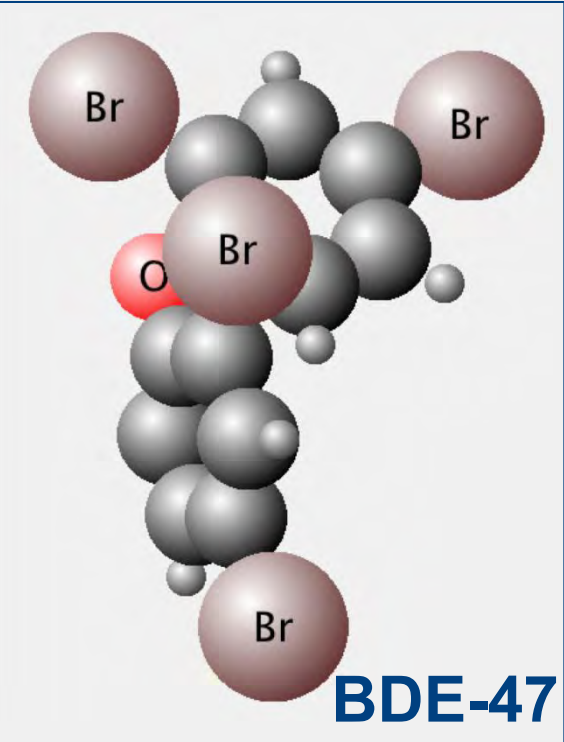
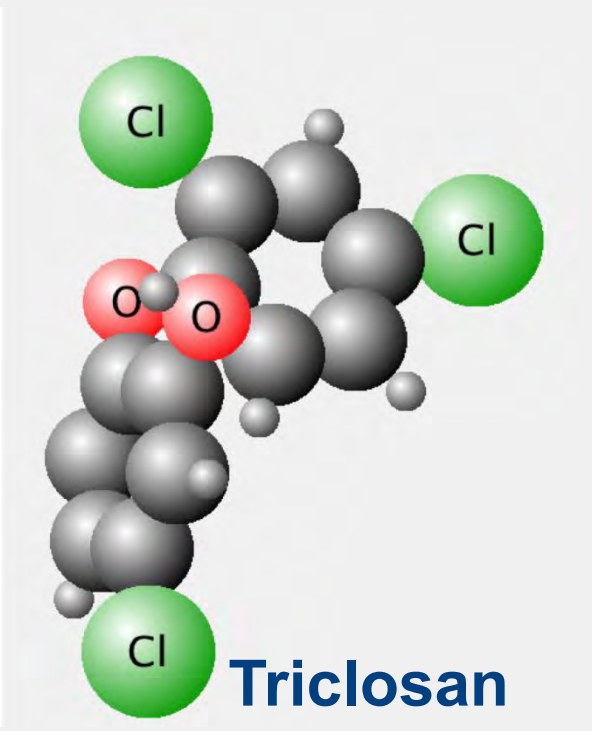
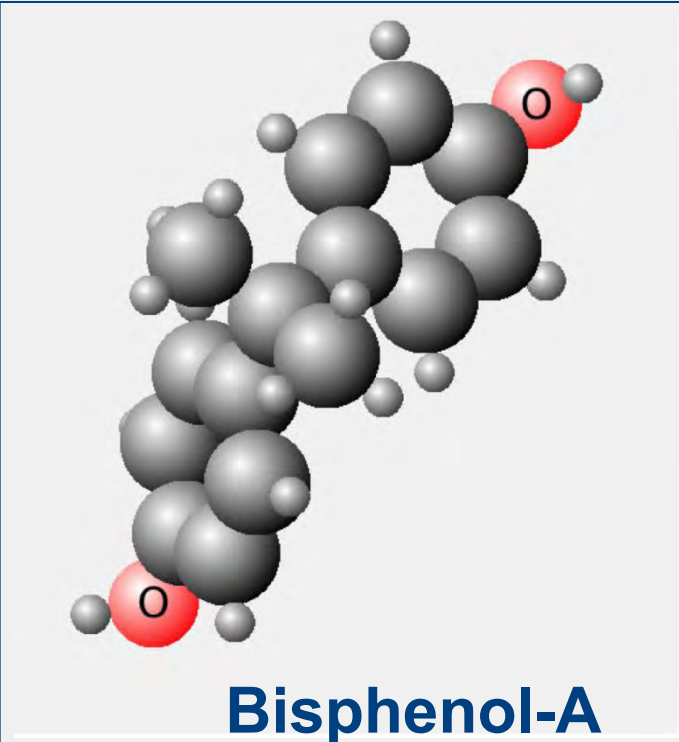
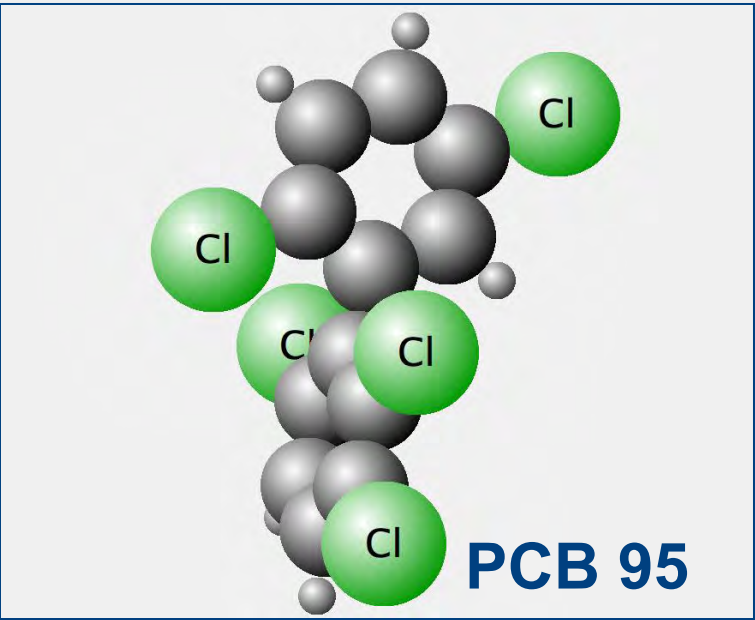
ENVIRONMENTAL
HEALTH
PERSPECTIVES

**Toxicology in the Fast Lane: Application of
High-Throughput Bioassays to Detect
Modulation of Key Enzymes and Receptors**

**Christophe Morisseau, Oleg Merzlikin, Amy Lin,
Guochun He, Wei Feng, Isela Padilla,
Michael S. Denison, Isaac N. Pessah, and Bruce D. Hammock**

doi: 10.1289/ehp.0900834 (available at <http://dx.doi.org/>)

Online 31 July 2009





PBDEs and Autism susceptibility?

Environ. Sci. Technol. **2010**, *44*, 2648–2653



PBDEs in 2–5 Year-Old Children from California and Associations with Diet and Indoor Environment

MELISSA ROSE,[†]
DEBORAH H. BENNETT,^{†,*}
ÅKE BERGMAN,[§] BRITTA FÄNGSTRÖM,[§]
ISAAC N. PESSAH,[‡] AND
IRVA HERTZ-PICCIOTTO[†]



PCBs, PBDEs and non-dioxin-like environmental contaminants

Role in autism risk?

Projects 2,3

Journal of Neuroimmunology 208 (2009) 130–135



Contents lists available at [ScienceDirect](#)

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim



Preliminary evidence of the *in vitro* effects of BDE-47 on innate immune responses in children with autism spectrum disorders

Paul Ashwood^{a,d,e}, Joseph Schauer^{b,d,e}, Isaac N. Pessah^{c,d,e}, Judy Van de Water^{b,d,e,*}

Impairments of mitochondrial bioenergetics in autism?

Scheme of the mitochondrial electron transport chain and its complexes

