# RECENT FINDINGS ON THE ROLE OF BPA AND BRAIN DEVELOPMENT

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Alberta Children's Hospital Research Institute

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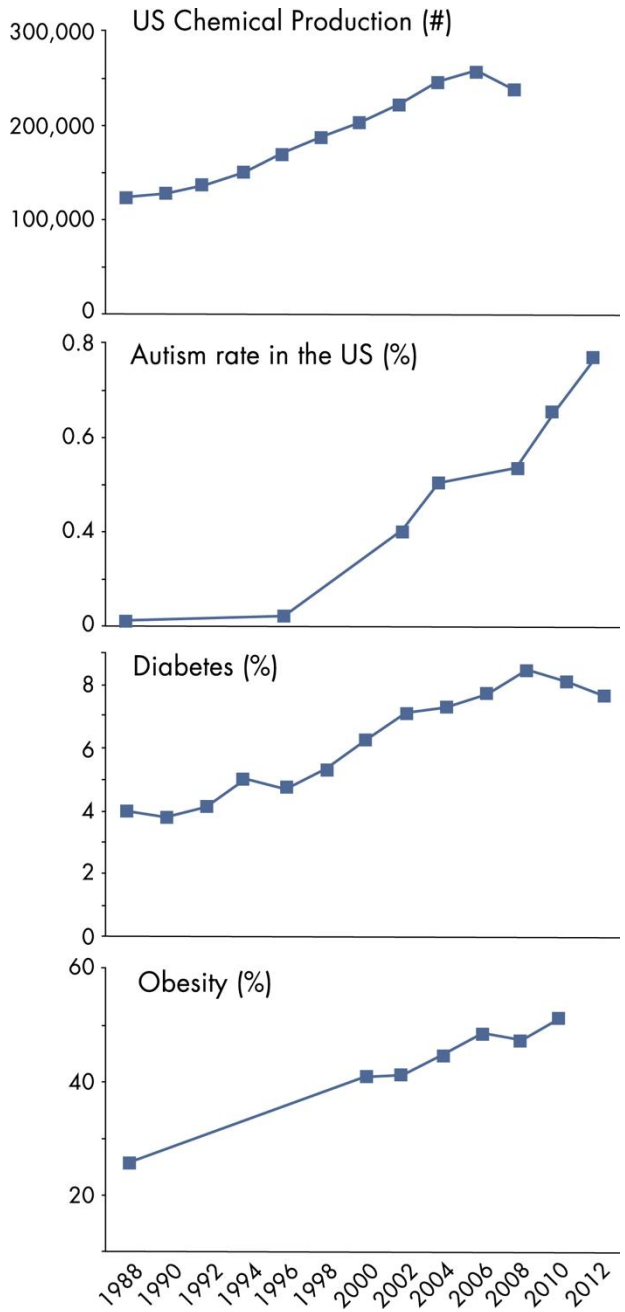
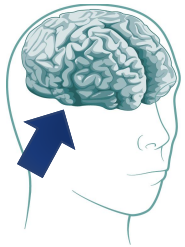
# Correlation between chemical production and disease



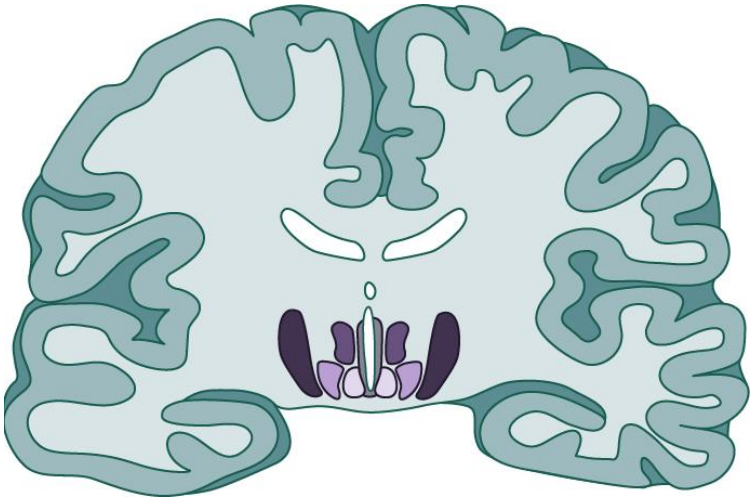

Gore et al, *Endocrine Reviews,* 2014

# The hypothalamus is the functional link between nervous and endocrine systems



Reproduction

Thermoregulation



Parenting/
Attachment
Behaviors

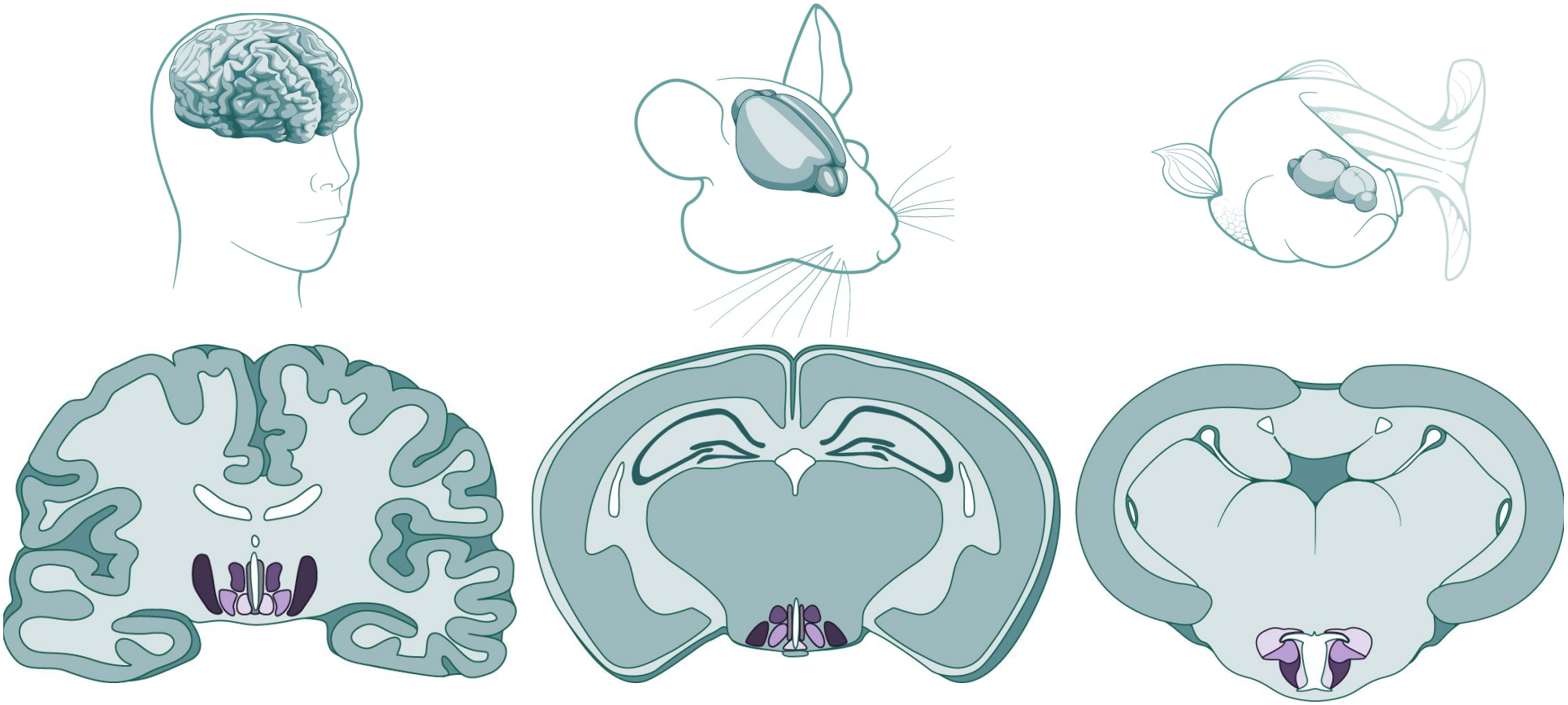
Hunger &
Satiety

Sleep

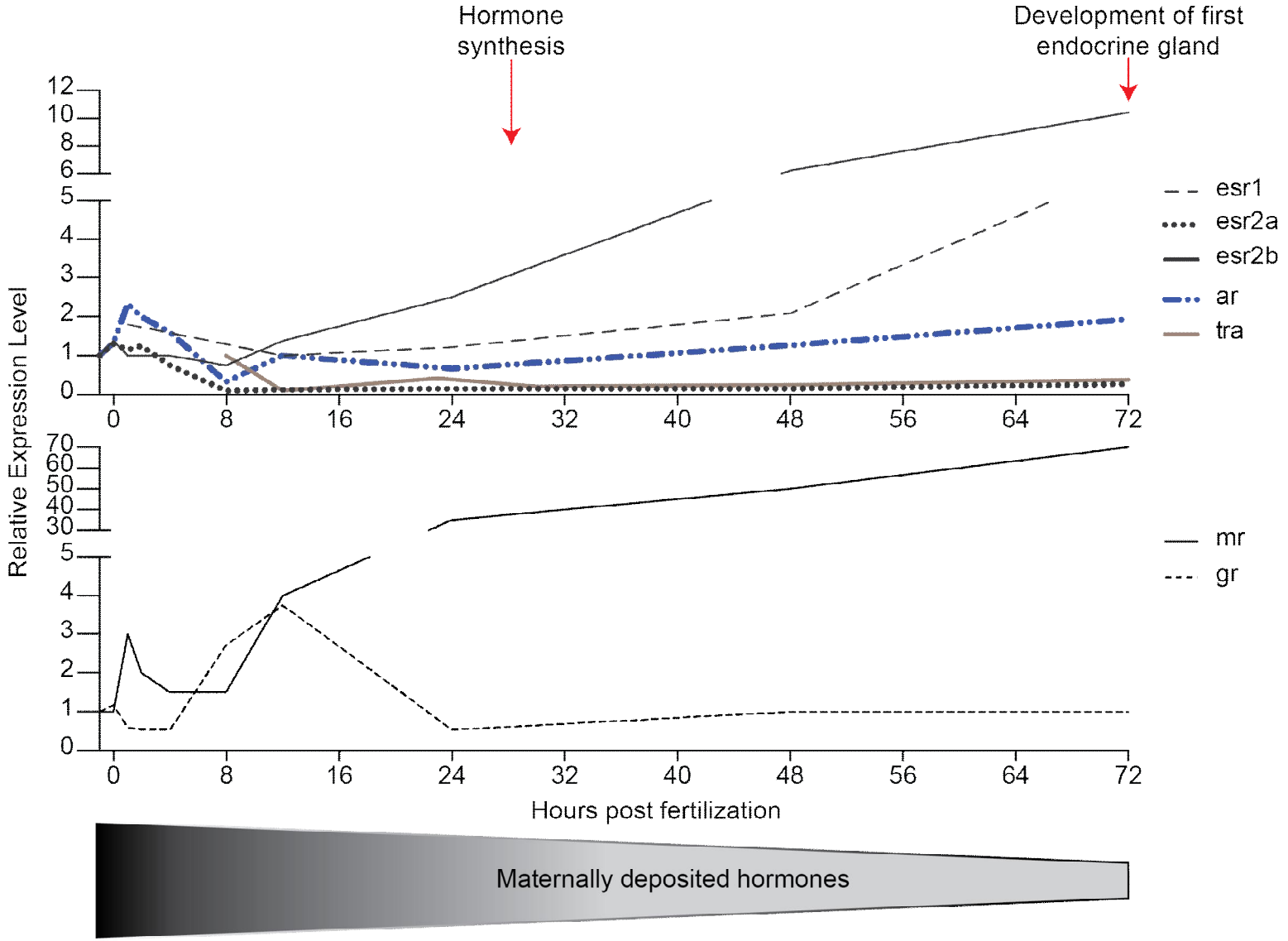
Thirst

Circadian
Rhythms

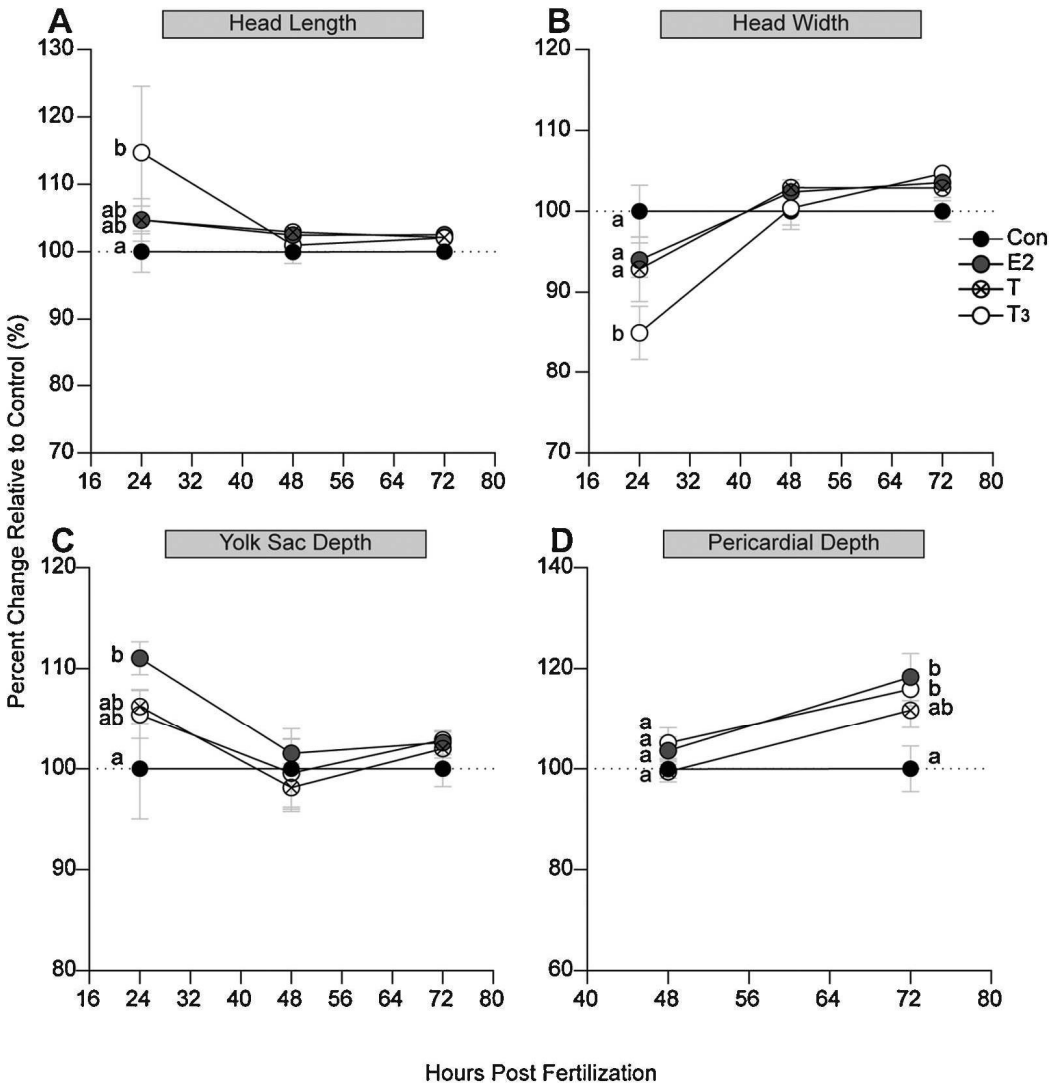
# Hypothalamic neuronal clusters are conserved



# Hormone receptors are expressed throughout development



# Hormones influence embryogenesis




Kinch et al, *Aquatic Tox*, 2016

# Estrogenic properties of BPA known since inception

- Discovered in 1930s by Edward Charles Dodd, British medical researcher looking for “mother substance” (synthetic estrogen)
- In 1950s US and Switzerland discovered how to synthesize epoxy resins and polycarbonate plastics
- These resins and plastics were quickly adopted because cheaper to make and strong enough to replace steel and clear enough/shatterproof to replace glass

# BPA exposure particularly during 2nd trimester leads to behavioral problems during childhood

## Impact of Early-Life Bisphenol A Exposure on Behavior and Executive Function in Children

**AUTHORS:** Joe M. Braun, MSPH, PhD,[a] Amy E. Kalkbrenner, MPH, PhD,[b] Antonia M. Calafat, PhD,[c] Kimberly Yolton, PhD,[d] Xiaoyun Ye, PhD,[c] Kim N. Dietri PhD,[e] and Bruce P. Lanphear, MD, MPH[d,f]

## Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children

Kim G. Harley[a], , , Robert B. Gunier[a], Katherine Kogut[a], Caroline Johnson[a], Asa Bradman[a], Antonia M. Calafat[b], Brenda Eskenazi[a]

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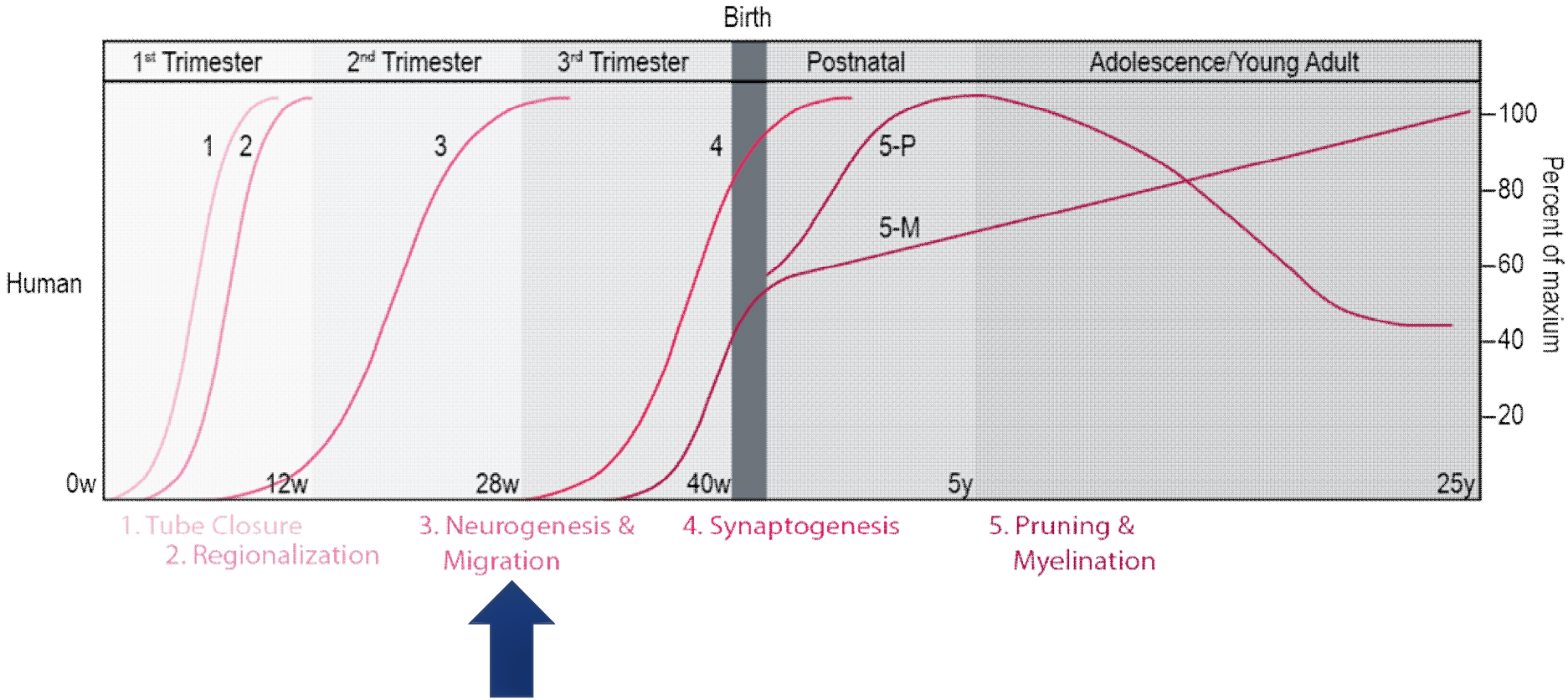
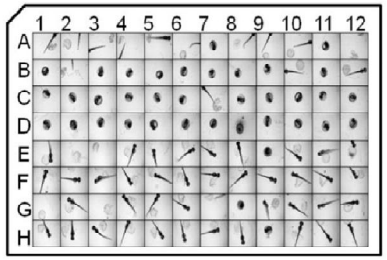
[b] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA

# Neurodevelopment as a protracted series of steps



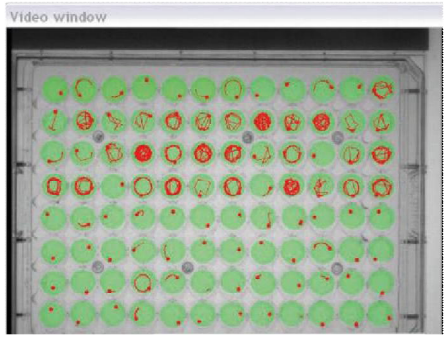

Schuurmans C and Kurrasch DM, *Clinical Genetics*, 2013

# Behavioral analyses using zebrafish



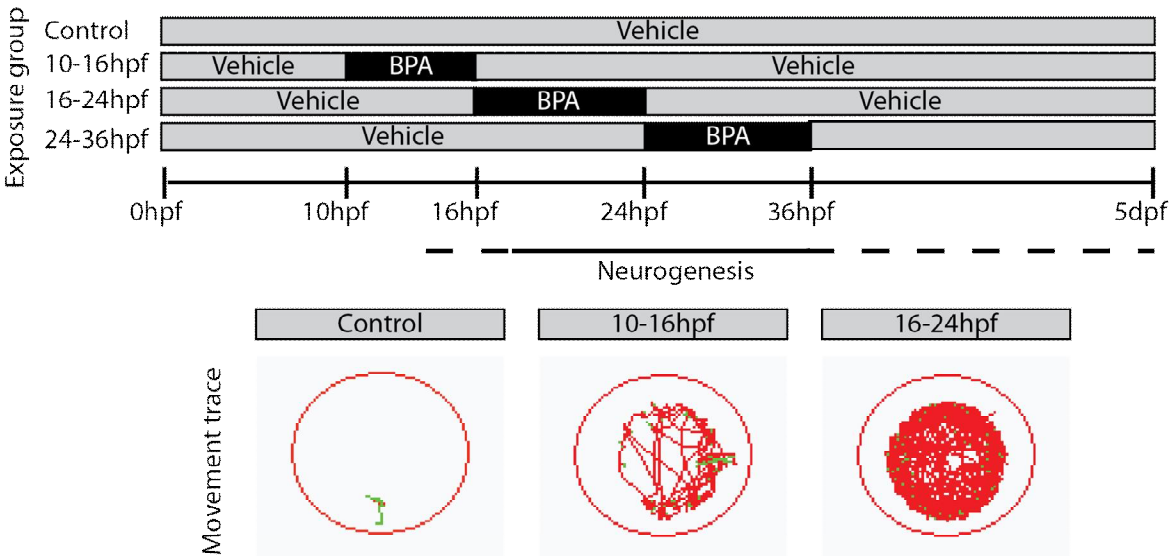

Larvae seeded into 96-well plate
+
Exposed to compounds

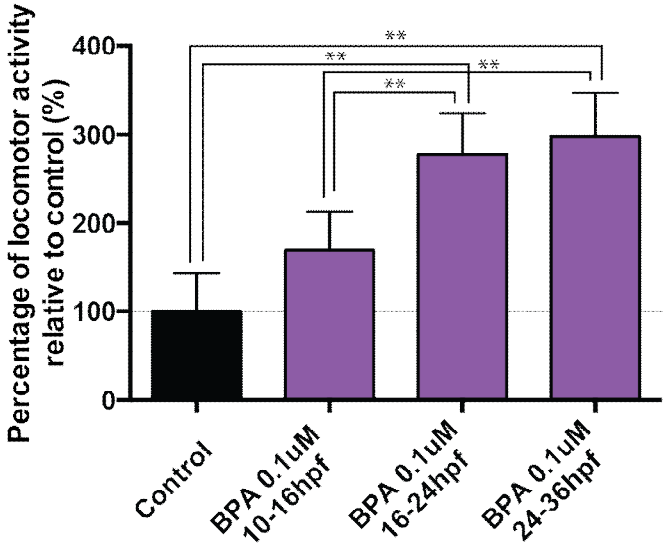
96-well plates are loaded into ZebraLab behavioral box




Overall activity levels is captured
(red scripe = movement of a fish)

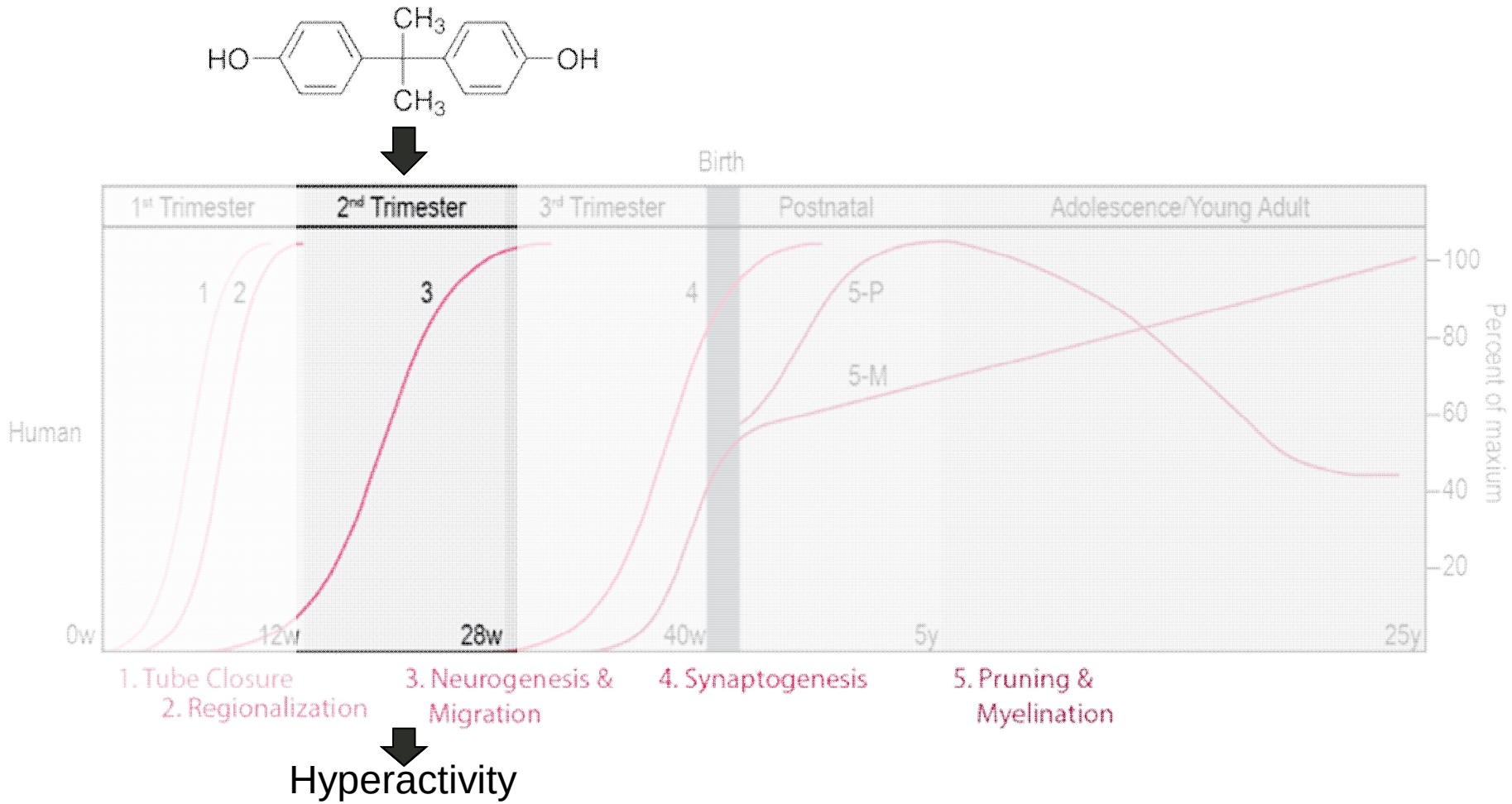
# Critical windows of BPA behavioral effects



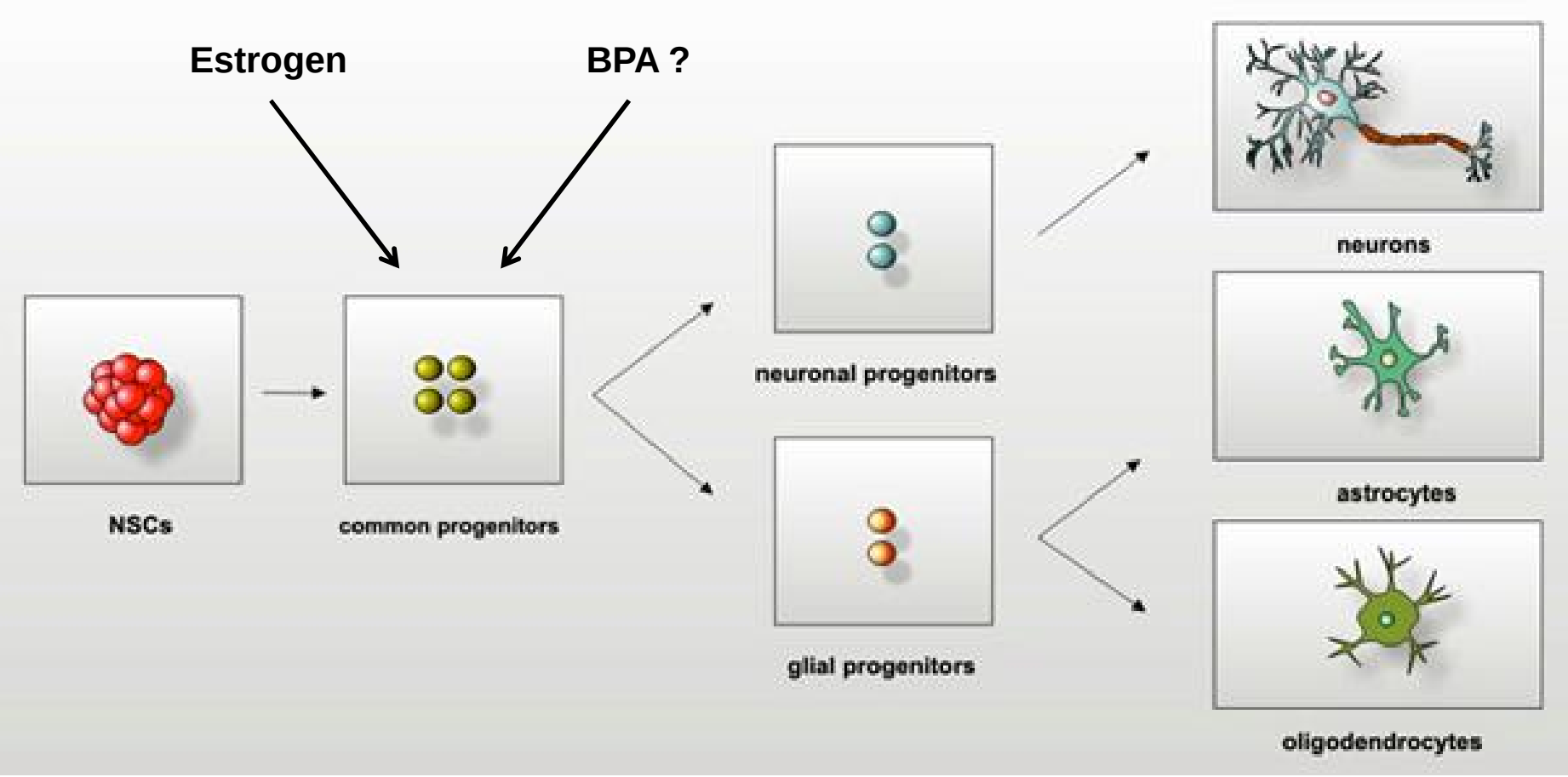




Kinch CD et al, *PNAS*, 2015

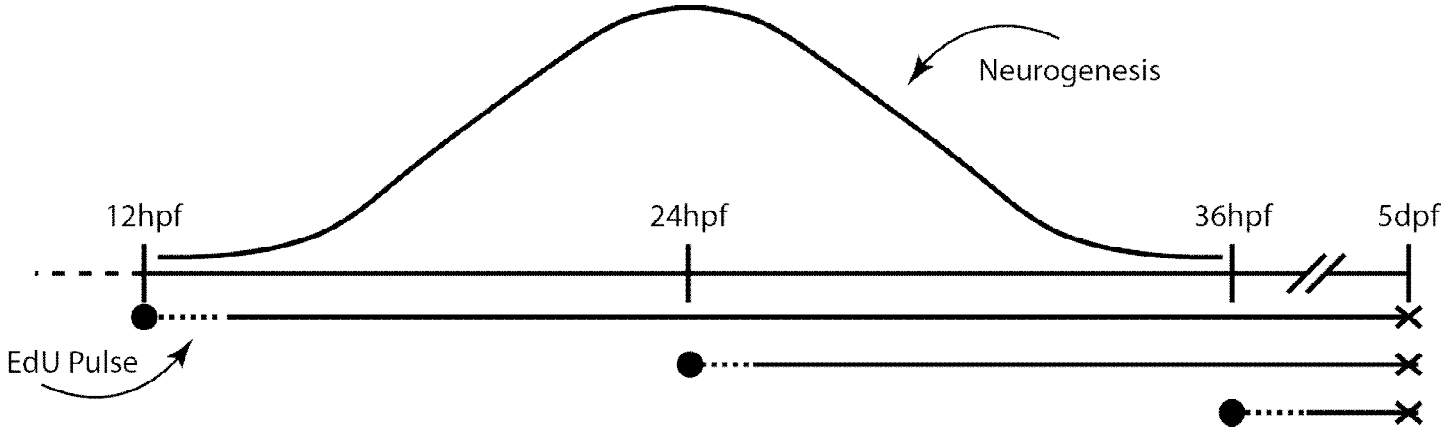
# What BPA-mediated neurodevelopmental insults transduce into childhood behavioral disorders

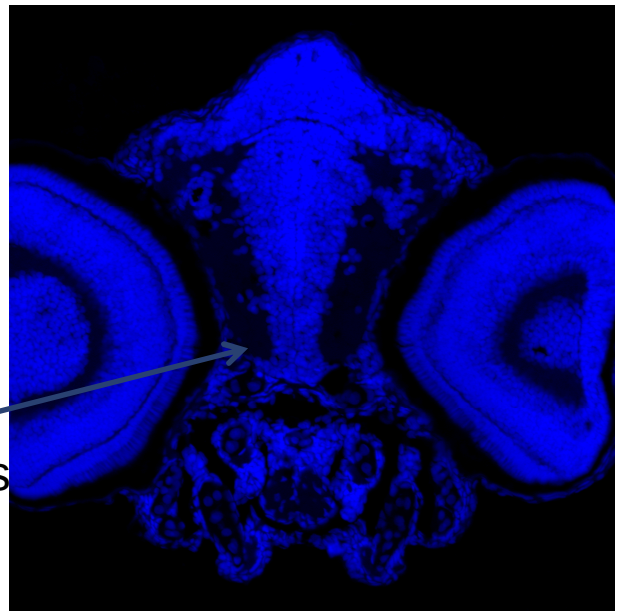


# Neural progenitors are responsive to estradiol

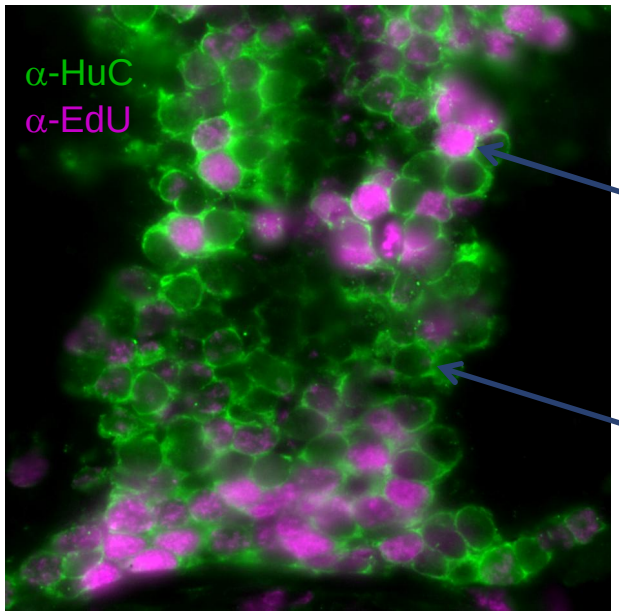


# Measure neurogenic phase in zebrafish hypothalamus



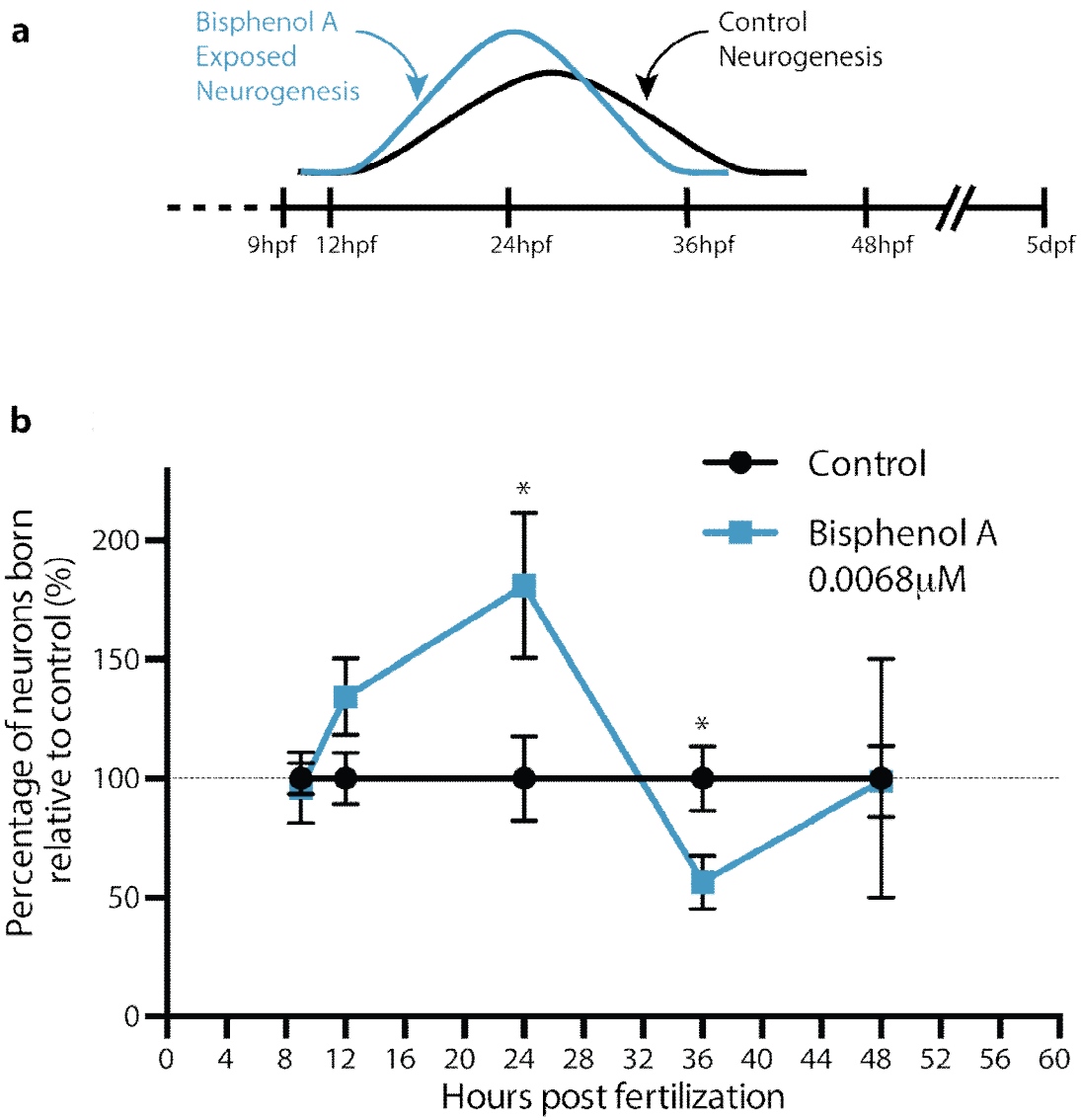
Hypothalamus




Neuron born at EdU pulse

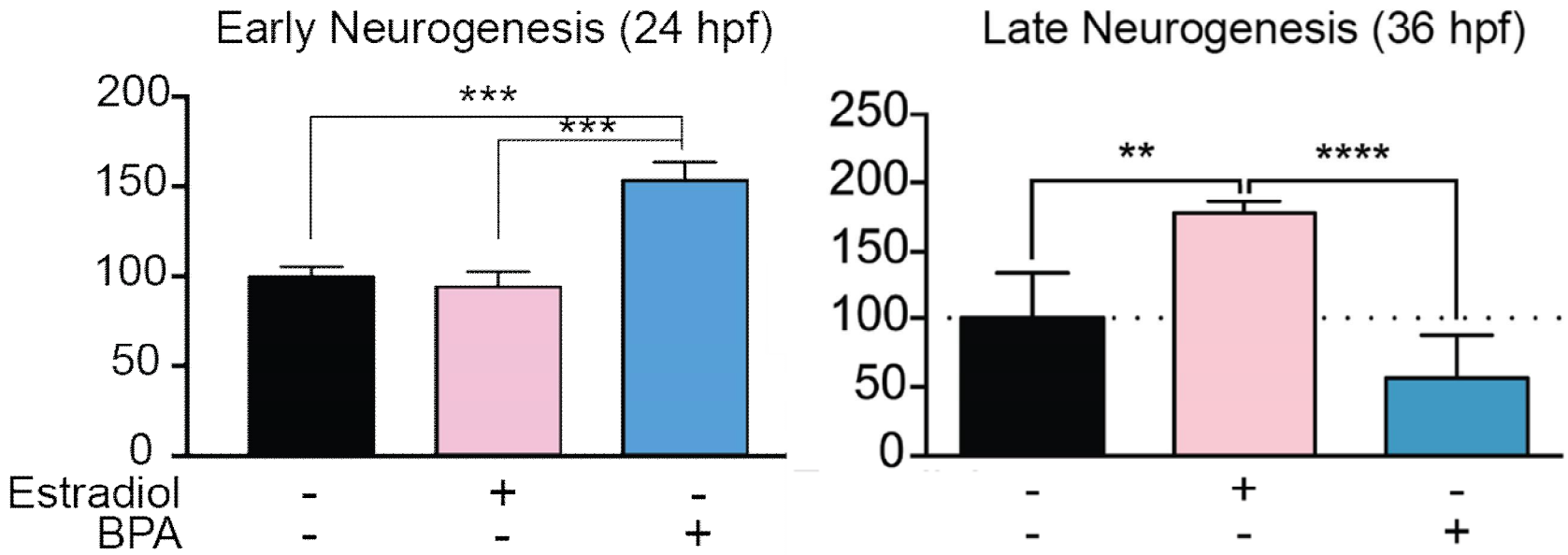
Neuron

# BPA induces a two-fold increase in the number neurons born at peak neurogenesis



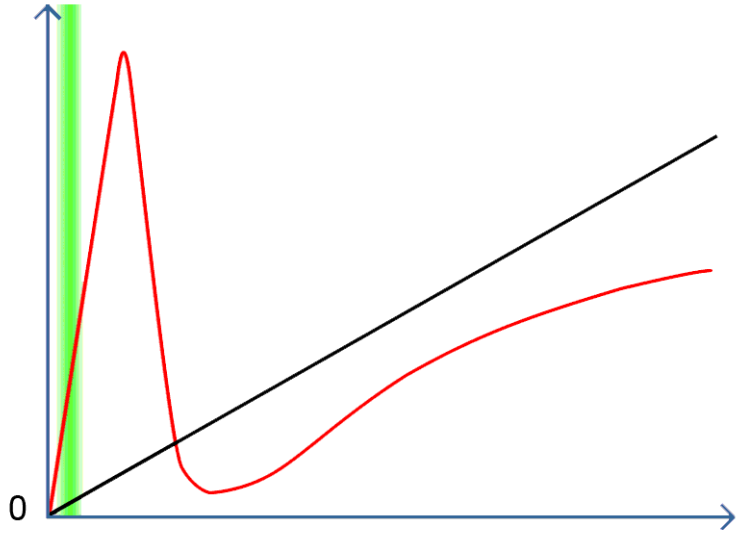

Kinch CD, *PNAS*, 2015

# Estradiol does induce precocious neurogenesis, but at a later timepoint

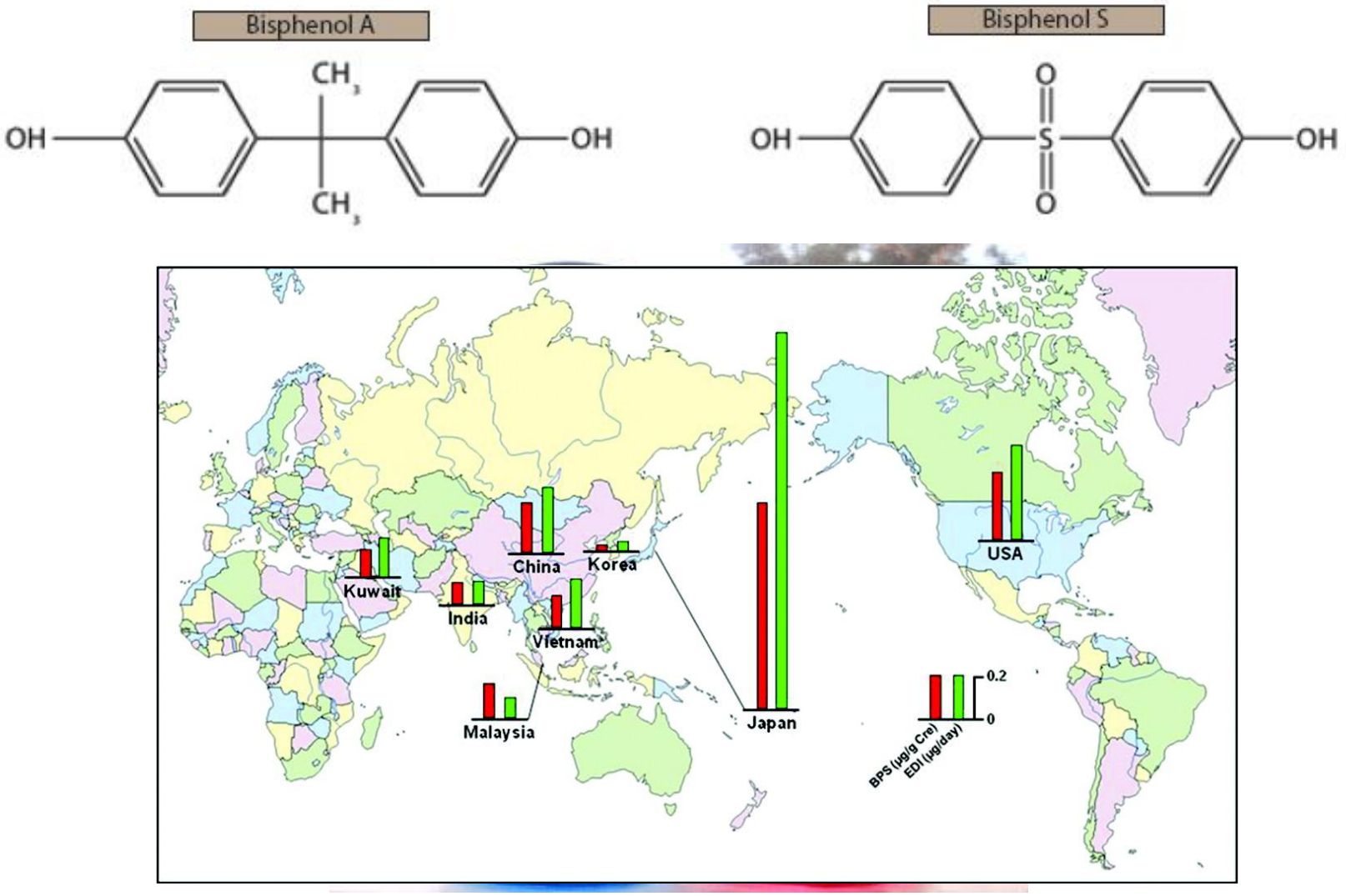


# Low dose effects, biphasic curves

- An assumption is if higher doses cause no harm, then lower doses must be safe
- The lowest observed adverse effect level of 50mg/kg body weight/day was used to calculate the EPA reference dose of 0.05mg/kg body weight/day
- The endocrine system does not follow this linear relationship
- Many studies show significant effects much lower than 0.05mg/kg body weight/day

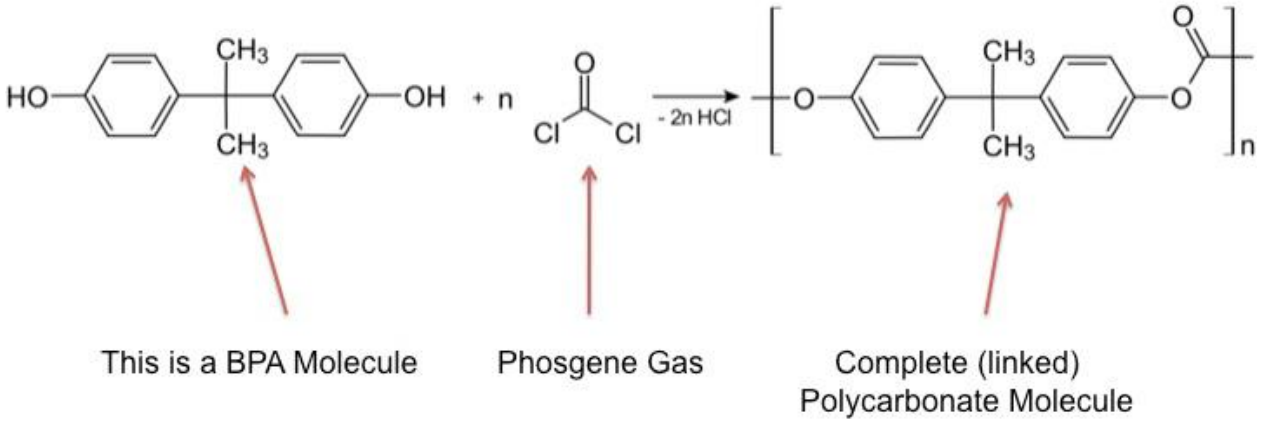


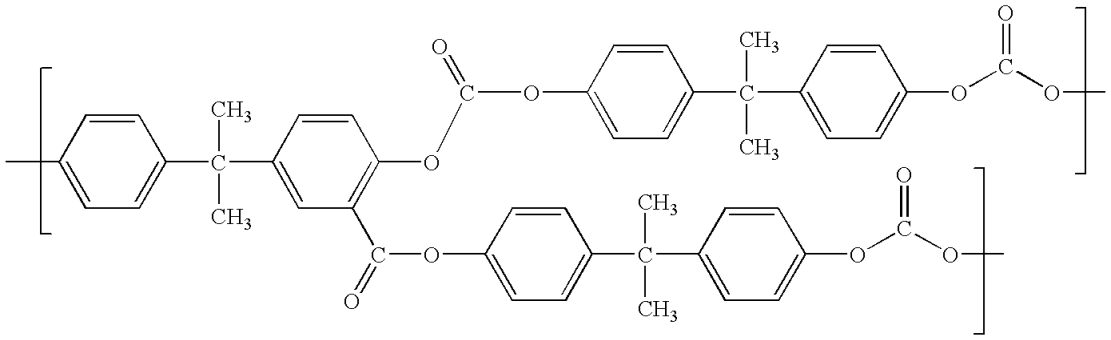
# Are BPA-free products safe?




Liao et al, *Environmental Science and Technology*, 2012

# How plastics are hardened



(III)

# BPS also induces precocious neurogenesis

# Is precocious neurogenesis conserved in mammals?

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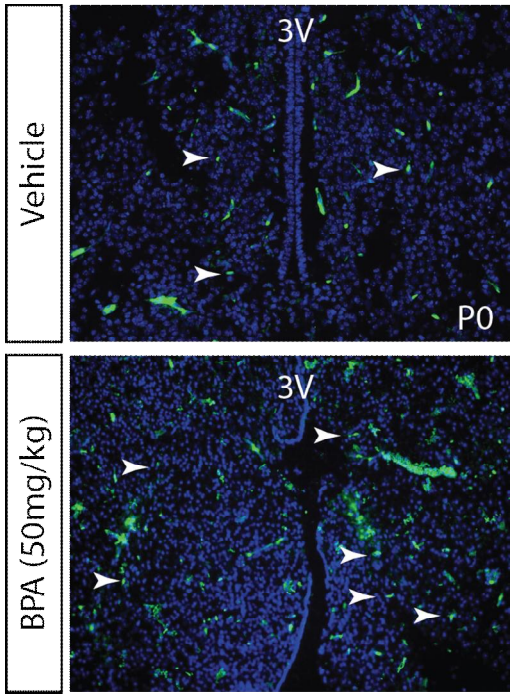
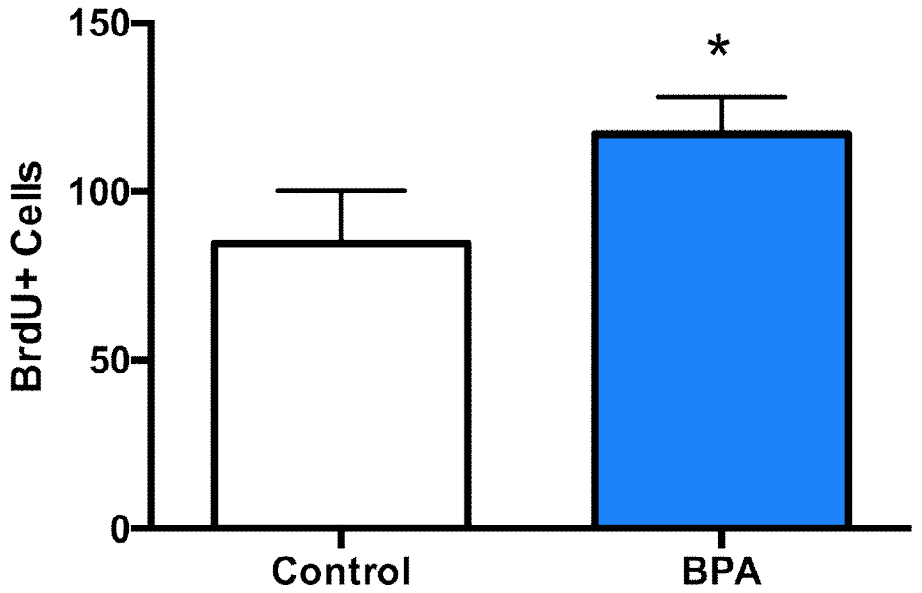
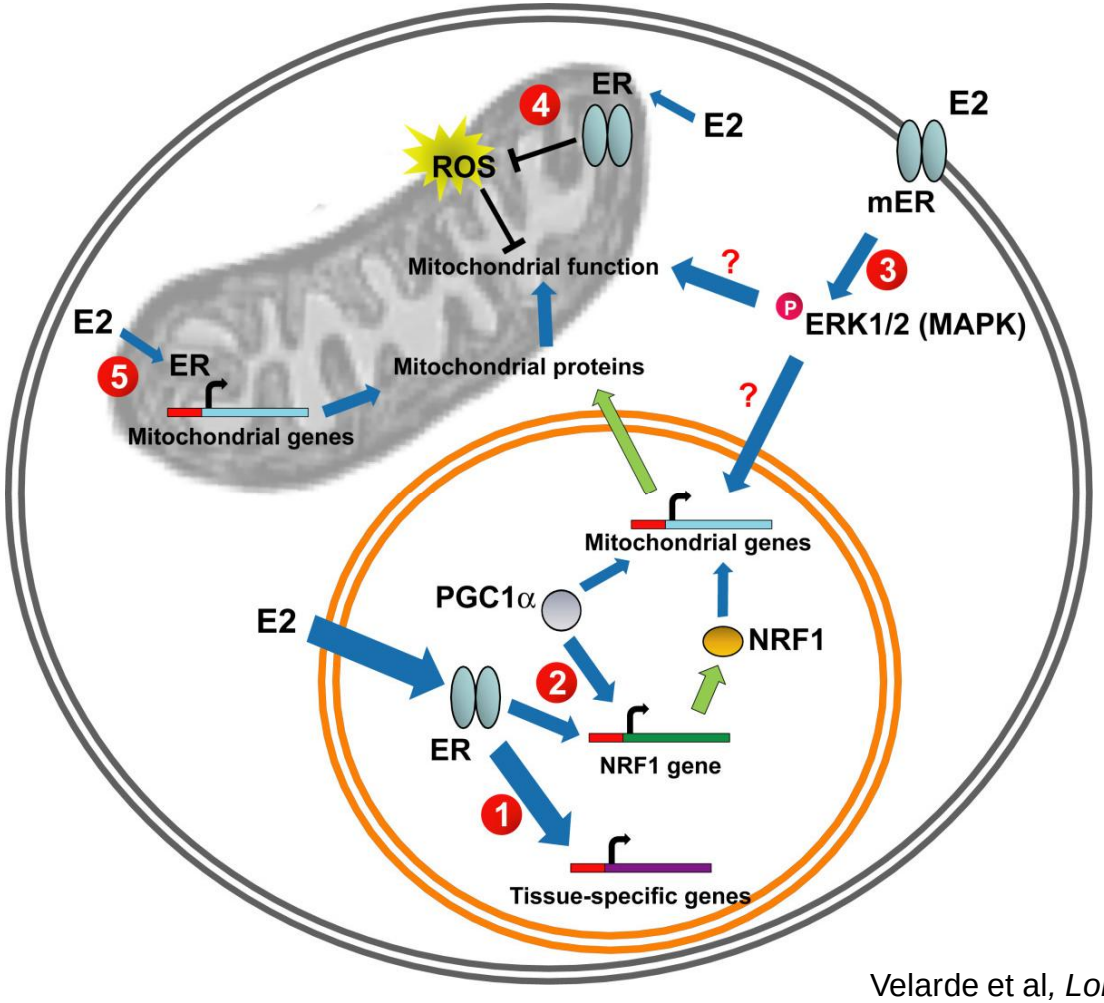
# BPA increases neurogenesis in developing mouse brains



# How does estradiol mechanistically influence proliferation?




Velarde et al, *Longevity & Healthspan*, 2012

# Emerging role for sex steroids in regulating neurogenesis

## 17α-Ethinylestradiol and nonylphenol affect the development of forebrain GnRH neurons through an estrogen receptors-dependent pathway

Mélanie Vosges[a], Olivier Kah[b], Nathalie Hinfray[a], Edith Chadili[a], Yann Le Page[b], Yves Combarnous[c], Jean-Marc Porcher[a], François Brion[a,*]

[a] *Unité d'évaluation des risques écotoxicologiques, Direction des Risques Chroniques, Institut National de l'Environnement Industriel et des Risques (INERIS), BP 2. F-60550 Verneuil-en-Halatte, France*
[b] *Neurogenesis and Oestrogens, Université de Rennes 1, UMR CNRS 6026, IFR140, Campus de Beaulieu, 35042 Rennes cedex, France*
[c] *INRA, CNRS, Université François Rabelais de Tours, Physiologie de la Reproduction et des Comportements Nouzilly, France*

## 17β-Estradiol enhances neuronal differentiation of mouse embryonic stem cells

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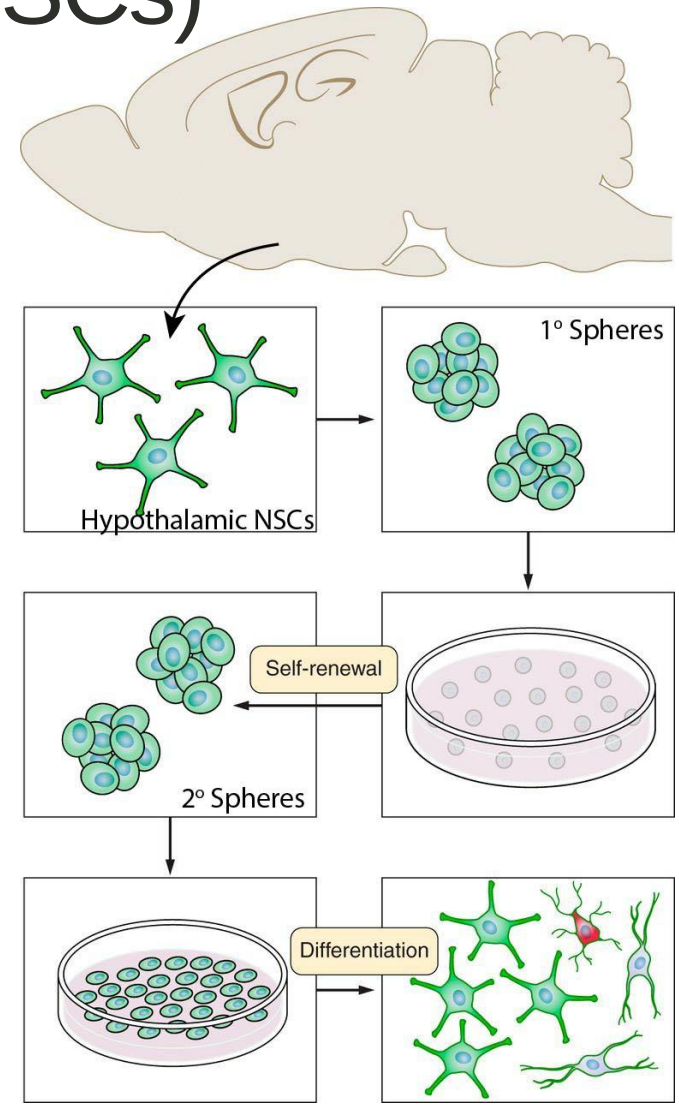
*Department of Physiology, East Carolina University School of Medicine, Brody Bldg. #6N-98, 600 Moye Blvd., Greenville, NC 27858, USA*

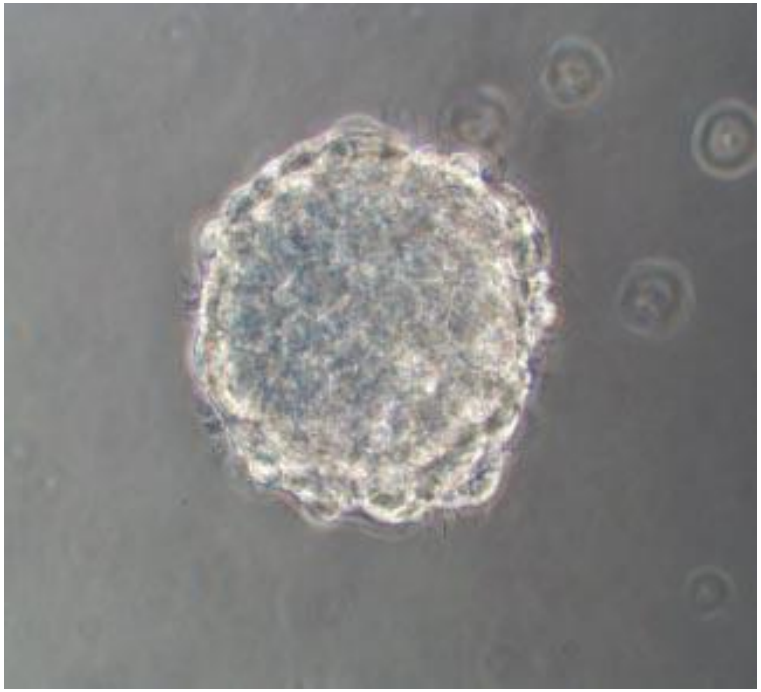
## Estradiol stimulates progenitor cell division in the ventricular and subventricular zones of the embryonic neocortex

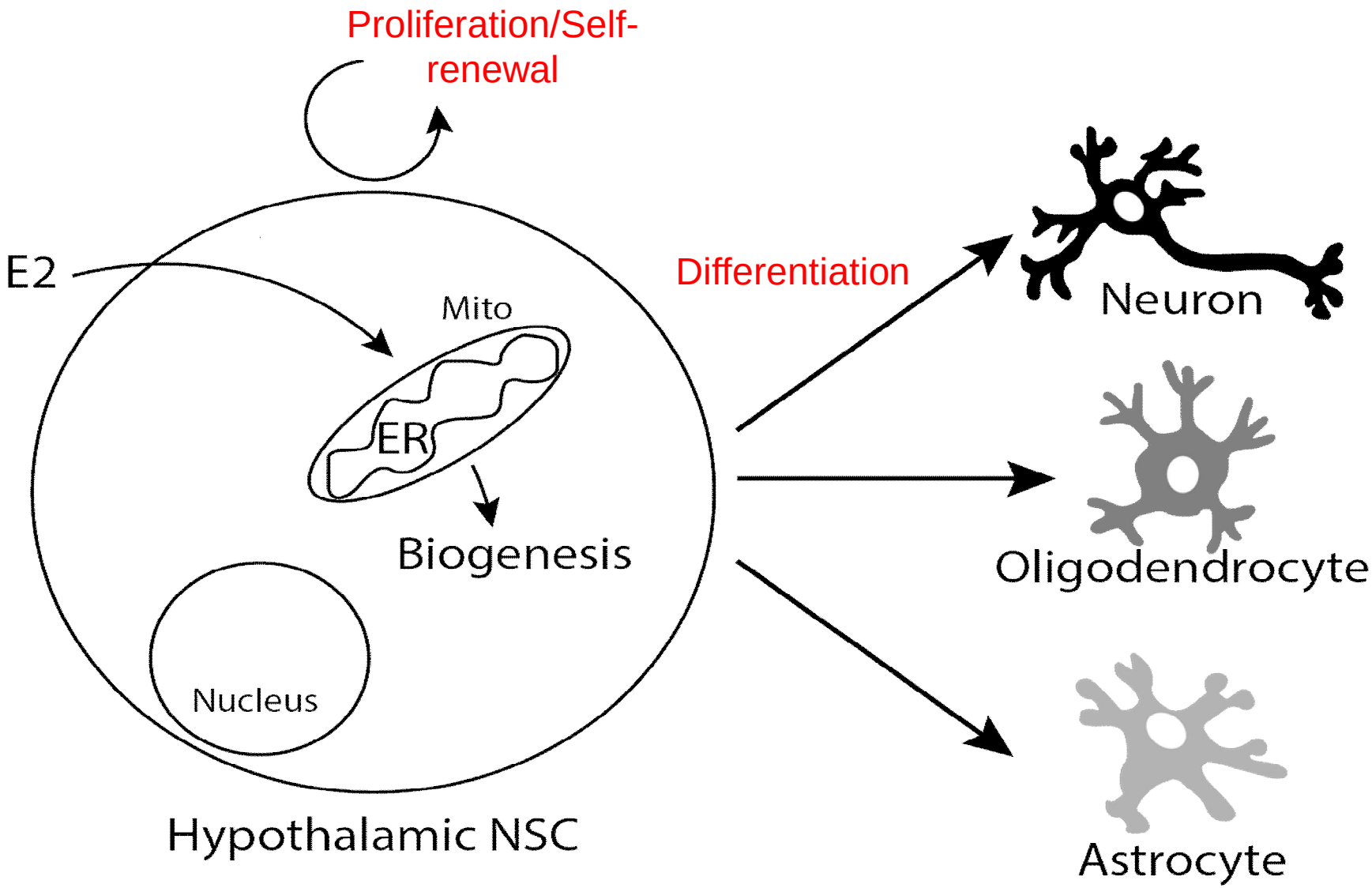
Verónica Martínez-Cerdeño, Stephen C. Noctor and Arnold R. Kriegstein
Department of Neurology and Program in Developmental and Stem Cell Biology, 513 Parnassus Avenue, HSW 1201, Box 0525, University of California San Francisco, San Francisco, California 94143, USA

# Culturing hypothalamic neural stem cells (NSCs)

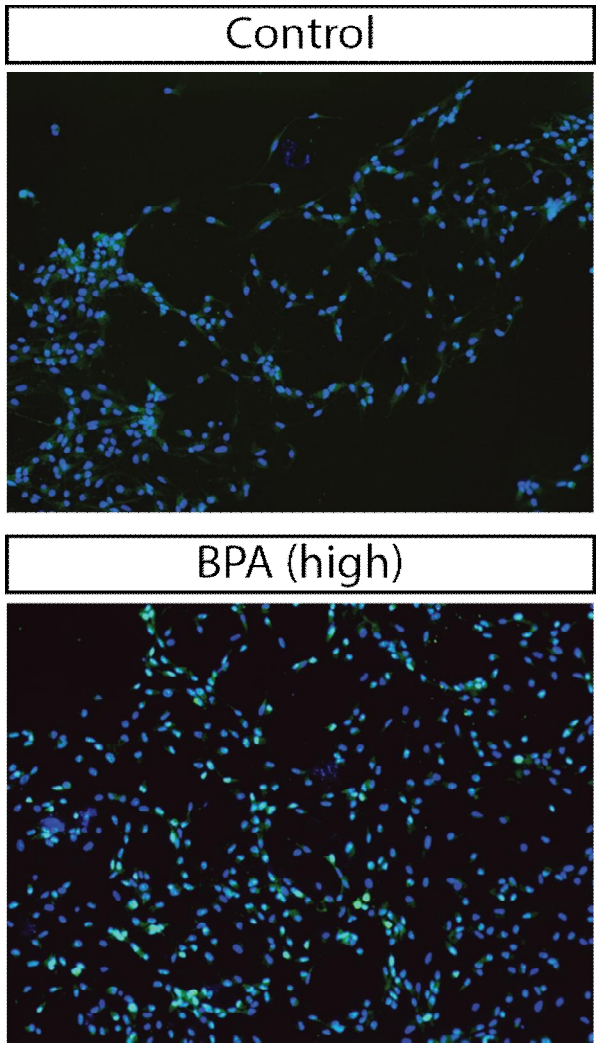


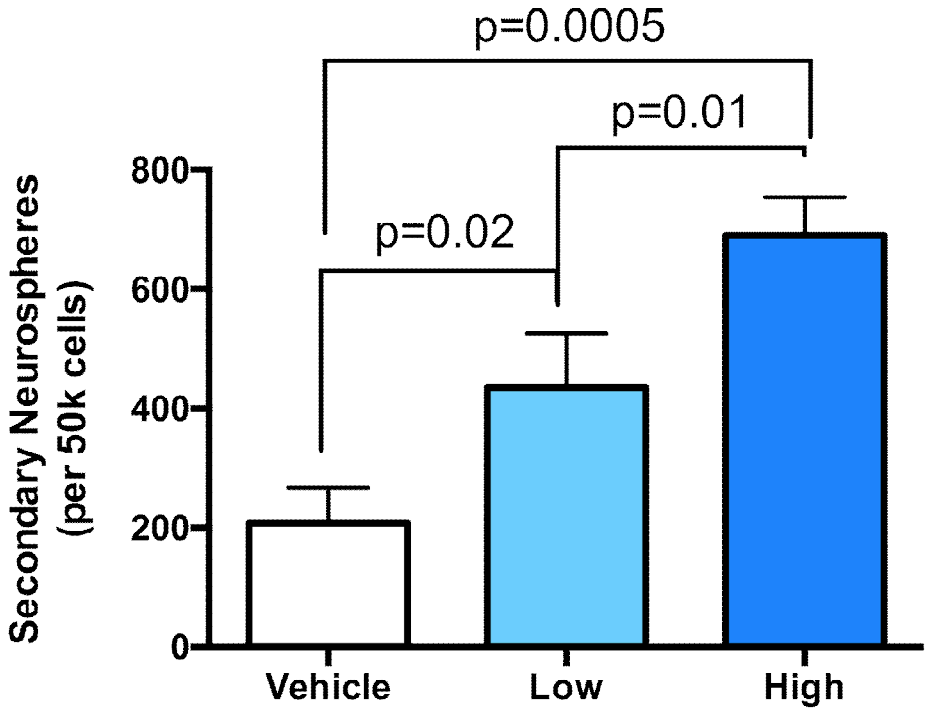

Dimou and Gotz, *Physiological Reviews* 2014



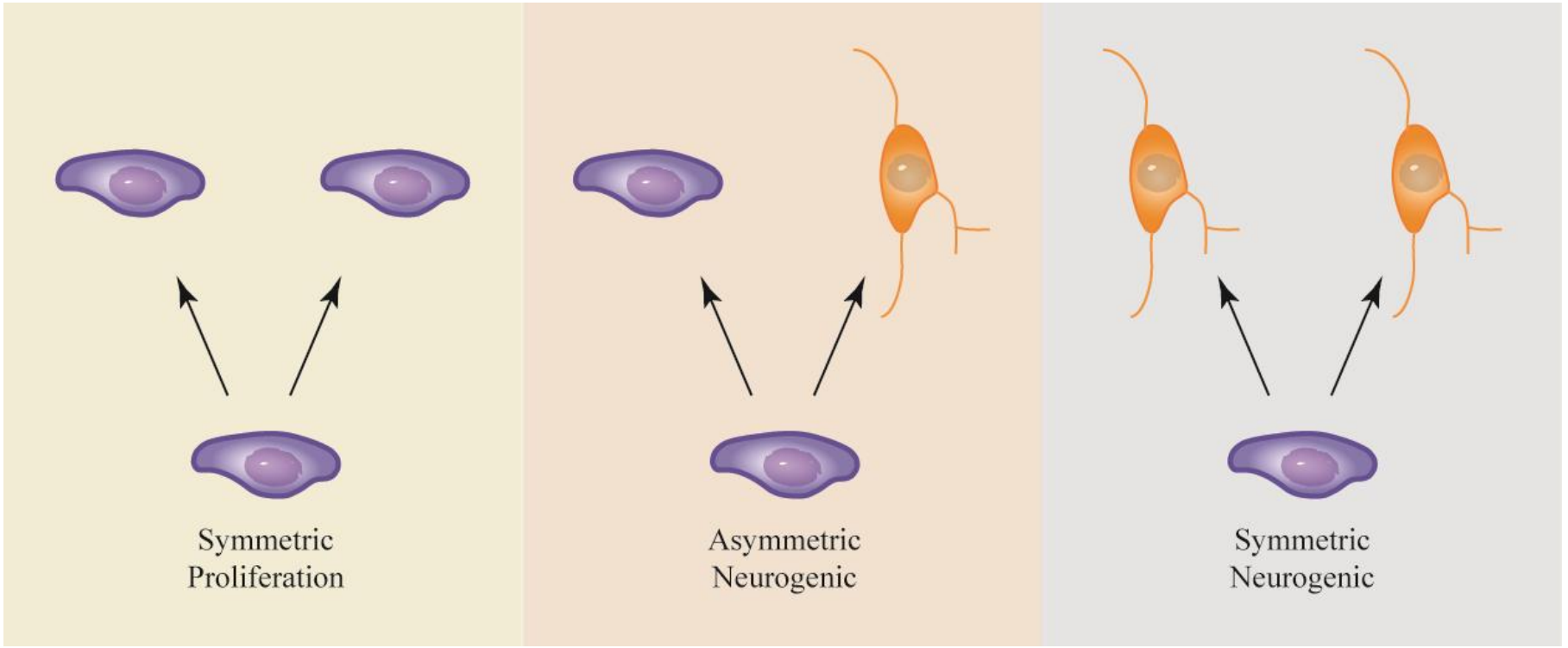

Proliferation/Self-renewal
E2
Mito
ER
Biogenesis
Nucleus
Hypothalamic NSC
Differentiation
Neuron
Oligodendrocyte
Astrocyte

# 2º hypothalamic NSCs demonstrate increased stemness following exposure BPA

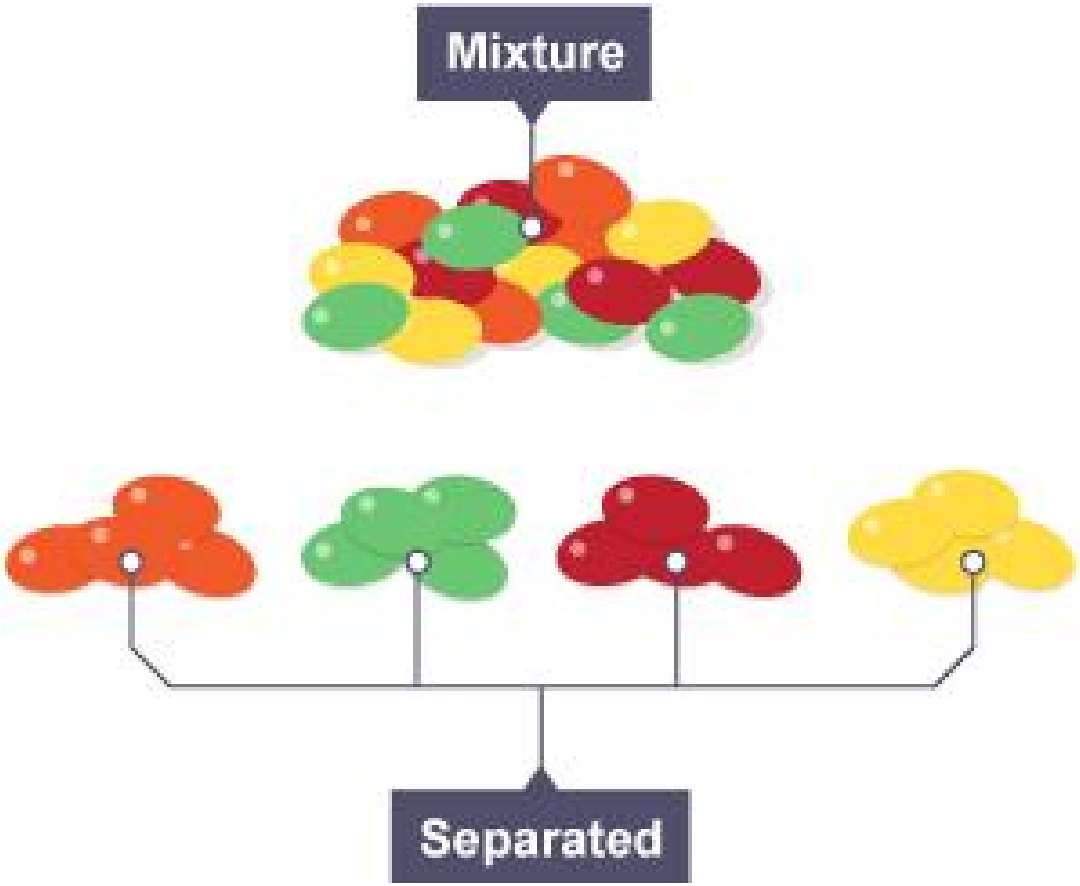


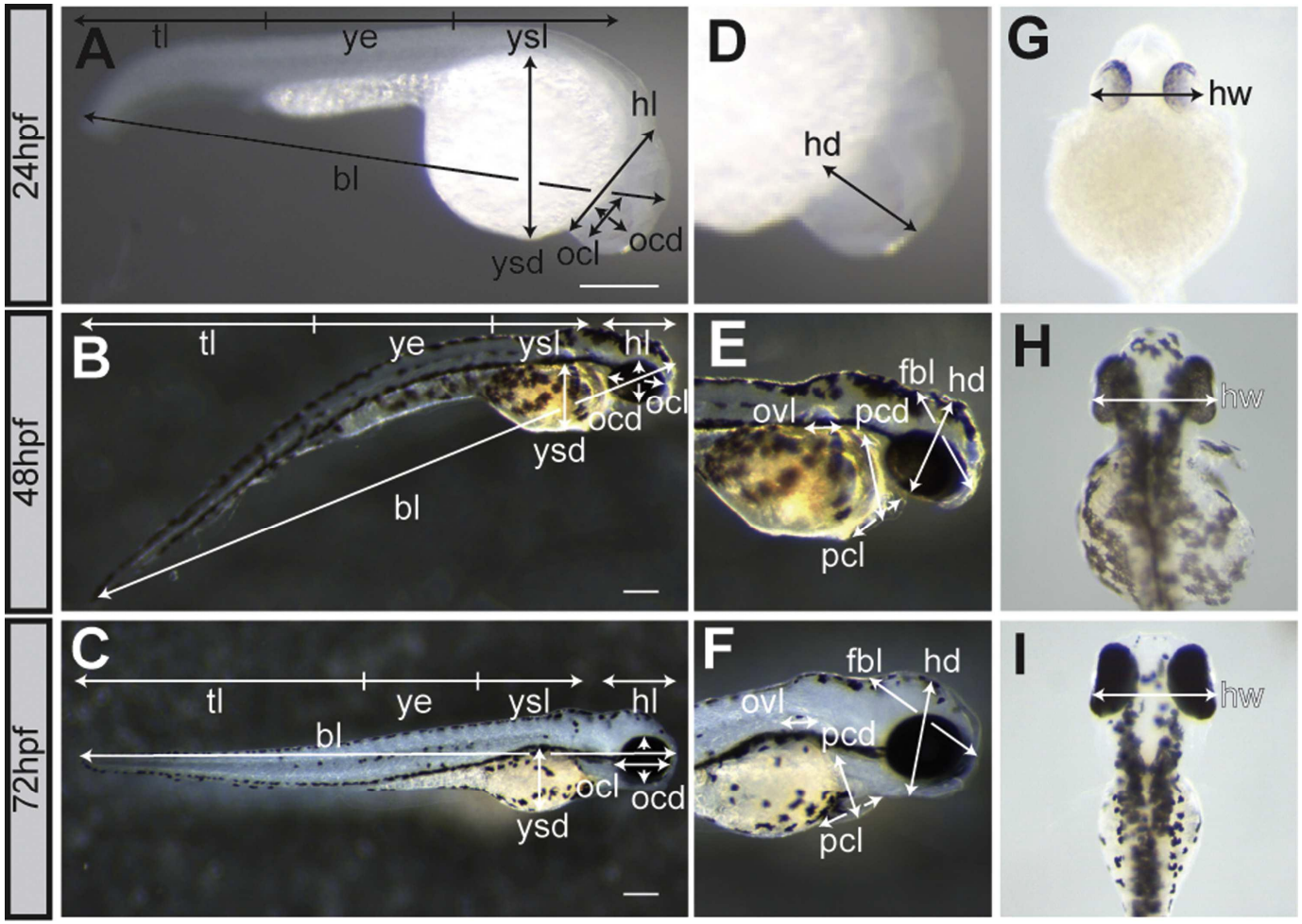
# Symmetric vs Asymmetric Proliferation



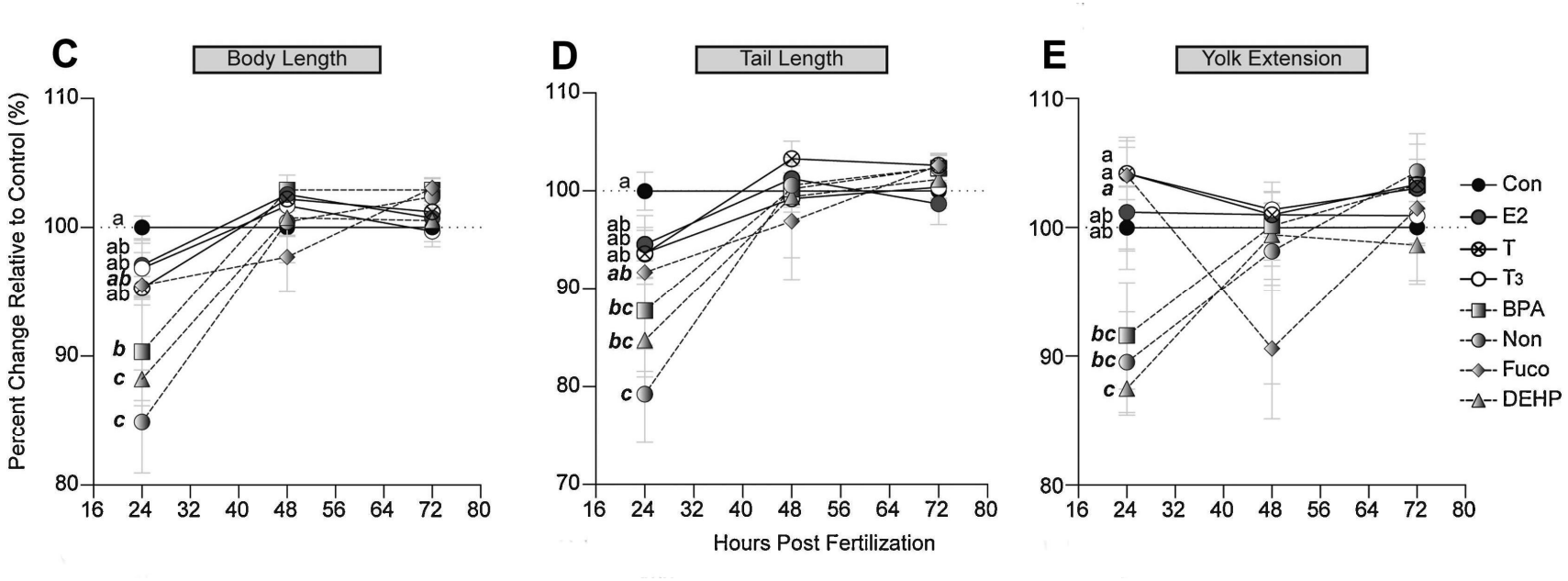
# We study chemicals in isolation, but we are exposed to chemicals in mixture



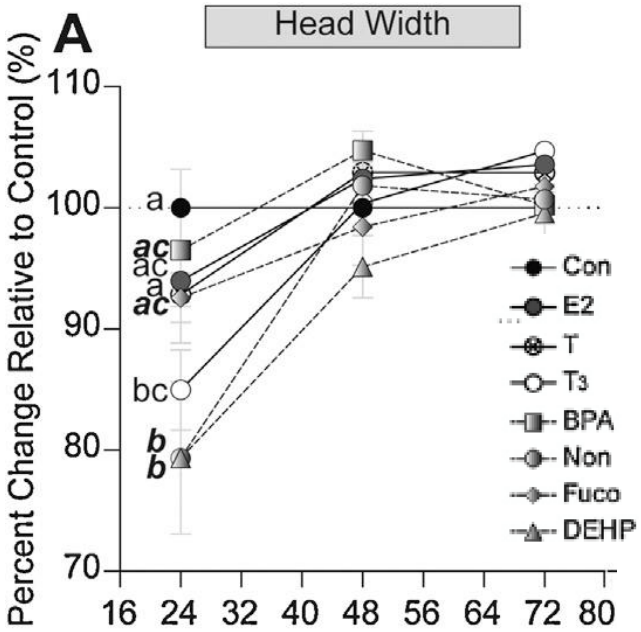
# Morphological measurements in developing zebrafish

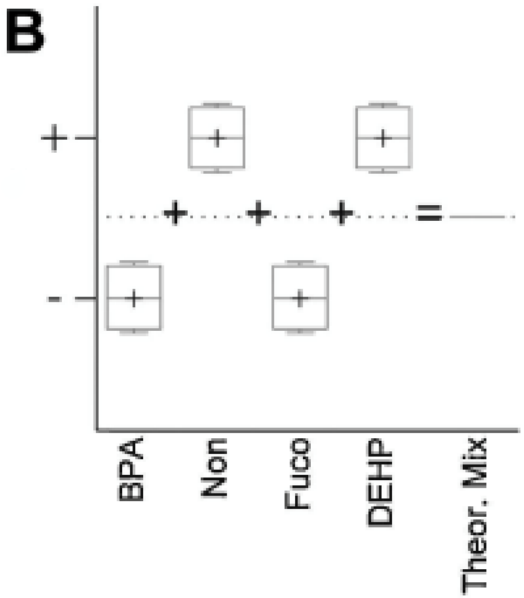


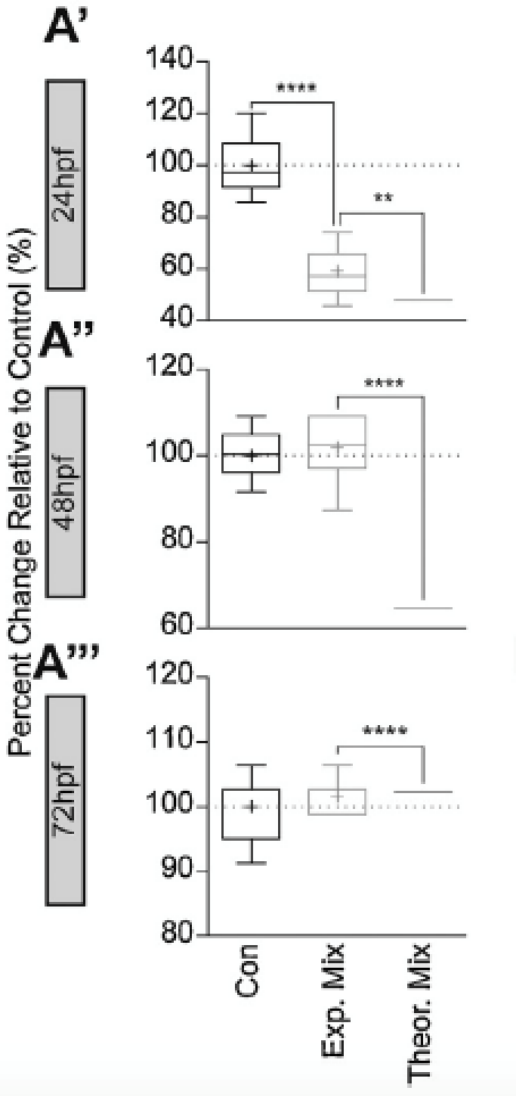
# Differential effects of hormones and contaminants



# Synergistic effects of contaminants in mixture







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kids cancer care

Brain Canada