Neuromuscular systems as a convergent target of environmental stress in Ocean and Human Health

Fritsch, Erika B.

University of California Davis

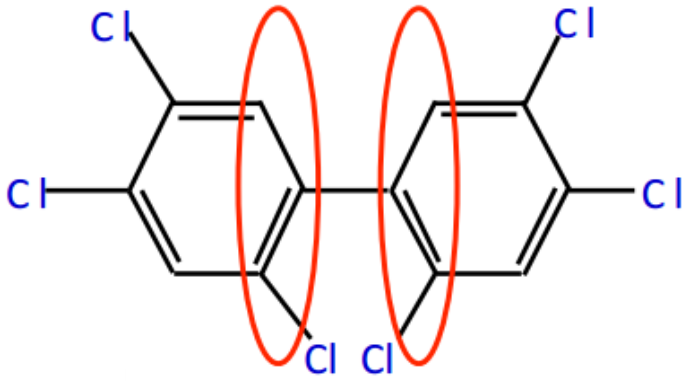
National Institute of Environmental Health Sciences

National Heart, Lung And Blood Institute

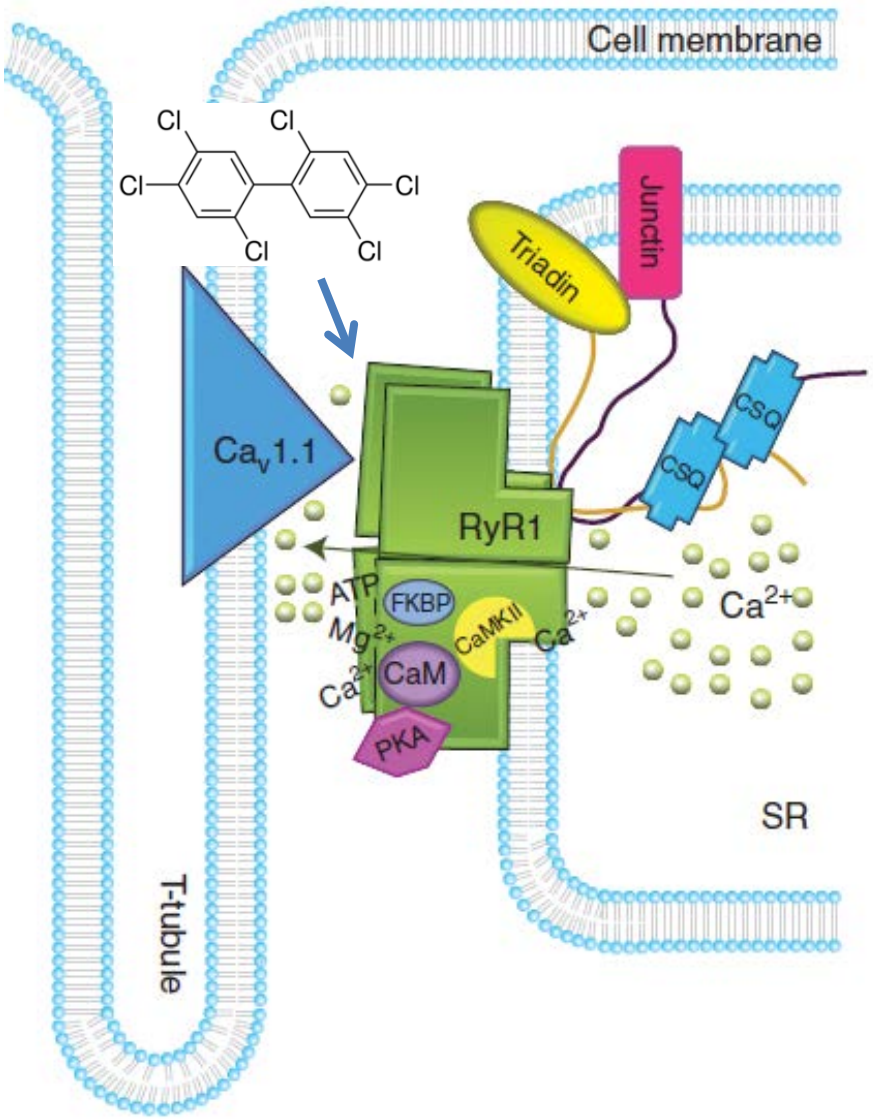
Superfund Research Program UCDAVIS

Chemicals and Neurodevelopmental Disorders

- Persistent Organic Pollutant exposure correlates with neurodevelopmental deficits
- *Example:* Pre and post-natal exposure to PCBs associated with lower IQ, attention deficit disorder, and motor impairments
- Of the 209 congeners, *ortho* PCBs are known to target important neuronal pathways



Ryanodine Receptor as a Molecular Target



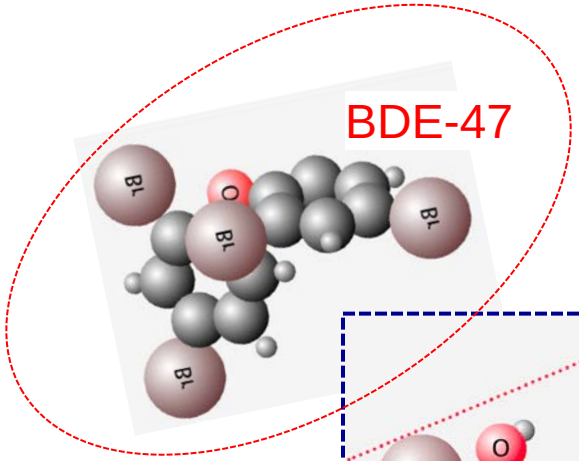
Important for proper:

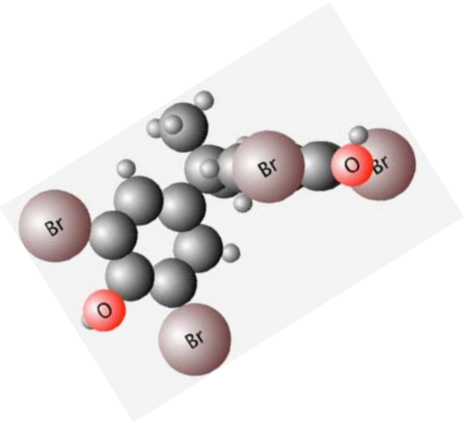
- Neuronal health and development
- Cardiac and skeletal muscle physiology, contractility, health
- Endocrine signaling

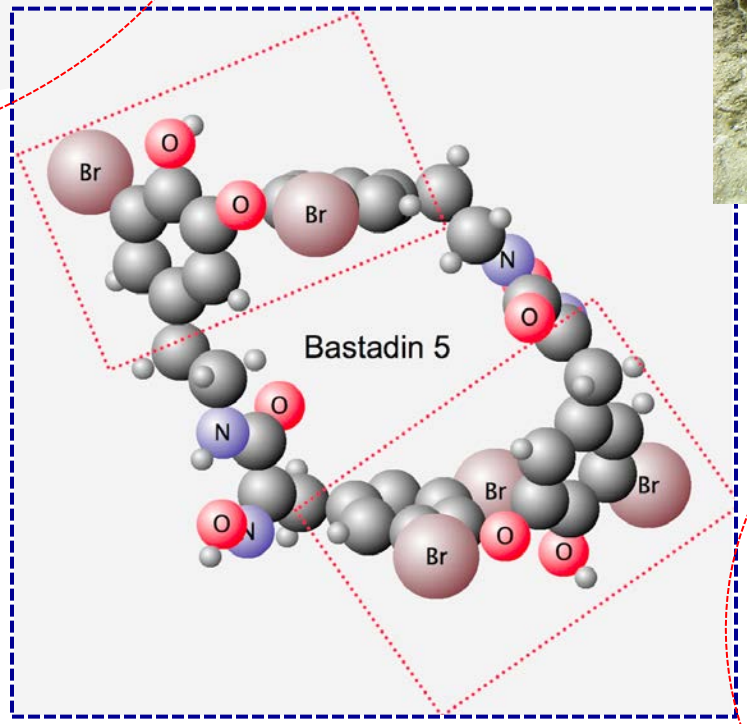
Alterations associated w/

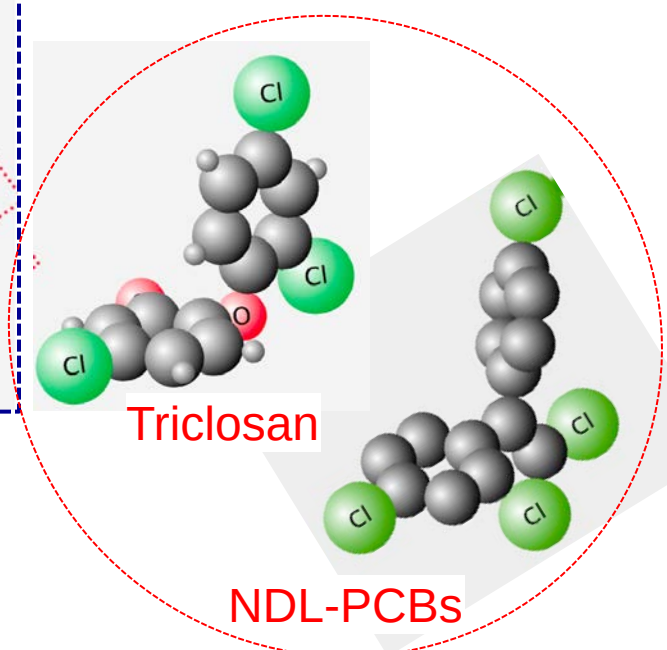
- Cardiac arrhythmias, failure
- Skeletal muscle myopathies
- Altered neuronal signaling and potential contribution to neuronal degeneration

Importance of Structure at the RyR









Mack MM et al. J Biol Chem. 1994 Sep 16;269(37):23236-49
Chen L et al. J Biol Chem. 1999 Nov 12;274(46):32603-12
Masuno MN et al. J Med Chem. 2006 Jul 27;49(15):4497-511
Eltit JM et al. Proc Natl Acad Sci 2011 Apr 26;108(17):7046-51.

RyR-related Toxic Outcomes

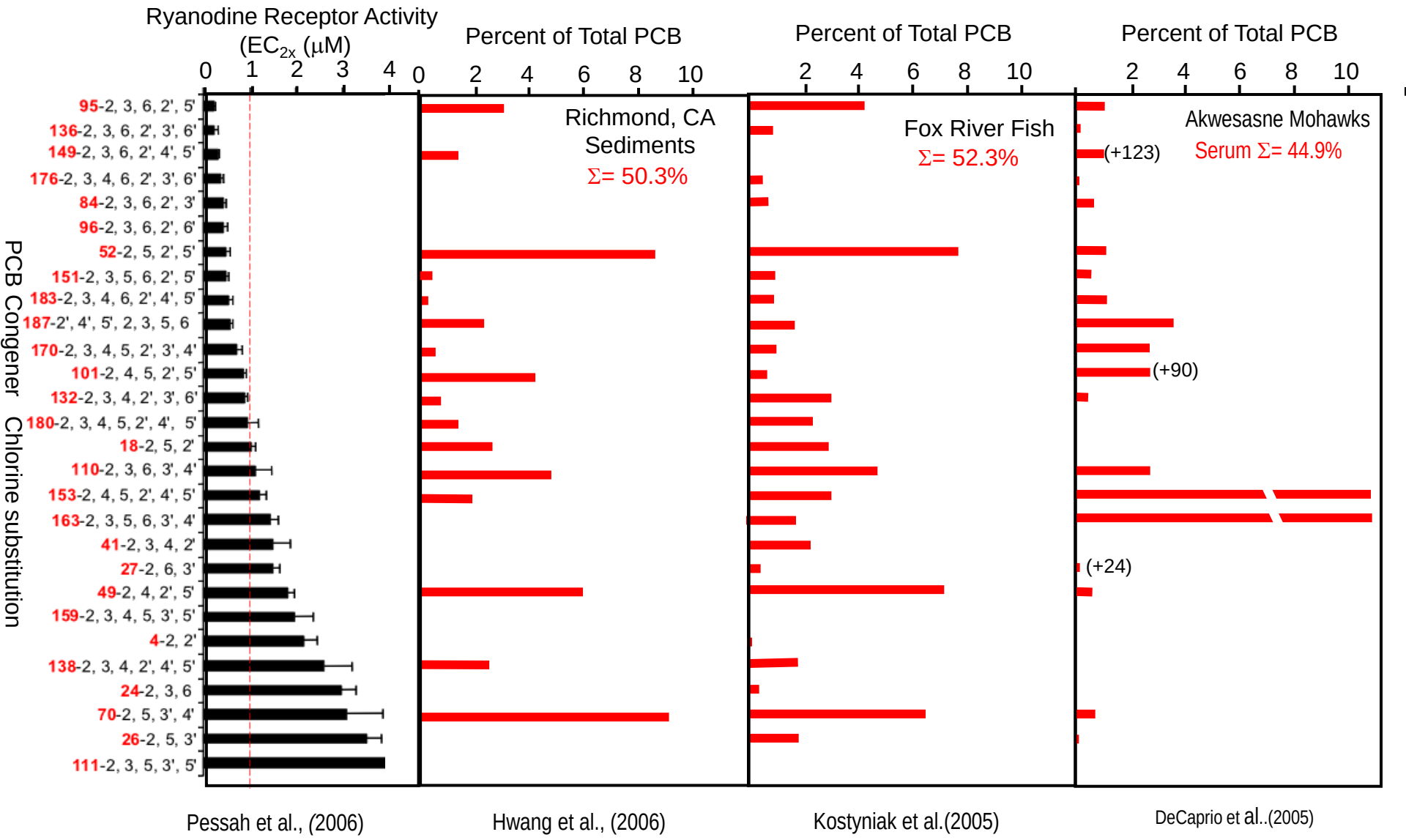
PCBs, PBDEs or their metabolites

- Neurotoxicity
  - Increased neuronal activity
  - Altered neuronal growth and morphology
  - Altered synaptic and network connectivity
- Muscle Toxicity
  - Altered excitation-contraction coupling
  - Altered expression of crucial muscle proteins

Triclosan

- Reduced cardiac output
- Reduced skeletal muscle contractility
- Decreased muscle strength (mice) and swimming performance (fish)

RyR Toxicity and Ocean and Human Health



Other Compounds (*ex. Triclosan*)

Potential drinking water contaminant

Urinary Concentrations of Triclosan in the U.S. Population: 2003–2004

Antonia M. Calafat, Xiaoyun Ye, Lee-Yang Wong, John A. Reidy, and Larry L. Needham

Triclosan persistence through wastewater treatment plants and its potential toxic effects on river biofilms

Marta Ricart[a,b,*], Helena Guasch[b], Mireia Alberch[c], Damià Barceló[a,d], Chloé Bonnineau[b], Anita Geiszinger[b], Marinel·la Farré[d], Josep Ferrer[c], Francesco Ricciardi[b], Anna M. Romaní[b], Soizic Morin[e], Lorenzo Proia[b], Lluís Sala[f], David Sureda[c], Sergi Sabater[a,b]

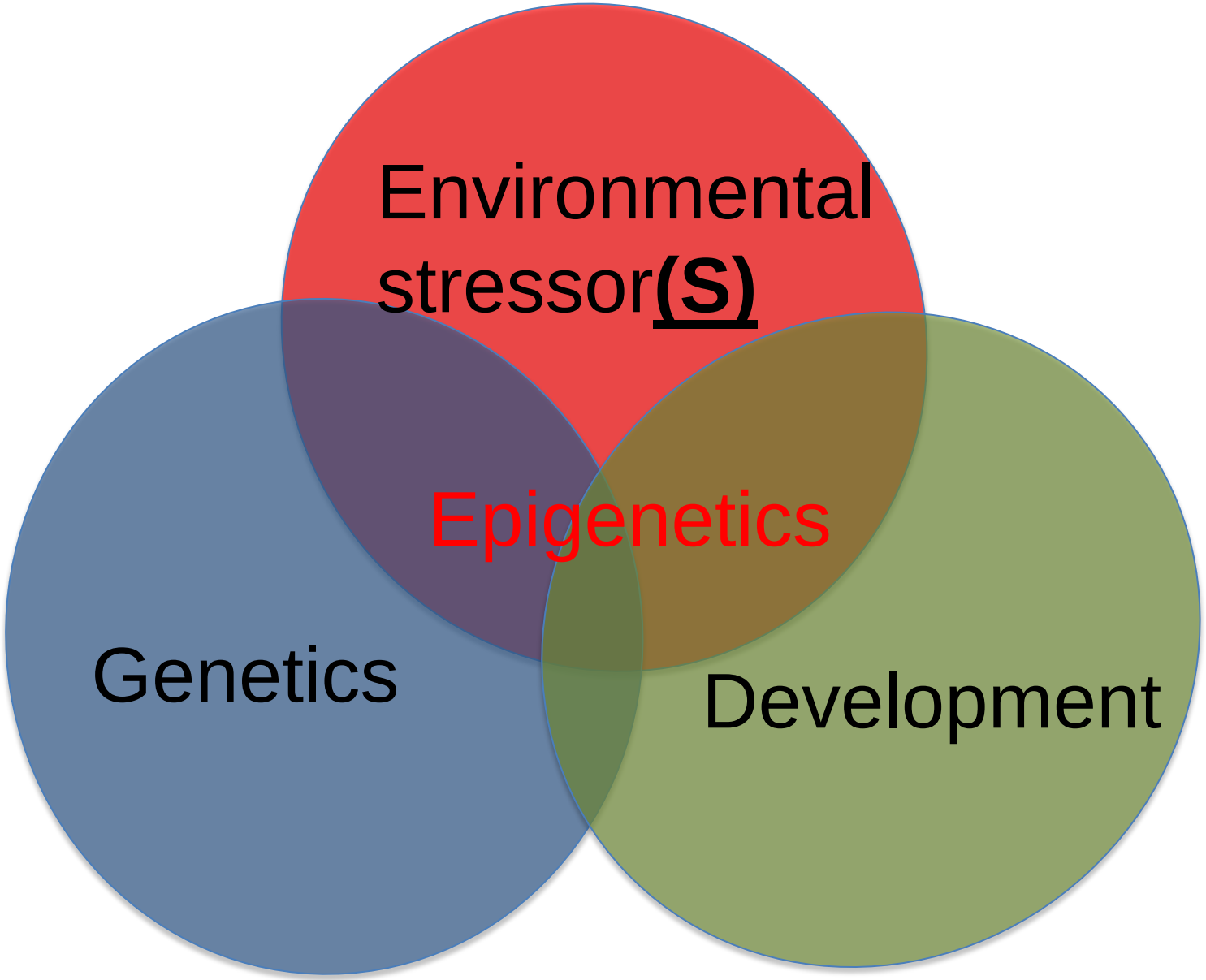
Temporal trends of triclosan contamination in dated sediment cores from four urbanized estuaries: Evidence of preservation and accumulation

Mark G. Cantwell[a,*], Brittan A. Wilson[b], Jun Zhu[c], Gordon T. Wallace[c], John W. King[d], Curtis R. Olsen[c], Robert M. Burgess[a], Joseph P. Smith[e]

Occurrence of triclosan in plasma of wild Atlantic bottlenose dolphins (*Tursiops truncatus*) and in their environment

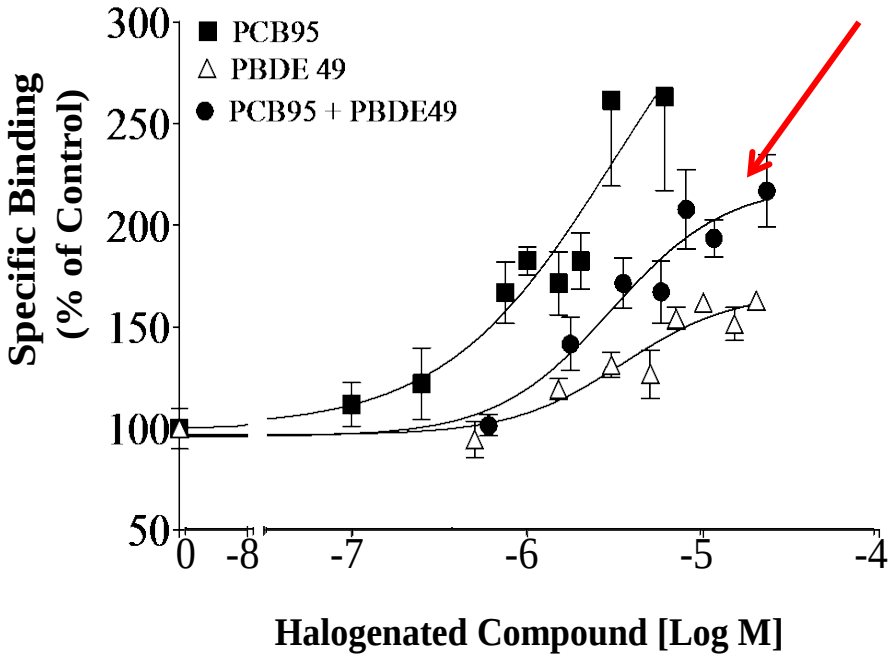
Patricia A. Fair[a,*], Hing-Biu Lee[b], Jeff Adams[a], Colin Darling[b], Grazina Pacepavicius[b], Mehran Alaee[b], Gregory D. Bossart[c,1], Natasha Henry[a], Derek Muir[b]

Understanding Complex Etiologies

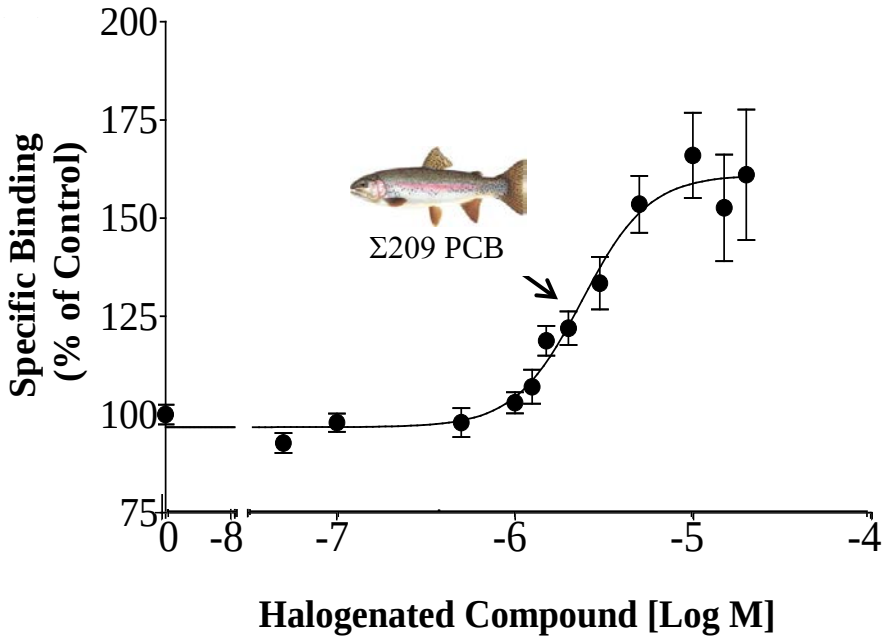


Mixtures at the RyR

(**A**) Activity of non-coplanar compounds (PCBs and PBDEs) are additive at the receptor



(B) NDL PCB mixtures currently detected in fish tissue activate the receptor



Fritsch and Pessah. 2013

Environmental Stress X Genetic Disorders?

RyR x Heart

Heart Failure
Arrhythmias (CPVT; ARVD2; TS)
Sympathetic Dysregulation
Ischemic Injury
Cardiomyopathies

RyR x skeletal muscle

Malignant Hyperthermia
Central Core Disease
Heat Stress
Aging related weakness
Myopathies (MG, MD…)

RyR x Brain

Alzheimer's Disease
Parkinson's Disease
Anxiety disorders

RyR x Endocrine

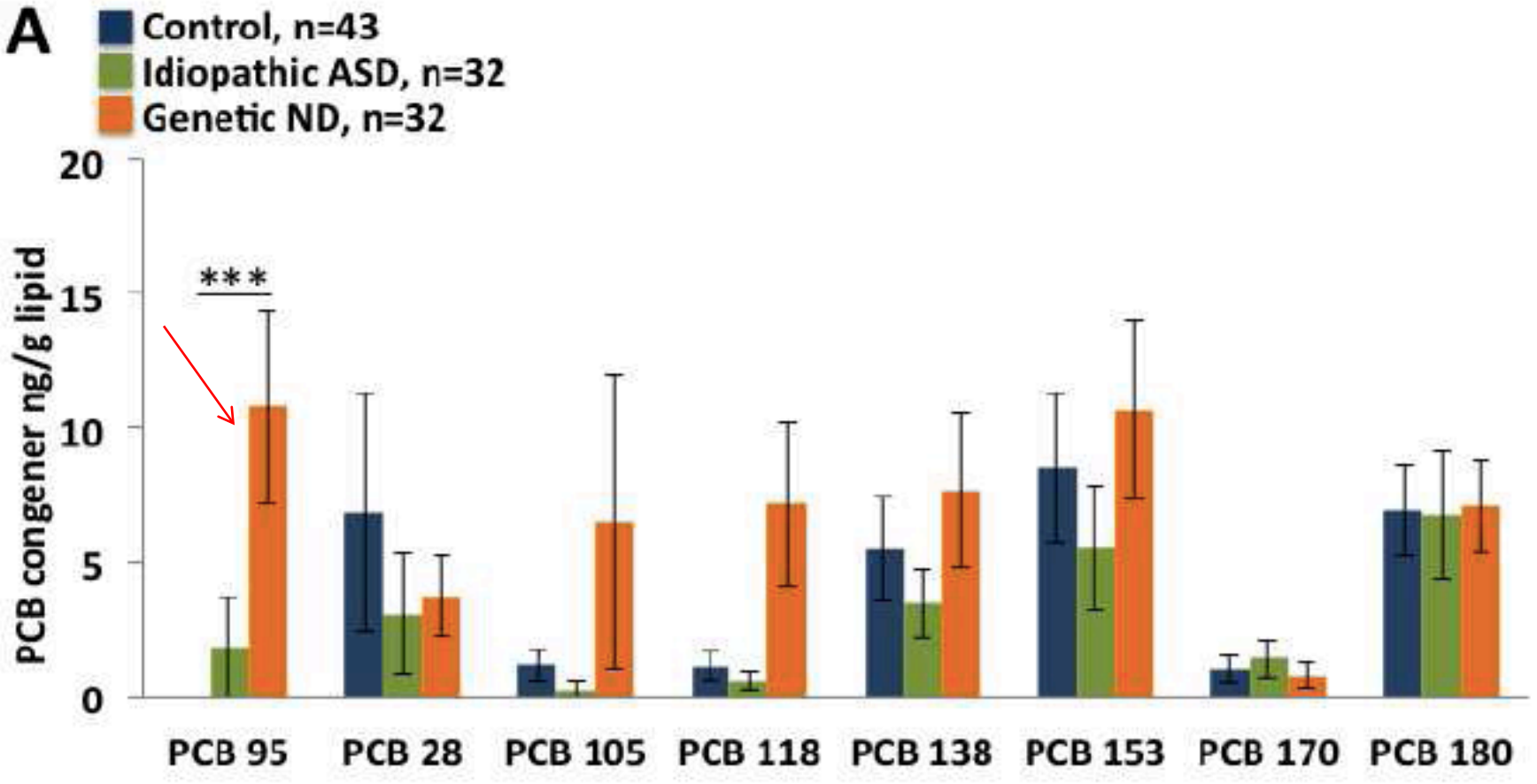
Metabolic Syn/Type1&2 Diabetes
Pituitary hormone secretion
GPER signaling (estrogen signaling)
AR signaling (androgen signaling)

RyR x Immune

Dendritic cell activation
T cell activation (HIV)

Combined genetic and chemical associations?

(*ex*) PCB Levels and15q forms of Autism



(Mitchell et al., 2012)

Looking Forward

- Define sensitive species, individuals and developmental stages
- Combined effects of multiple stressors
  - Similar mechanisms
  - Convergent molecular or physiological systems
  - Changing environmental factors (heat+chemical)
- Long-term population impacts
  - Pollutants affecting Ocean and Human Health have now spanned multiple “generations”
  - Little information regarding contribution to disease incidence