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

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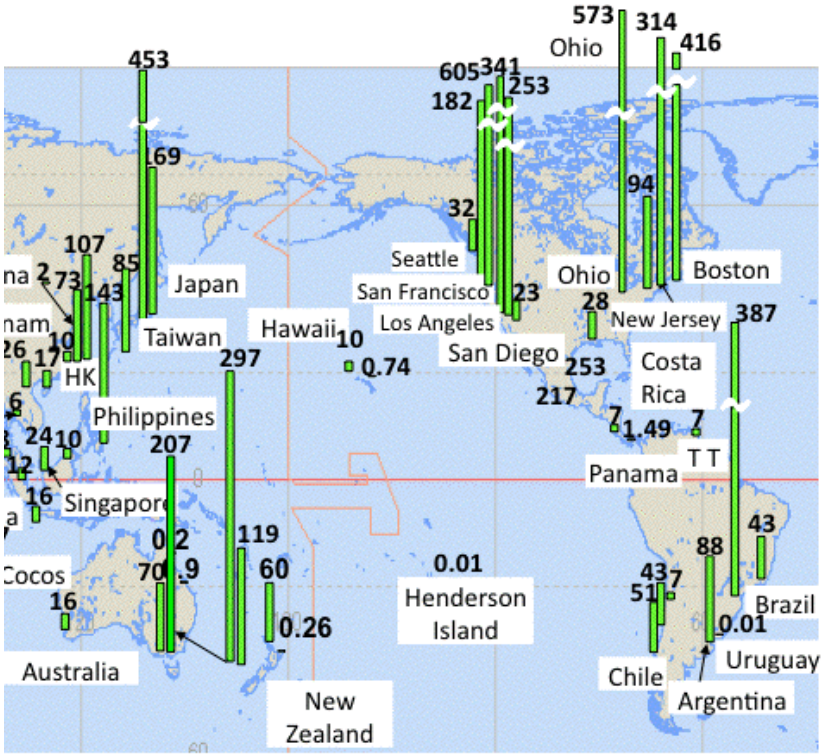
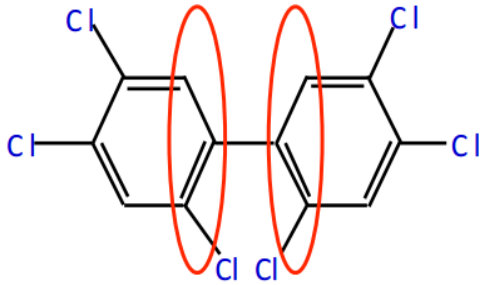
Chemicals and Neurodevelopmental Disorders

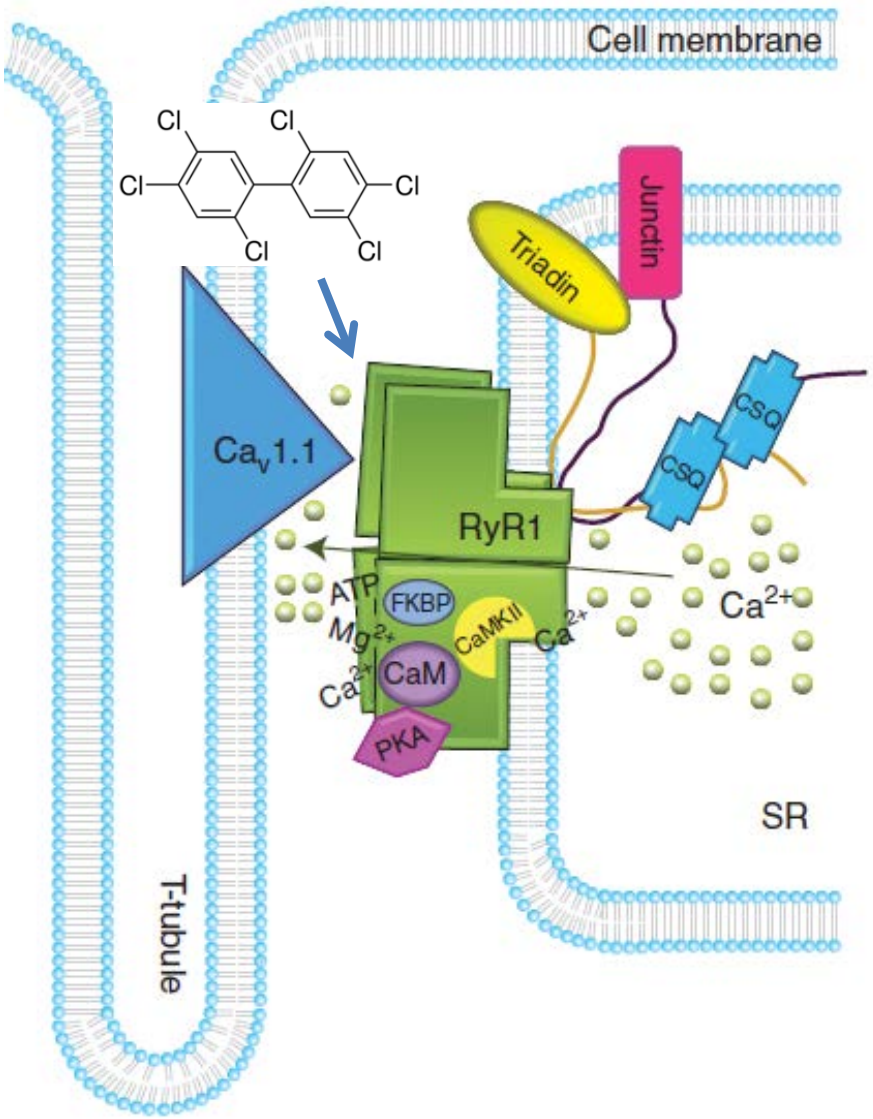
- Persistent Organic Pollutant exposure correlates with neurodevelopmental deficits
- *Example:* Pre and post-natal exposure to PCBs associated with lower IQ, attention deficit disorder, and motor impairments
- Of the 209 congeners, *ortho* PCBs are known to target important neuronal pathways

PCBs found in plastics washed on to the worlds' beaches (ng/g-pellet; pelletwatch.org)





Ryanodine Receptor as a Molecular Target



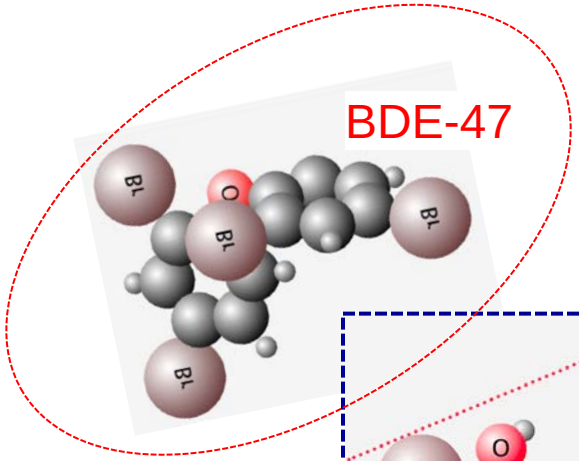
Important for proper

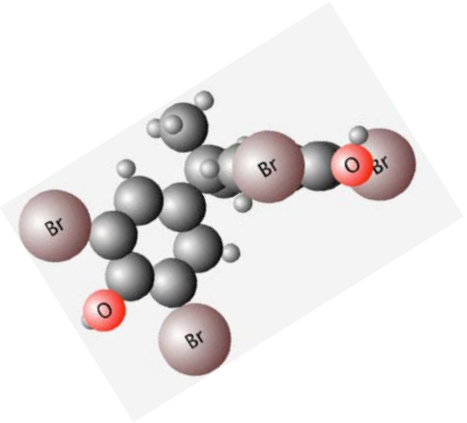
- Neuronal health and development
- Cardiac and skeletal muscle physiology, contractility, health
- Endocrine signaling

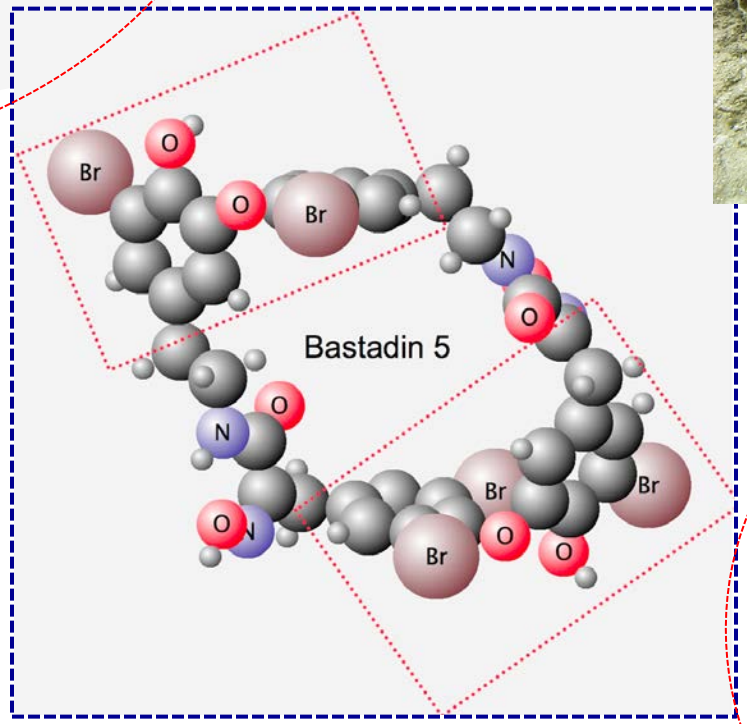
Alterations associated w/

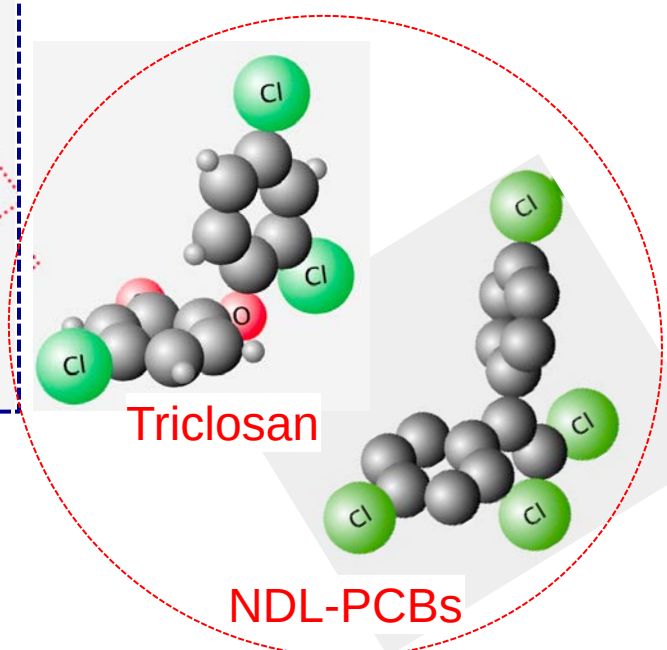
- Cardiac arrhythmias, failure
- Skeletal muscle myopathies
- Altered neuronal signaling and potential contribution to neuronal degeneration

Importance of Structure at the RyR









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RyR-related Toxic Outcomes

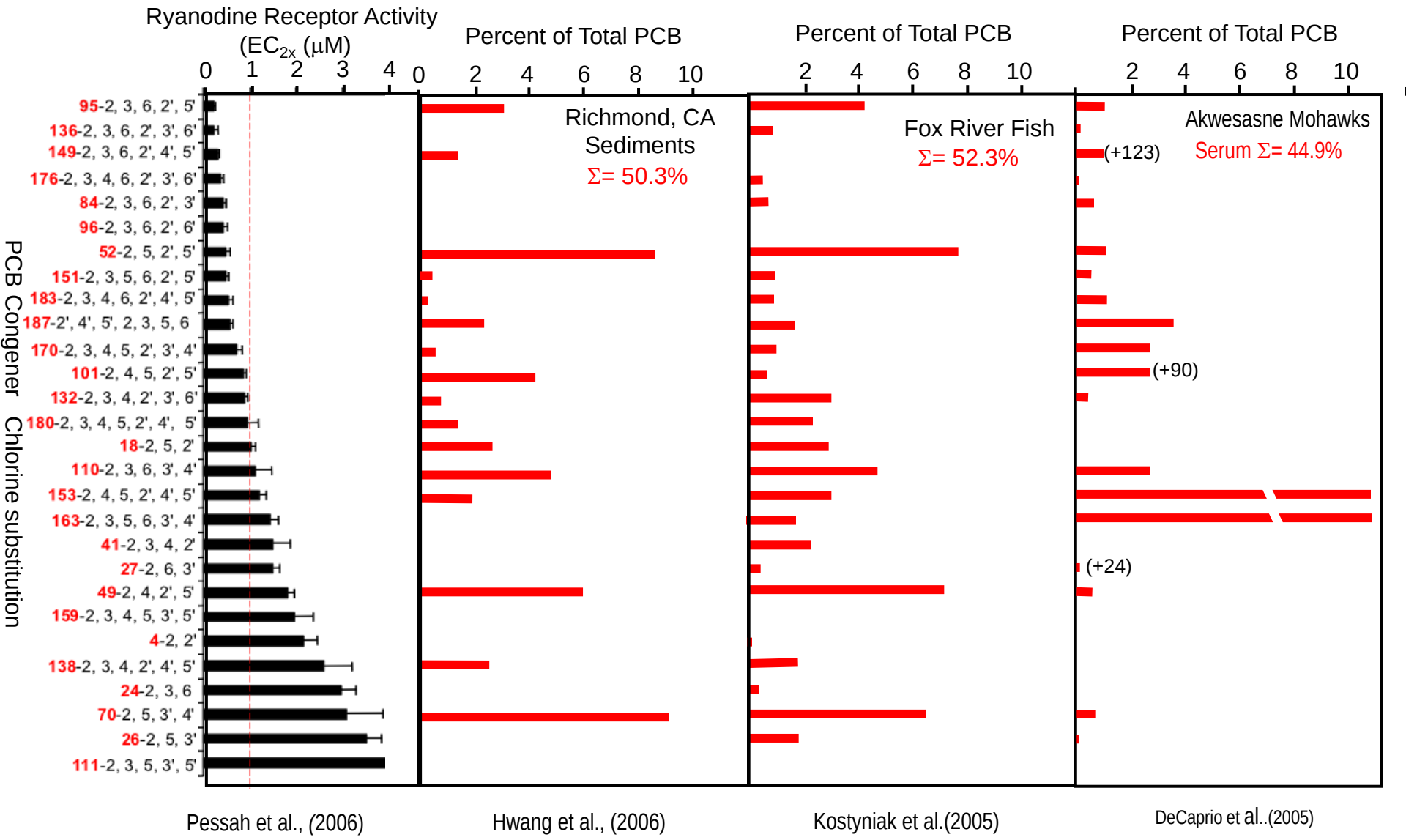
PCBs, PBDEs or their metabolites

- 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]

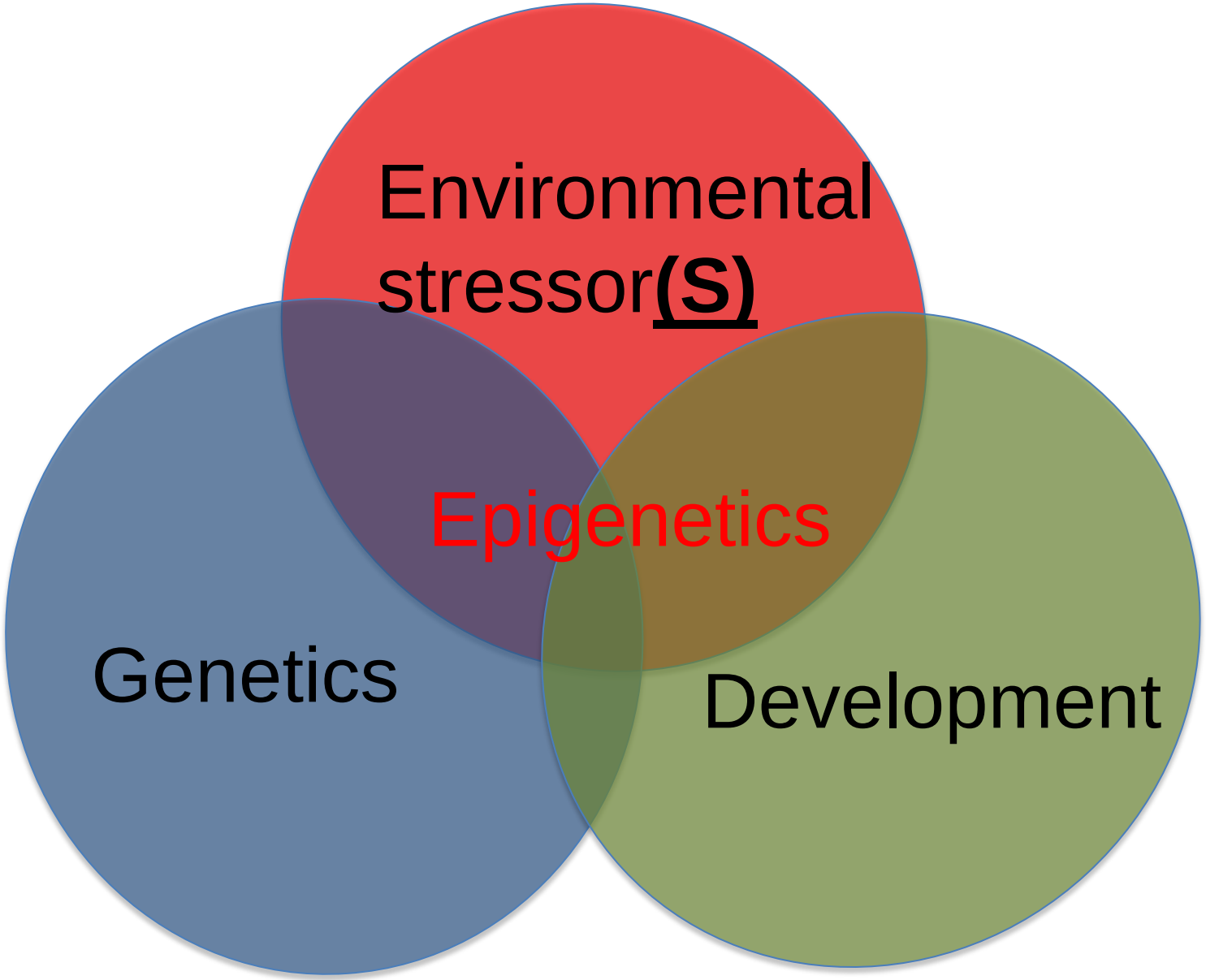
Temporal trends of triclosan contamination in dated sediment cores from four urbanized estuaries: Evidence of preservation and accumulation

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

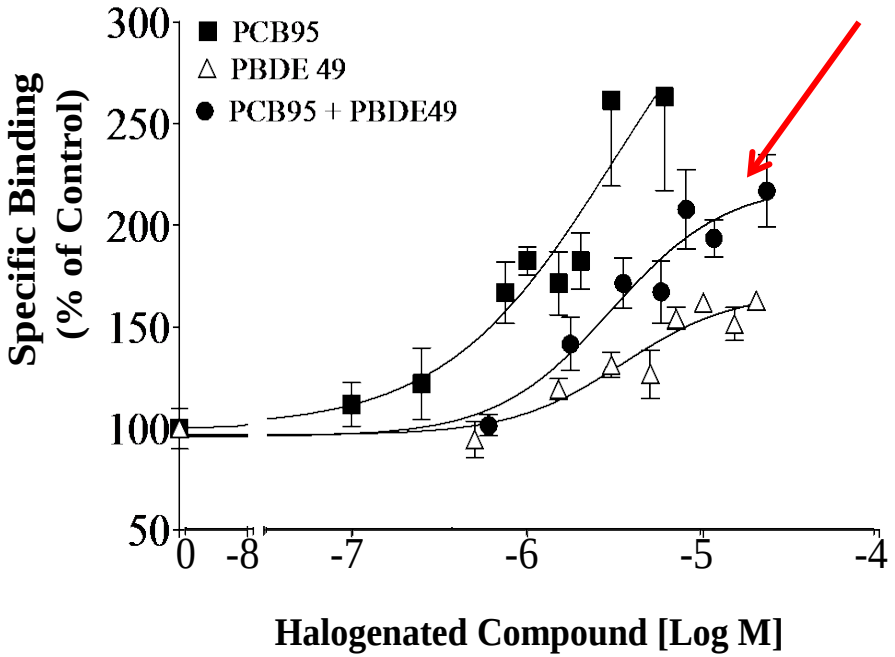
Patricia A. Fair[a,*], Hing-Biu Lee[b], Jeff Adams[a], Colin Darling[b], Grazina Pacepavicius[b], Mehran Alaee[b], Gregory D. Bossart[c,1], Natasha Henry[a], Derek Muir[b]

Understanding Complex Etiologies

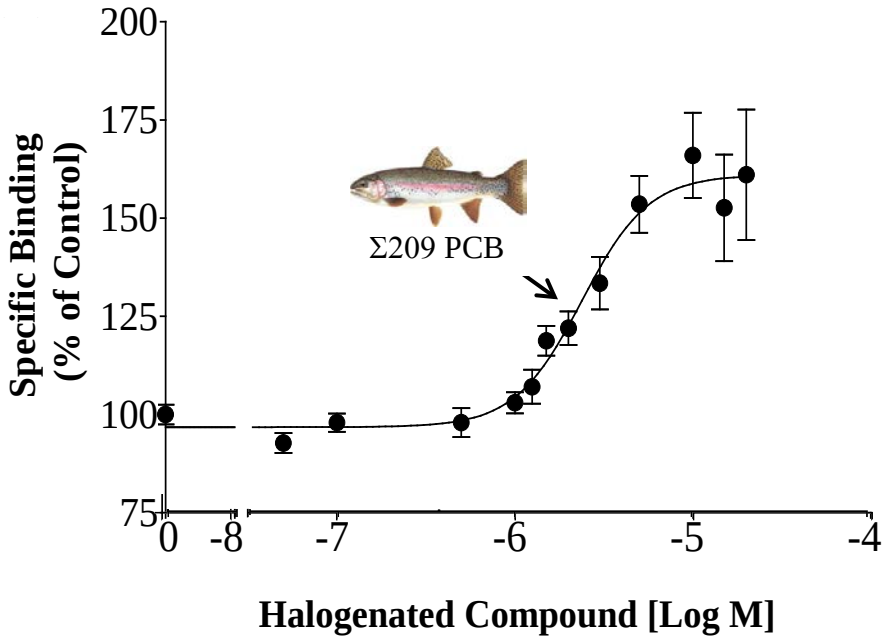


Mixtures at the RyR

(**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

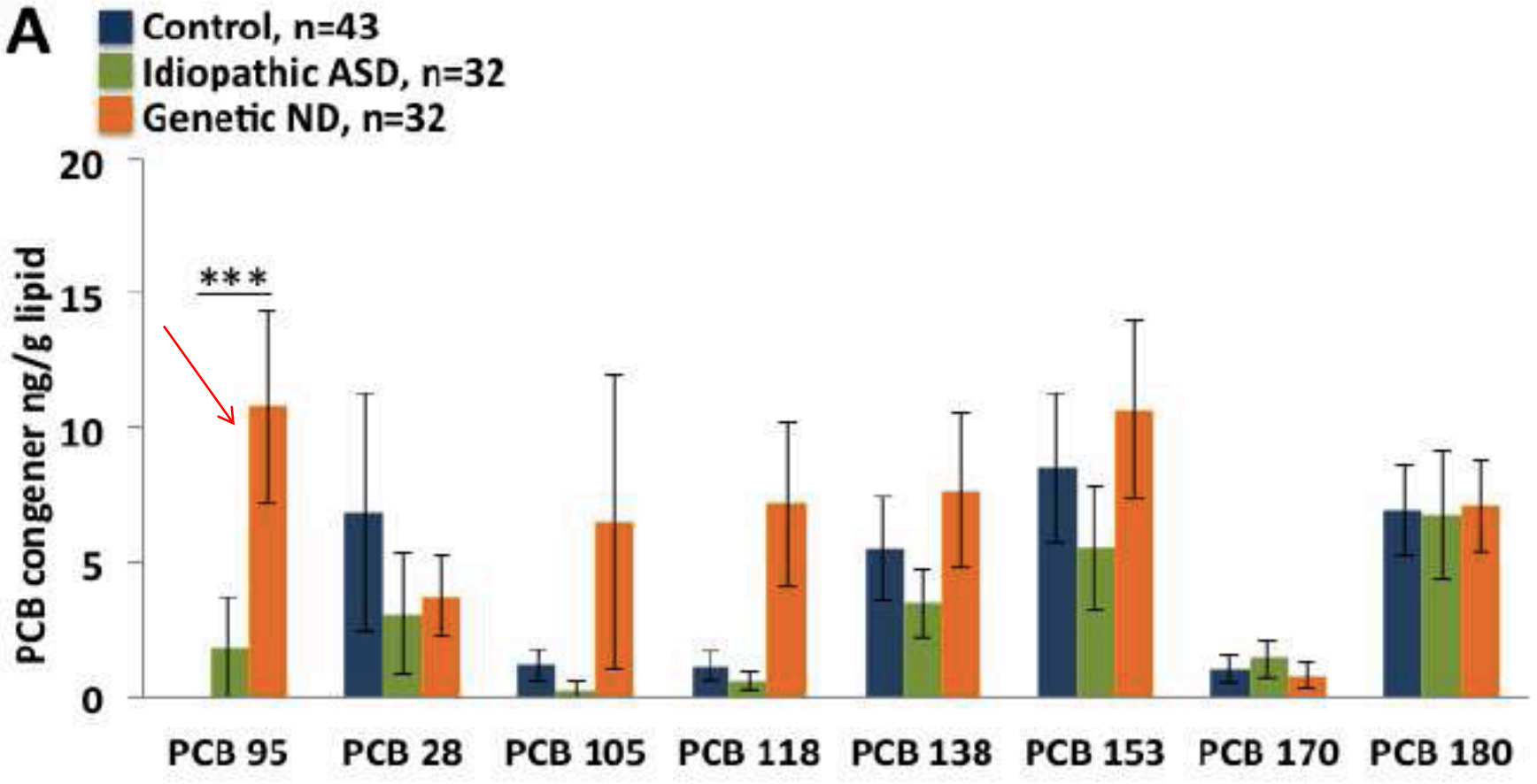
Metabolic Syn/Type1&2 Diabetes
Pituitary hormone secretion
GPER signaling (estrogen signaling)
AR signaling (androgen signaling)

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