

POPs: A Plethora of Developmental Effects

Josef Warkany Lecture

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I HAVE NO CONFLICTS OF INTEREST TO DISCLOSE



Persistent Organic Pollutants (POPs)

- Organic Chemicals that are “resistant to environmental degradation through chemical, biological, and photolytic processes. Because of their persistence, POPs bioaccumulate with potential adverse impacts on human health and the environment. (Wikipedia)
- PBTs =
 - Persistent – half-life > 6 mos in soil and sediment, 2 days in air, 2 mos in water
 - Bioaccumulative - $BCF > 5000$, $\text{Log } K_{ow} > 5$
 - Toxic
 - Undergoes Long Range Transport

Seeks the elimination or restriction of production and use of all intentionally produced POPs (i.e., industrial chemicals and pesticides) AND the continuing minimization and ultimate elimination of release of unintentionally produced POPs



Original “Dirty Dozen”

- Aldrin
- Chlordane
- Dieldrin
- DDT
- Endrin
- Heptachlor
- HCB
- Mirex
- Toxaphene
- PCBs
- PCDDs
- PCDFs



+ Chlordecone, Dicofol, Endosulfan, Lindane
HBB, HBCDD, PBDEs, PCP, PFOA, PFOS, PCNs, SCCPs



Latent Effects of Early Life Exposure

David Barker



- Developmental Basis of Disease
 - Reproduction, Immune, Cardiovascular, Endocrine, Pulmonary, Liver/Kidney, Neuro/Neurodegeneration, Cancer
- Complex Diseases can be caused by exposures occurring during development OR even in past generations
- Role of Epigenetics - Imprinting in germ line vs somatic cells
- Implications for Research
 - Are we exposing animals at the wrong time? (i.e., is our model wrong?)
 - Are we trying to correlate exposure and effect at the wrong time? (If its prenatal or early life-stage exposure that's important, why are we measuring environmental chemicals in people with cancer?)



Developmentally-Induced Diseases linked to Exposures

Reproductive/Endocrine

- Breast/prostate cancer (BPA)
- Endometriosis (PCBs, **Dioxin**)
- Infertility (Phthalates, Estrogens, Pesticides)
- Diabetes/metabolic syndrome (BPA)
- Early puberty (Estrogens, BPA)
- Obesity (BPA, Tributyl Tin, Organochlorine Pesticides, **PFAS**)

Immune/autoimmune

- Susceptibility to infection (**Dixon**, **PCBs**, **PFAS**)
- Autoimmune disease (**Dioxin**)

Pulmonocardiovascular

- Asthma (Air Pollution)
- Heart disease/hypertension (BPA)
- Stroke (**PCBs**)

Brain/Nervous system

- Alzheimer's disease (Lead)
- Parkinson's disease (Pesticides)
- ADHD/learning disabilities (**PCBs**, Lead, Ethanol, Organochlorine Pesticides, **BFRs**)



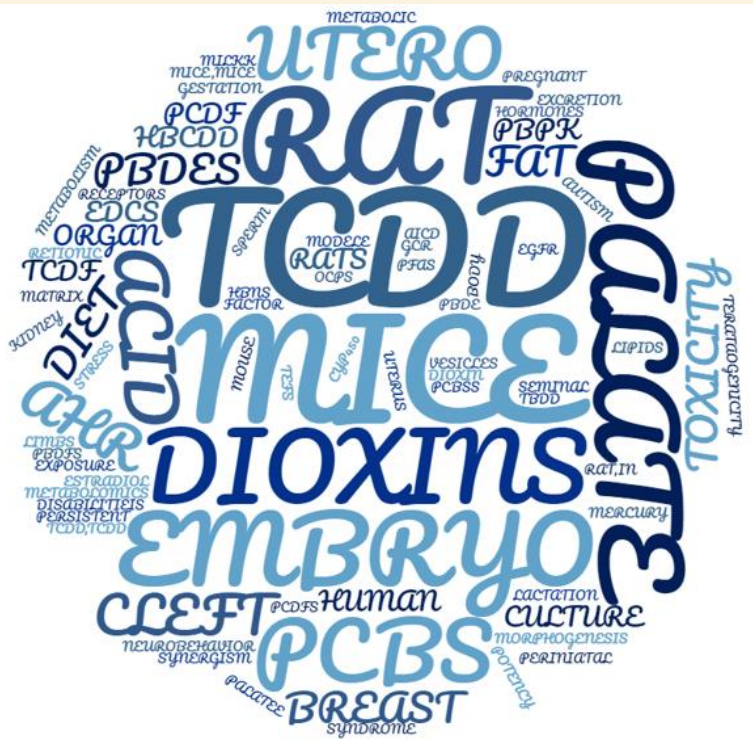
My Winding Road....

(**>45 Papers on POPs and Development**)

Birnbaum LS. My Winding Road: From Microbiology to Toxicology and Environmental Health.

Annual review of
pharmacology and
toxicology. 2016;56:1-17.
Epub 2015/10/31. doi:

<http://dx.doi.org/10.1146/annurev-pharmtox-010715-103255>. PubMed PMID: 26514198.

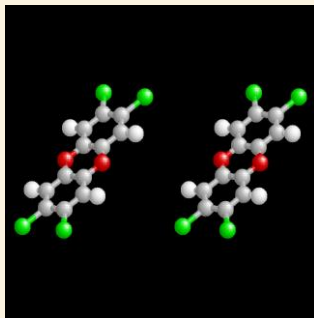


Birnbaum LS. How Did I
Ever Get Here? The 2018
Mildred S. Christian Award
Winner. International
journal of toxicology.
2018;37(4):272-5. Epub
2018/07/19. doi:
[http://dx.doi.org/10.1177/
1091581818781316](http://dx.doi.org/10.1177/1091581818781316).
PubMed PMID: 30016916.

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin: “The Most Toxic Man-Made Compound”

- *Prototype for family of structurally related compounds*

- *Chlorinated, brominated and mixed dioxins and furans (unwanted byproducts)*
- *Chlorinated and brominated biphenyls, naphthalenes, azoxybenzenes (major industrial chemicals)*
- *Lateral halogenation*



- *Common mechanism of action*
- *Common spectrum of biological responses*
- *Environmentally and biologically persistent*

(Basis for TEQ approach)



Adverse Effects in Wildlife, Domestic, and Laboratory Animals

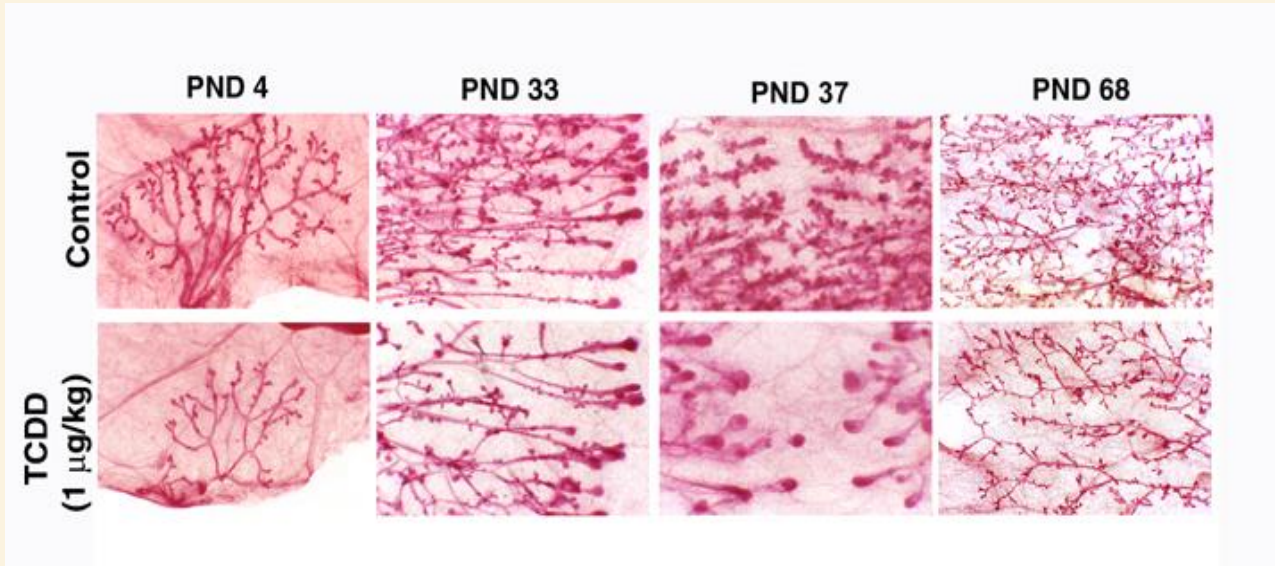
- All Vertebrate Classes
 - Fish, Amphibians, Reptiles, Birds, Mammals
 - Rats, Mice, Guinea Pigs, Hamsters, Dogs, Non-Human Primates
- Great Lakes fish, birds, mammals and Baltic seals, Porpoises, Dolphins
 - Effects Seen at Environment Levels
 - (Develop/ Repro/Immune)*
- Cows, Horses, Sheep, Chickens
 - Effects Observed During Poisonings
- Adverse Effects
 - Lethality/Wasting
 - Gonadal/Lymphoid Atrophy*
 - Hyperplasia/Metaplasia
 - Endocrine Disruption*
 - Carcinogenicity*
 - Repro/Developmental toxicity*
 - Functional Devpt. Toxicity*
 - Dermal Toxicity*
 - Immunotoxicity*
 - Neurotoxicity*
 - Hepatic Toxicity
 - Cardiovascular Toxicity
 - Bone/Teeth Toxicity*

Dioxins' Effects in People

- Cardiovascular Disease
- Diabetes*
- Cancer
- Porphyria
- Endometriosis
- Early Menopause
- Decreased Testosterone*
- Altered Immune Responses*
- Skin, Tooth, Nail Abnormalities (eg, Chloracne)*
- Altered Growth Factors/Receptors*
- **Developmental***
 - Thyroid Status
 - Immune Status
 - Neurobehavior
 - Cognition
 - Dentition
 - Reproductive Effects
 - Altered Sex Ratio
 - Delayed Breast Devpt



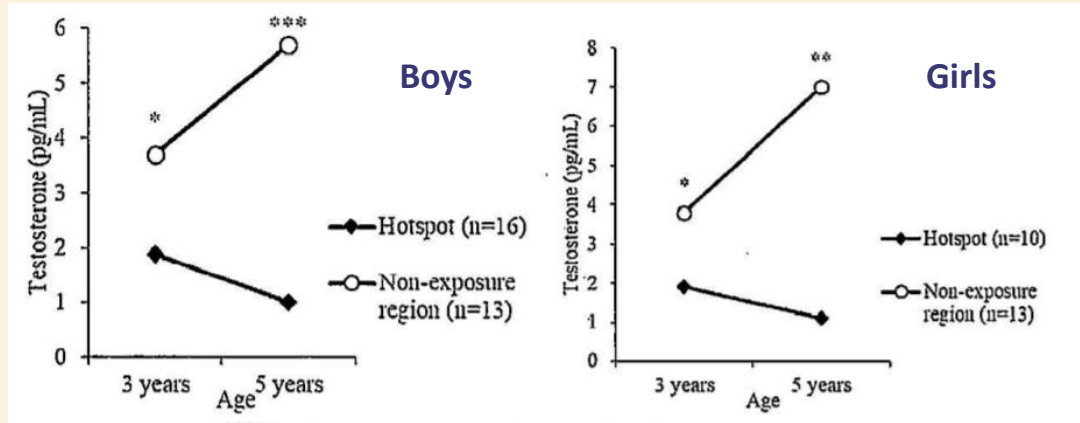
TCDD-Induced Delays in Mammary Gland Development



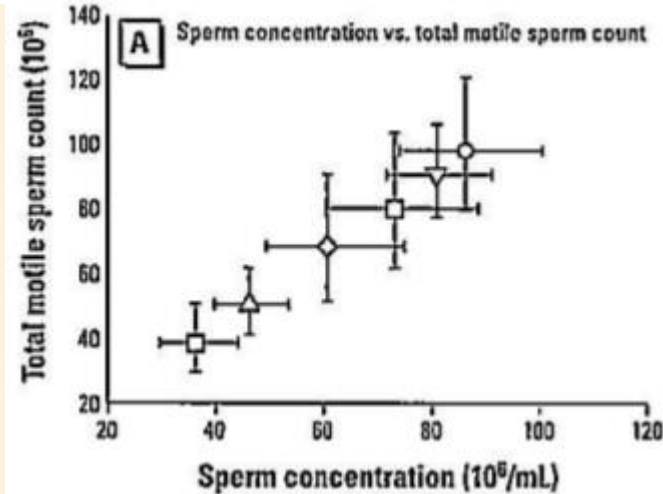
Fenton et al., Toxicol Sci. , 2002

Maternal Dioxin and Impacts on Offspring

-Perinatal TCDD associated with lower adrenal androgens in both boys and girls in Vietnam (Sun et al., 2020)

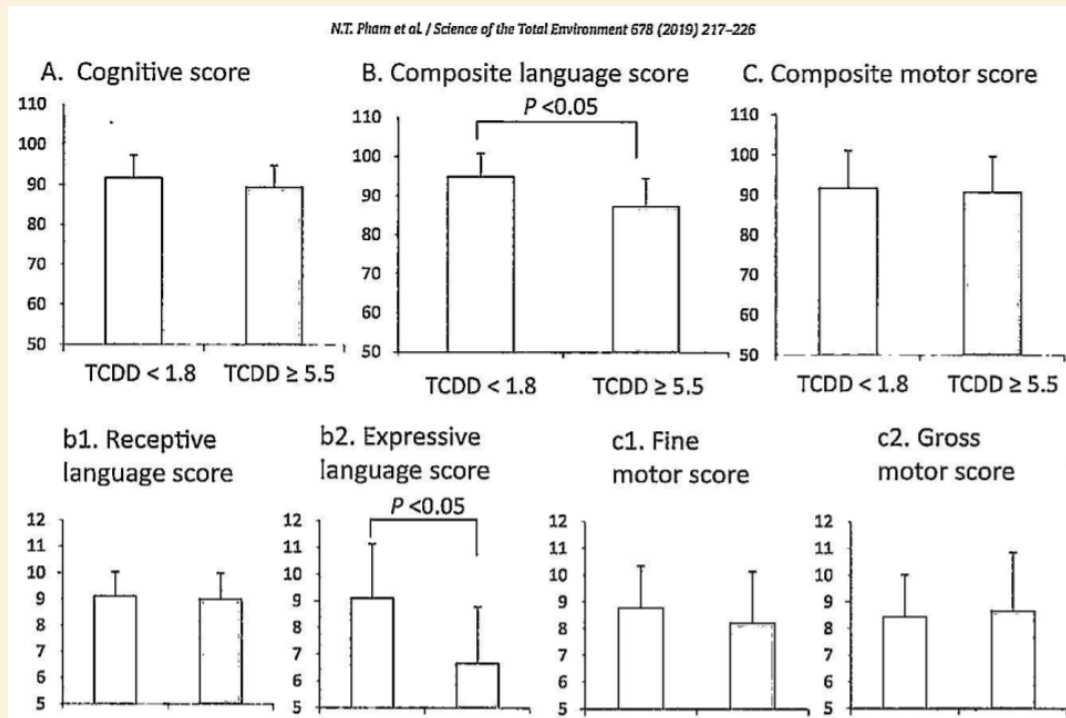


-Perinatal TCDD associated with decreased sex ratio, reduced sperm concentration, progressive motility, and total motile count and higher FSH and lower inhibin B in Seveso F1 boys suggesting effects on Sertoli cell proliferation (Mocarelli et al., 2011)



Dioxin and Neurodevelopment in Vietnam

- Perinatal (breastmilk) TCDD affects development of language
- Perinatal TCDD affects neuronal activity and functional connectivity between brain regions which may lead to poor language development (Nghiem et al., STE 667 (2019) 718-729).
- Perinatal TCDD has adverse effects on learning in 8 yr old boys (The et al., Int. J. Hygiene Env. Health 223 (2020) 132-141).

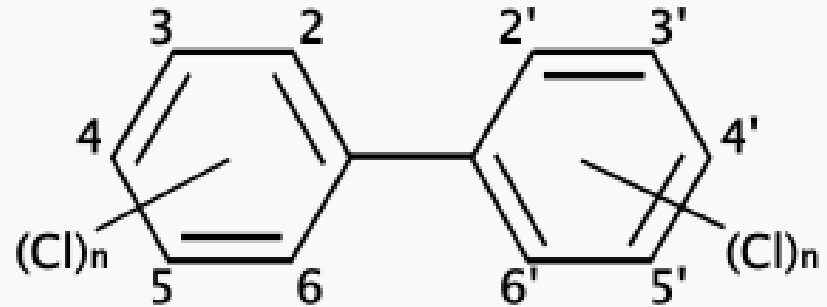


Pham et al., Sci Total Environ 2019



PCBs

- 209 Possible Congeners
- Small Subset Are “Dioxin-Like”
- Majority Have Own, Inherent, Toxicities
- Multiple, Overlapping, Structural Classes
- Can Interact, Additively, Synergistically, and/or Antagonistically With Dioxins and With Other PCB Congeners



PCBs and Human Development

- **Rice-Oil Poisonings**
 - Japan, '68 (Yusho); Taiwan (Yu-Cheng, '79)
 - Perinatal Deaths
 - Low Birth Weights
 - Hyperpigmentation
 - Gum hypertrophy
 - Delayed Maturation
 - Cognitive Deficits
- **Environmental Exposures**
 - **Cohorts**
 - Fish Eaters (LM, EU)
 - Nursing Mothers (NC)
 - Gen. Population (NL, EU)
 - **Motor Deficits** - Hypotonia
 - **Learning & Memory Deficits**
 - **Immune Impairments**
 - **Thyroid Effects** - (TSH, T4)
 - **Prenatal Critical Period**



PCBs are Developmental Neurotoxicants

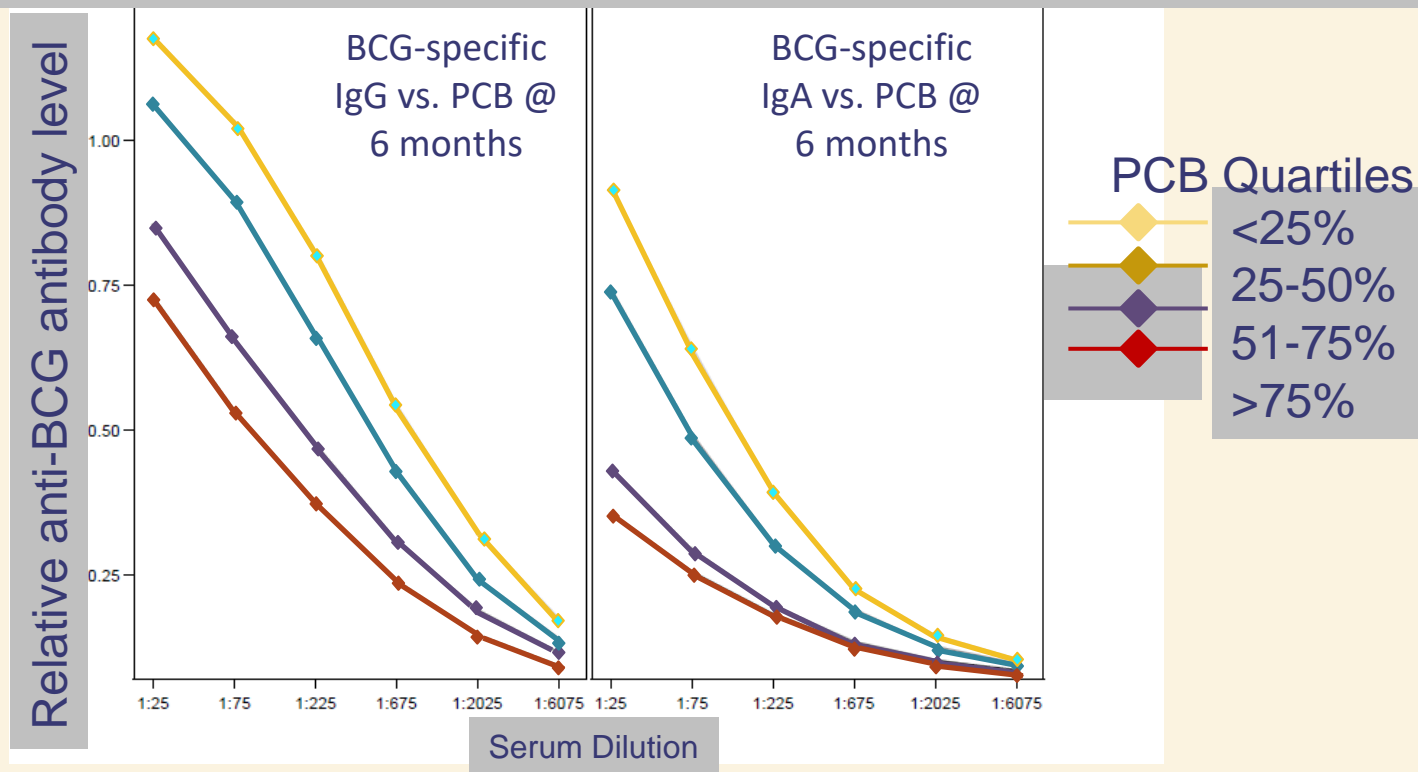
Animal

- Impaired Learning and Memory
- Maturational Delays
- Altered Operant Behavior
- Altered Visual Discrimination
- Impaired T-Maze Delayed alteration
- Altered Shock-motivated Avoidance

Human

- Cognitive Dysfunction
- Behavioral Problems
- Delayed Development
- Hearing Loss

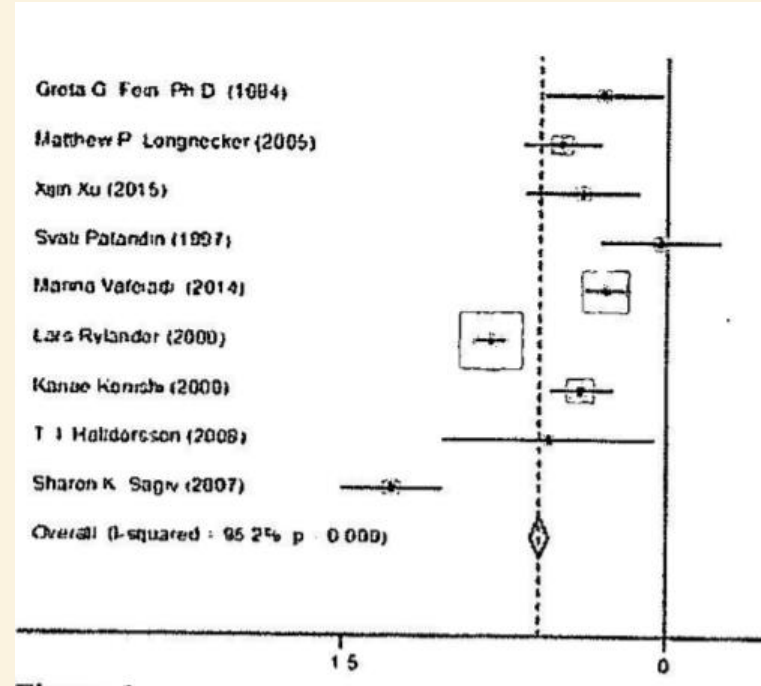
Early life PCB exposure is associated with reduced antibody responses to tuberculosis vaccination



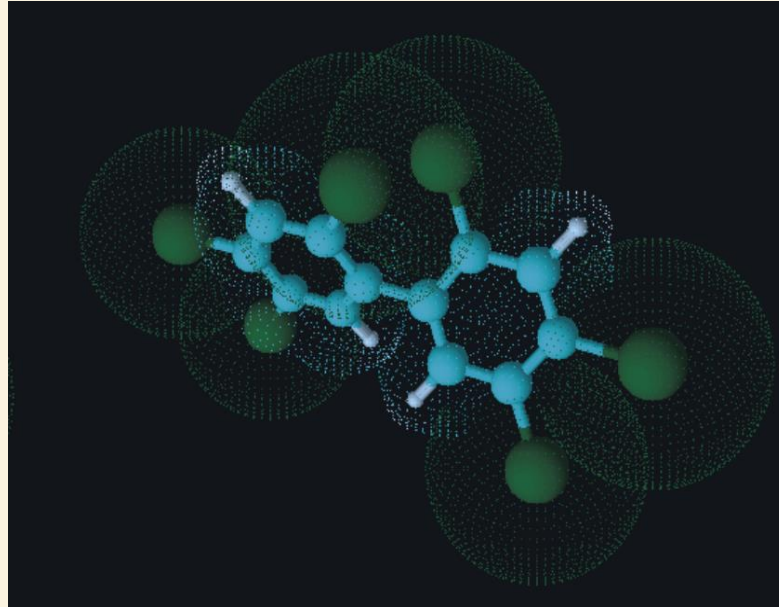
PCBs and Neonatal Effects

- *In utero* exposure to PCBs associated with reduced anogenital distance in male newborns (R. Sheinberg et al, Repro Toxicol. 2020)
 - Higher background exposures associated with anti-androgenic effects
 - No effects on AGD in female infants
- Decreased birth weight (H. Zou et al., Asian Pac J Cancer Prev. 2019)
 - Forest Plot – Association between PCBs (1 μ g/l increments) and Birth Weight (β , 95% CI)
 - Meta analysis

Birth Weight Analysis

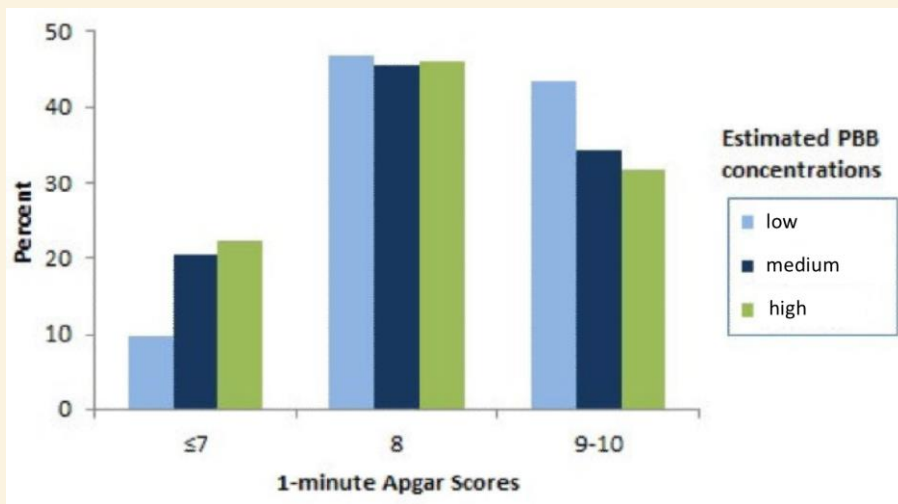


Persistent Organic Pollutant PBB 153



Effects of *In Utero* Exposure to PBBs

Apgar Scores



ML Terrell et al. Chemosphere 2014

Genitourinary Conditions in Male Offspring

Serum PBB	Odds Ratio	Confidence Interval	Trend P Value
Low	1.0		
Medium	2.16	0.74 - 6.33	
High	3.94	1.38 – 11.22	0.01

C Small et al., Environ Health Perspect. 2009

What have we learned about PBBs?

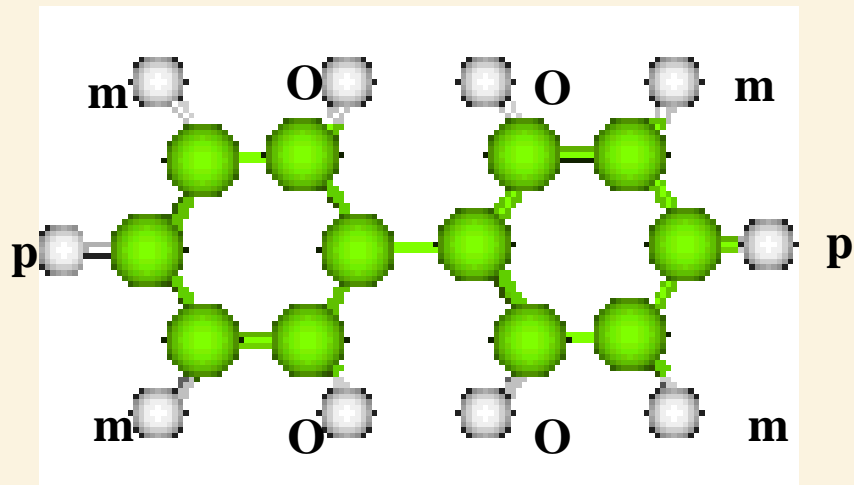
(Thanks to Michelle Marcus)

- 'Forever' chemical
- Transferred from mother to child in the womb and through breast milk
- Reproductive system
- Thyroid disorders
- Cancers
- Three generations have been impacted
- Epigenetics – regulation of genes

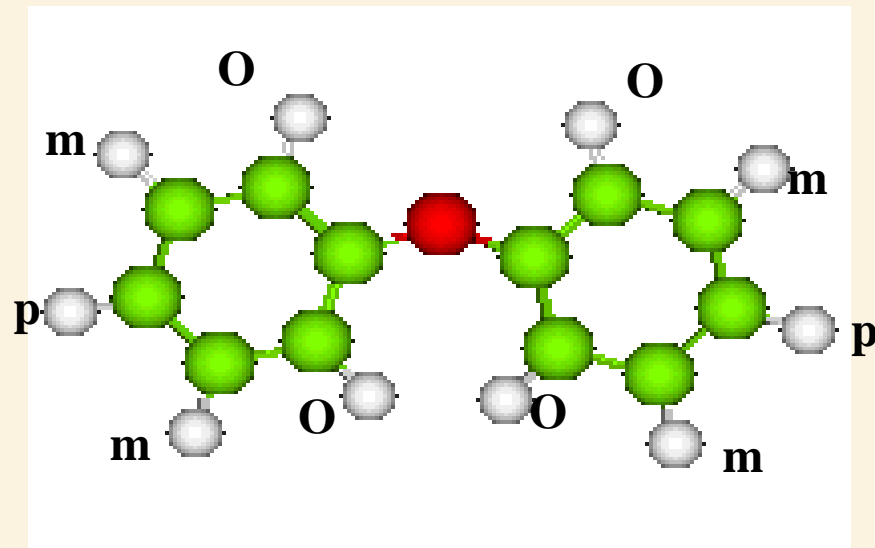


PCBs vs. PBDEs

Similar Structures and Similar Effects



**Biphenyl Ring
System**



**Diphenyl Ether Ring
System**

Developmental Effects of PBDEs

- DE71 ('Penta') pubertal exposures
 - Delay in puberty
 - Effects on male organs
 - Anti-androgenic *in vitro*
 - esp. BDE 100,47
- BDE-99/47– *in utero* exposures
 - Delay in puberty
 - Ovarian toxicity
 - Male organ effects and decreased sperm
- DE79 ('Deca')/BDE-209
 - Developmental Reproductive Toxicity
 - Decrease in Sperm Function (*Tseng et al, 2006*)
 - Increase in Oxidative Stress
 - Developmental Immunotoxicity
 - “Continuous exposure to high-dose PBDE-209 in female rats during pregnancy and lactation results in possible adverse effect on the immune function of the offspring rats.” (*Zhou et al, 2006*)
 - Changes in lymphocyte subsets

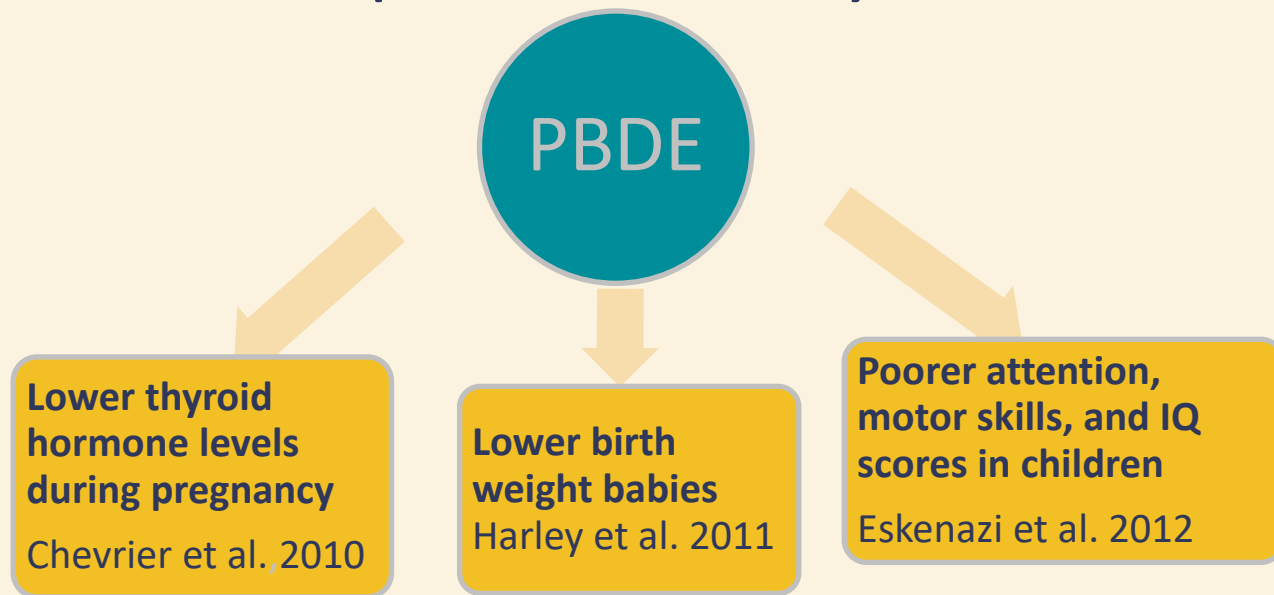


Developmental Neurotoxicity of PBDEs is similar to PCBs

- DE-71 – Rats
 - Deficits in sensory and cognitive function
 - Altered sex-dependent behaviors
 - Effects on thyroid, cholinergic, and dopaminergic systems
- BDE-99, 209 (47,153,203,206) - mice and rats
 - Infantile Exposure (“Rapid Brain Growth”) - Permanent effects on learning
 - Perinatal Exposure – Delay in sensory-motor development
- BDE-99+PCB-52 *or* PFOA *or* MeHg – Mice
 - Effects may be more than additive
- Both mice and rats
 - Mice very sensitive (clear effects at 0.8 mg BDE-99/kg) in infantile period
- Sensory and Cognitive Effects
- Mechanism Unknown
 - Depression in serum T4
 - Effects on Intracellular signaling
 - Effects on neurotransmitters

Effects Linked to Early (PBDE) Exposure

(Chamacos Cohort)



9/11 Birth Cohort

In Utero PBDEs Mental+Physical Development

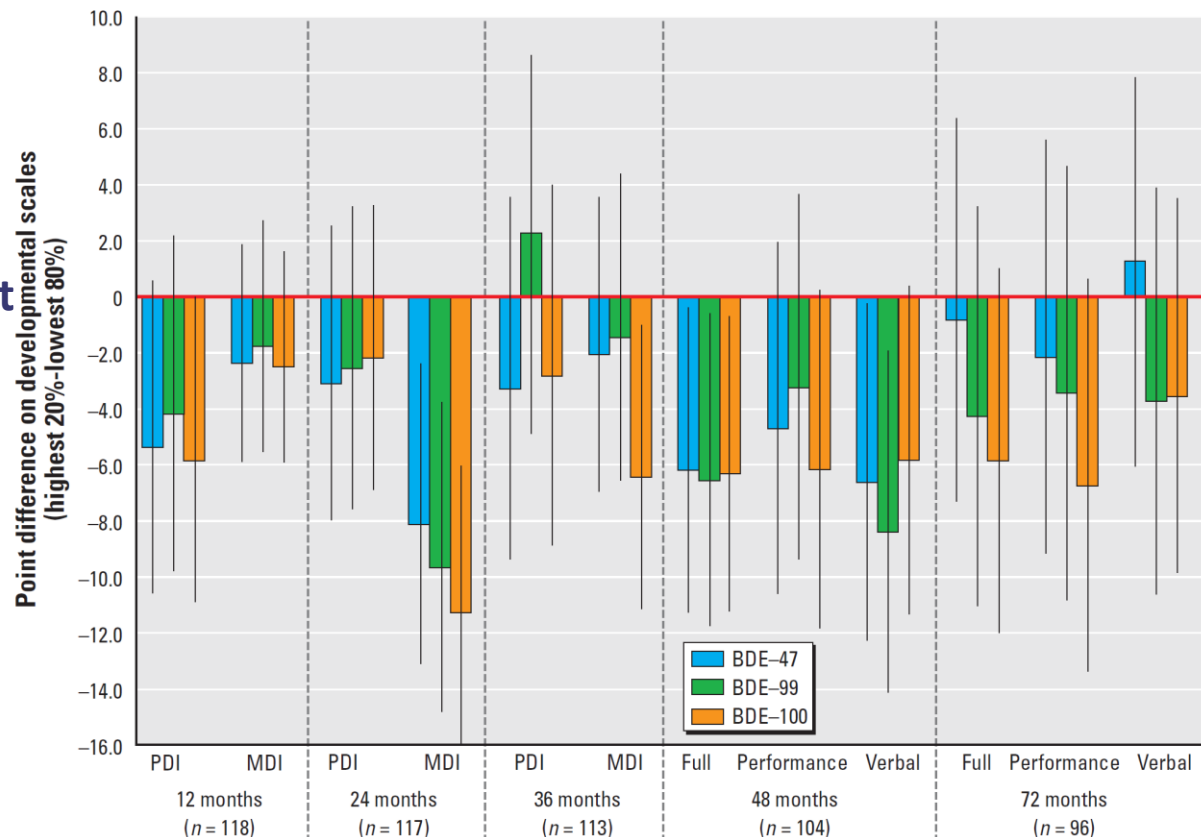


Figure 1. Difference in mean developmental score (and 95% confidence interval around the mean) comparing individuals in the highest quintile (20%) of exposure with those in the lower 80% of BDEs 47, 99, and 100. Mean differences were adjusted for age at testing, race/ethnicity, IQ of mother, sex of child, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, breast-feeding, language, and location of interview.

Herbstman et
al. 2010 EHP

Brominated Flame Retardants: Latent Developmental Effects

- Developmental Reproductive Toxicity
 - Delayed Puberty
 - Decreased Sperm Count
 - Ovarian Toxicity
- Developmental Neurotoxicity
 - Altered Learning and Memory
 - Decreased Reading Skills (A Vuong et al., Int J Hyg Environ Health 2020)
 - Altered Behaviors

“PBDEs were the greatest contributor to IQ Loss and intellectual disability”

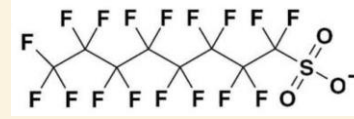
>Lead> Organophosphates> Methyl Mercury

(A Gaylord et al. Mol. Cell. Endocrinol. 2020)

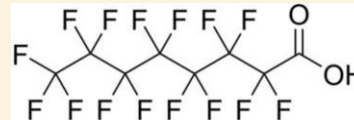


Per- and Polyfluoroalkyl Substances (PFAS)

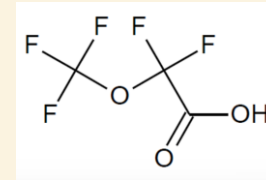
- Group of nearly 5,000 chemicals
- Mobile, persistent, and accumulate in the environment
- Resistant to grease, water, and oil ('amphipathic')
- One way we are exposed is through food contact materials
- Emergence of alternatives which are less well studied



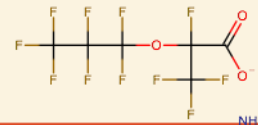
PFOS



PFOA



PFMOAA



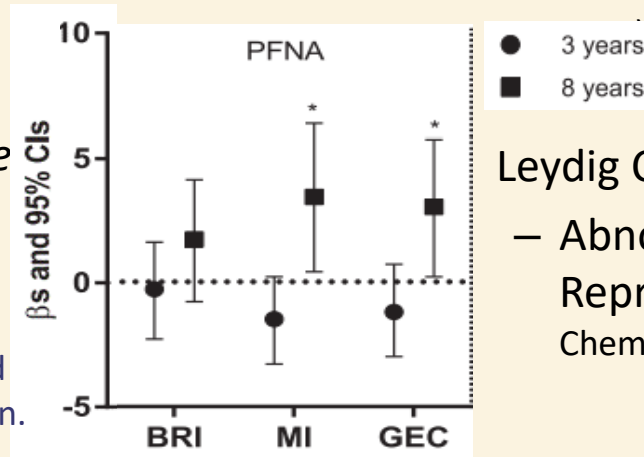
GenX

PFAS Health Effects

PFAS exposure has been linked to:

- *Altered immune function*
- Cancer
- *Decreased birthweight*
- Liver effects
- Kidney effects
- *Metabolic outcomes*
- *Neurodevelopmental outcome*
- *Endocrine disruption*

Higher PFNA conc. associated with poorer executive function. Vuong et al. Environ Int. 2016



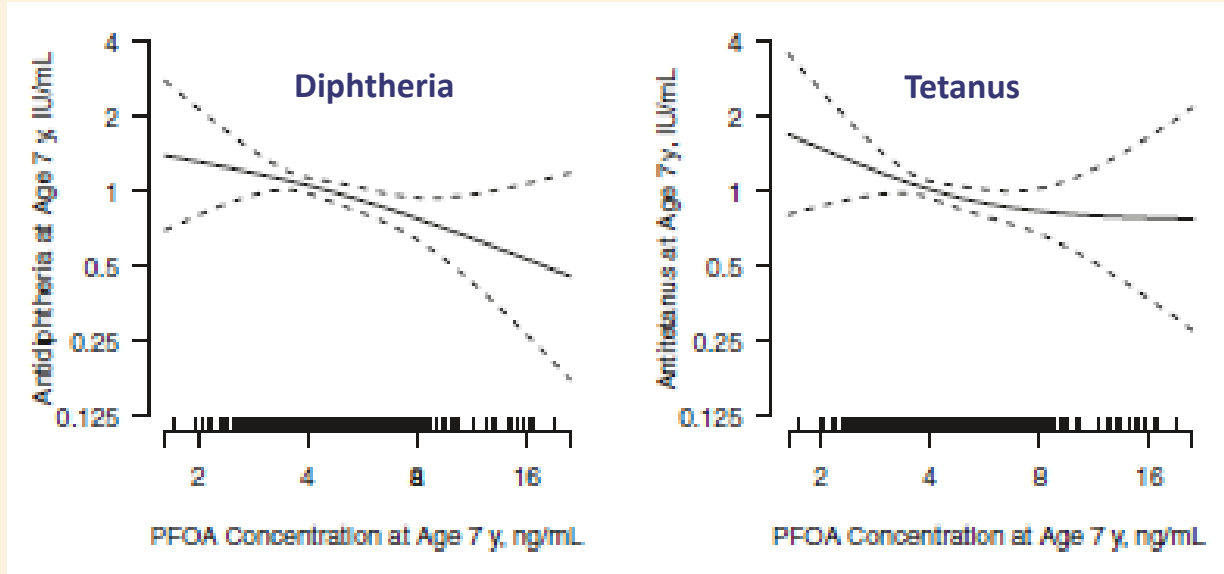
- Thyroid disruption
 - Project VIVA Cohort
 - “Combined effects of prenatal exposure to multiple PFAS on maternal and neonatal thyroid function” (EV Preston et al. Environ Int.)

Leydig Cell Dysfunction

- Abnormal Development of Male Reproductive Tract (Q Zhu et al. Chemosphere 2020)



Reduced Effectiveness of Childhood Vaccinations*



Mogensen et al.
Environ Health 2015

Immune responses are diminished as a function of PFAS concentrations in blood

* Reduced antibody response to vaccines also seen in adults (JC DeWitt et al., JESEE 2019)

Impacts of PFAS

Birth Outcomes (Case Control Studies)

Birth Outcomes (MCO Souza et al., Environ Res. 2020 - Brazil)

- Preeclampsia
- Low Birth weight
- Preterm birth
- Intrauterine growth restriction

Increase in Miscarriage (Z Liew et al. EHP 2020 - Denmark)

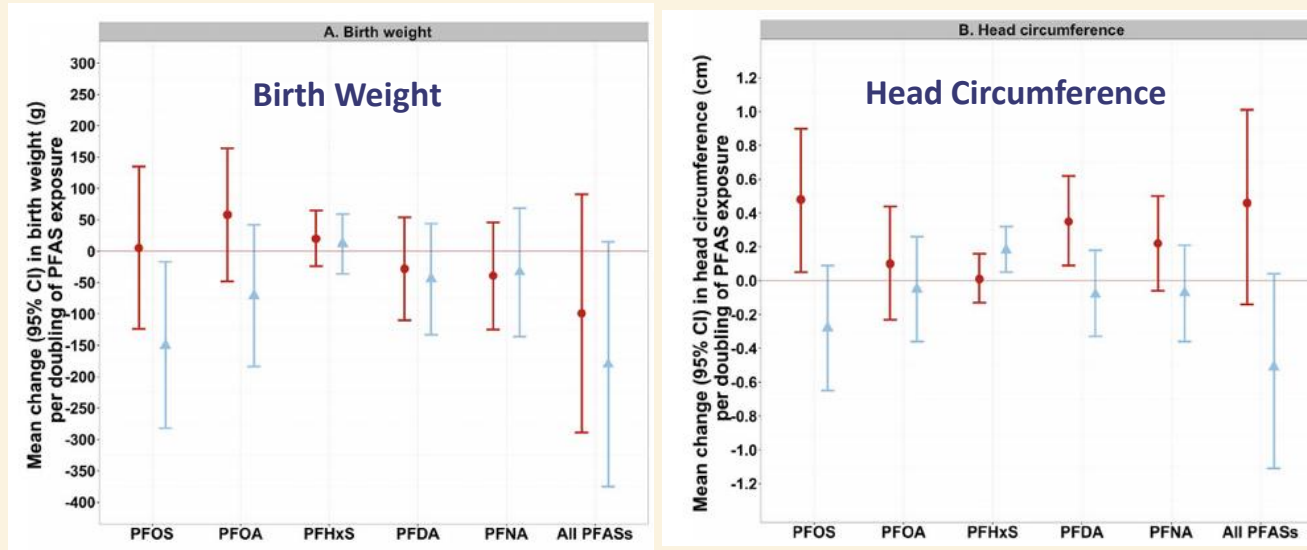
Fetal Hormones (Shanghai Birth Cohort)

- Short Chain PFAS (PFBS and PFHpA)
- Decreases in FSH and LH
- Negative association with Free Androgen Index (FAI)
- M Nian et al. ES&T 2020

PFAS also associated with Preeclampsia, Low Birth weight, Preterm birth, and Intrauterine growth restriction



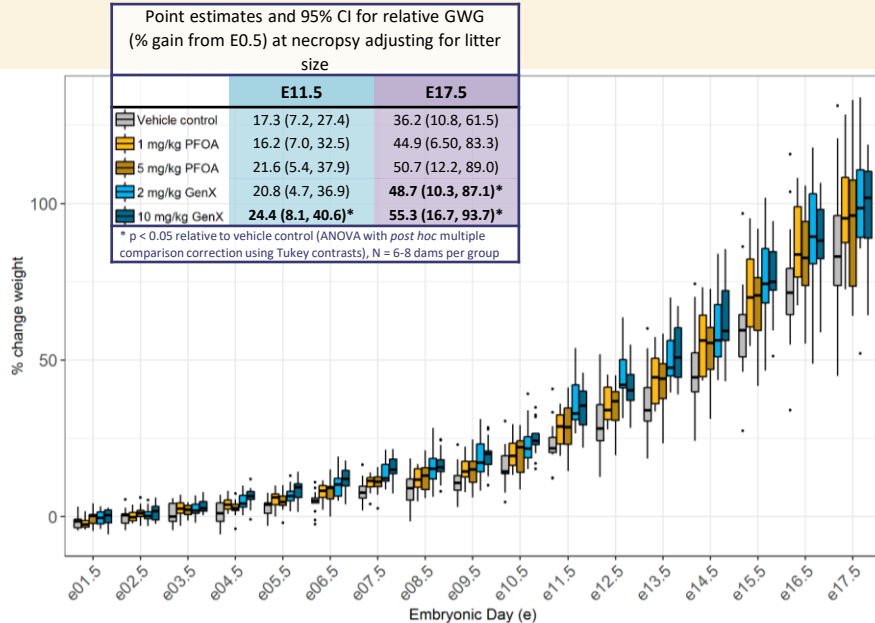
Ongoing PFAS exposure concentrations result in dimorphic effects in newborn children



-- Valvi et al., Environmental international, 2017, v. 107, pp. 205-215.

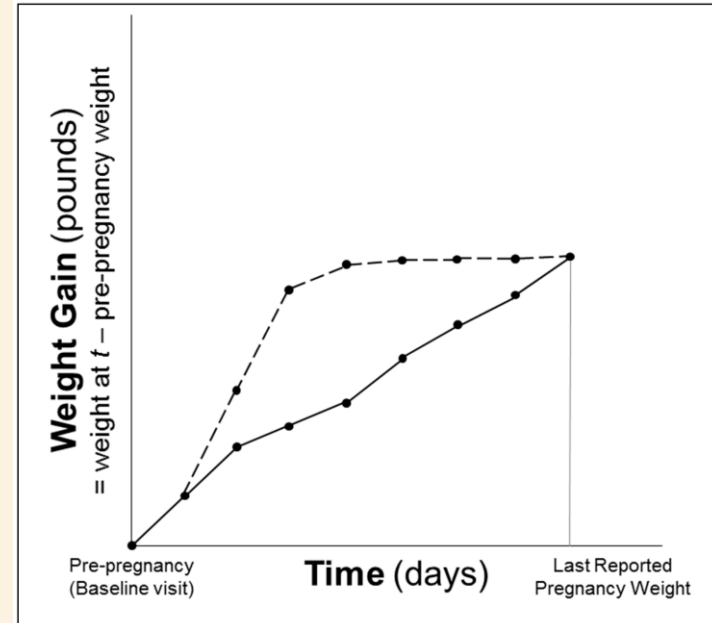
PFAS Associated with Increased Gestational Weight Gain (Rodents and Humans)

PFOA and GenX



B. Blake et al., EHP, 2020

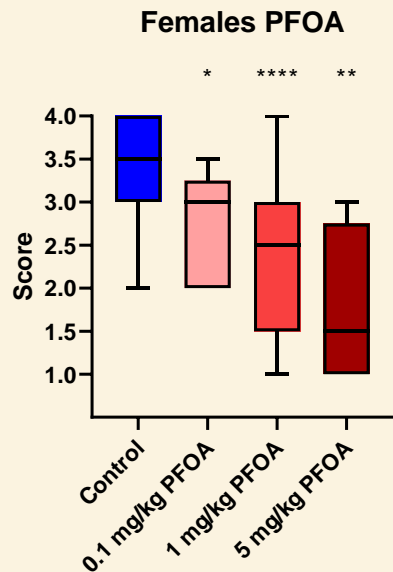
PFOS



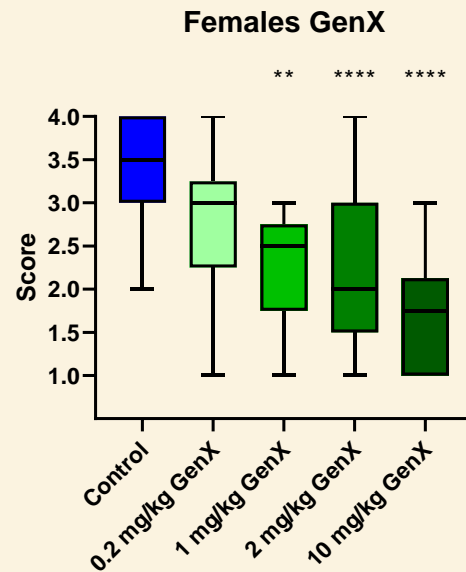
Jaacks et al., Int. J. Environ. Res. Public Health. 2016

Abnormal Female Mammary Gland Development

PFOA



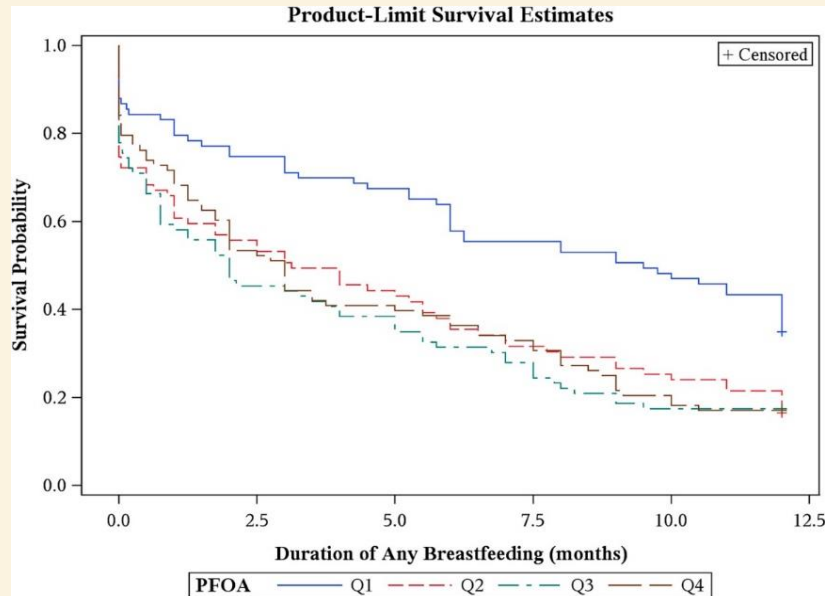
GenX



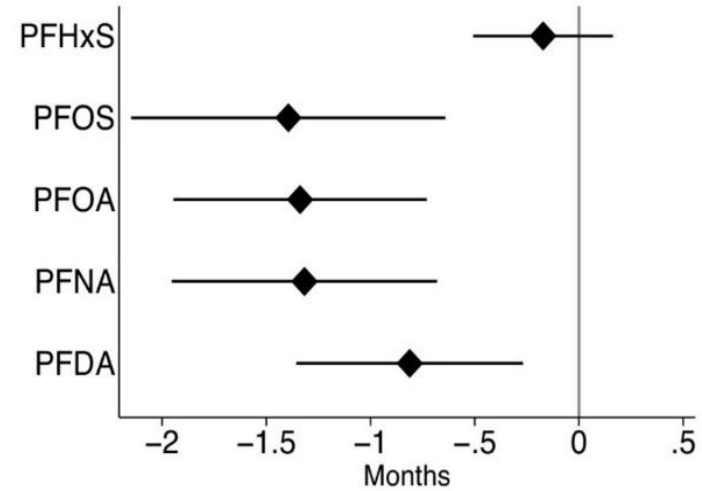
B. Blake et al., EHP 2020

PFAS Affect Breastfeeding Duration in Women

Romano et al. 2016, *Environ Res*



Breastfeeding duration difference at doubled exposure



Timmermann et al. 2017, *Reprod Toxicol*

THANK YOU!!!



All of my students and postdocs over >40 years

All of my mentors AND mentees

Specific help for this talk:

Sue Fenton

Paige Lawrence

Michele LaMerrill

Kim Gray

Thad Schug

Mark Miller

Christine Flowers

AND:

To Everyone Listening

and to BDRP for

Honoring me with the

Josef Warkany Lecture

QUESTIONS?????

