PER- AND POLY-FLUOROALKYL SUBSTANCES (PFAS) POTENTIAL RELATIONSHIPS BETWEEN ENDOCRINE EFFECTS

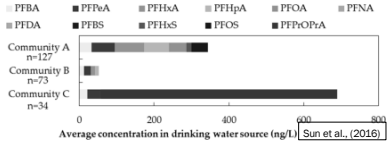
Wendy Heiger-Bernays
Department of Environmental Health
Boston University School of Public Health

*PFAA (perfluoroalkyl acids)

Outline

- Introduction to Challenges for Hazard Evaluation of Perfluorinated Alkyl Substances (PFAS)
- Low-Dose Toxicity Principles for Endocrine Active Chemicals
  - *Evidence for PFAS as EACs*
- Endocrine Physiology and Communication Between Systems
  - *PFOS as thyroid hormone modulator*
  - *PFOA/PFOS as effectors of lipid metabolism*
- Possible Approach for PFAS Hazard Assessment

PFAS Hazard Assessment Challenges



Sun et al., (2016)

Compound	Common Name	Carbon #
PFBA	Perfluorobutyric acid	C3-4
PFBS	Perfluorobutanesulfonic acid	C4
PFHxA	Perfluorohexanoic acid	C5-6
PFHxS	Perfluorohexane sulfonic acid	C6
PFOA	Perfluorooctanoic acid	C7-8
PFOS	Perfluorooctane sulfonic acid	C8
PFNA	Perfluorononanoic acid	C9

Bioaccumulation Potential – half-life
Biotransformation Potential

Mixtures of PFAS

In vitro data
Animal Models
Human and Epidemiological Studies

Hazard Data are Most Comprehensive PFOA and PFOS

PFOA and/or PFOS Effects in Animal and/or Epidemiology Studies	
Testicular cancer	Ovarian cancer
Kidney cancer	Prostate cancer
Ulcerative colitis	Obesity
High cholesterol	Liver malfunction
Pregnancy	Lower birth weight & size
Thyroid disruption	Delayed puberty, decreased fertility, early menopause
Hormonal changes	Reduced testosterone
Immunotoxicity: interference with child vaccine response	
Suppressed antibody response	Increased hypersensitivity

Level of Evidence?

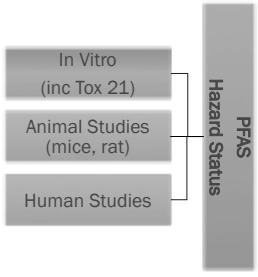
National Toxicology Program's Assessment of PFOS/PFOA Hazard Analysis

Table 7. PFOA Main Immune Effects Summary Table

Category of Immune Response	Immune Outcomes	Confidence Ratings in the Body of Evidence: Human	Confidence Ratings in the Body of Evidence: Animal	Level of Evidence in the Body of Evidence: Human	Level of Evidence in the Body of Evidence: Animal	Hazard Conclusion
Immunosuppression	Antibody response	Moderate	High	Moderate	High	Presumed to be an Immune Hazard to Humans
Hypersensitivity	Asthma and other hypersensitivity-related outcomes	Low	High	Low	High	Presumed to be an Immune Hazard to Humans

2016 National Toxicology Program Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate

Hazard Assessment: Disparate Data Streams



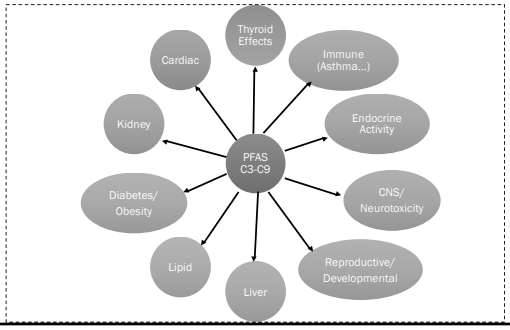
Evidence for Health Effects

Not Classifiable/Suspected/Presumed/Known

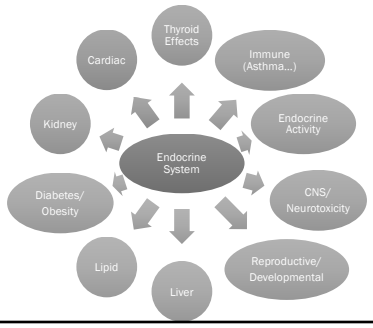
- Low/Inadequate
- Moderate
- High

NAS: Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. ISBN 978-0-309-45862-7 | DOI 10.17226/24758

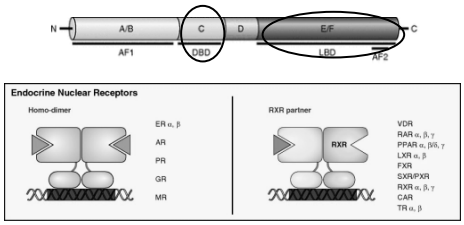
Categories of Endpoints Identified for PFAS (Matrix prepared for 9/27/17) TURI SAB



Connections Between Categories of Endpoints Identified for PFAS

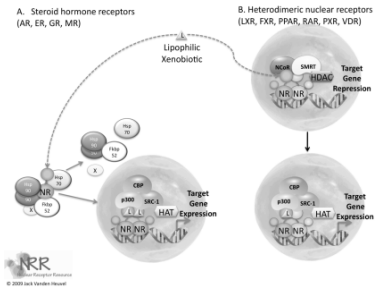


Nuclear Receptor Superfamily



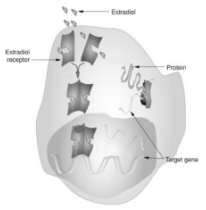
Imai et al. 2013 Physiol Rev

Nuclear Receptor Action



Estrogen Receptor (α and β)

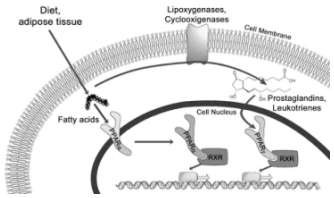
- Estradiol is primary agonist and is produced largely in the ovary in females and the testis, adrenal and pituitary glands in males
- Critical in female sexual development and fertility, male fertility, bone homeostasis, cardiovascular health….liver lipid health



5'-GGTCAnnnTGACC-3'

Bisphenol A, PFOA other PFAS

Peroxisome Proliferator Activated Receptors (PPAR)

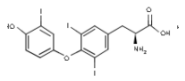


5'-AGGTCAnAGGTCA-3'

Phthalates
Organotins
OPFRs & PFOA

http://en.wikipedia.org/wiki/PPAR_modulator

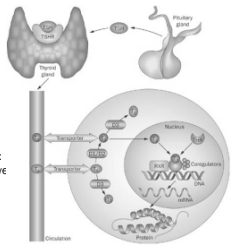
Thyroid Hormone Receptor



Triiodothyronine (T3)

- TR regulates metabolism and thermogenesis. Important role in development.
- Thyroid hormone comes in two forms: T4 is most abundant; T3 is most active

PBDEs, PCBs
PFOA



5'-(A/G)GGTCAnnnn(A/G)GGTCA-3'

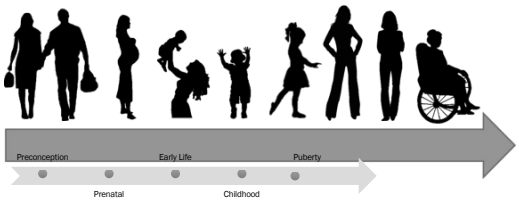
Dayan and Panicker. 2009. Nat. Rev. Endocrinol.

Low-Dose Toxicity Principles for Endocrine Active Chemicals

- **Doses that are expected to occur in humans**
  - *Responses observed in animal studies may not follow linear dose-response relationships;*
  - *Responses are specific for model, sex, developmental stage;*
  - *Responses may be observed in off-spring and NOT in parent.*

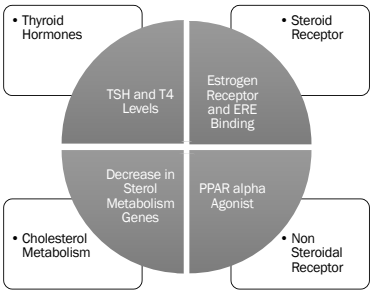
Modulate normal hormone function and small alterations can have lasting and significant effects on populations.

Critical Windows of Development



Most influential because of the multitude of systems in developmental flux

Subset of Cellular & Molecular Activities for PFOS



Modified from Gore et al., 2016

Selected PFAS (PFOS/PFOA) Endpoints and Endocrine Effects (by example)

Neurodevelopment
Thyroid and brain – induction of hepatic microsomal levels of P450s that result in increased biliary excretion of thyroid hormones in response to multiple PFAS.

Lipid Dysregulation
Liver – activation PPARα effecting lipid metabolism, cell growth. PFAAs may disrupt fatty acid binding and lipid regulation

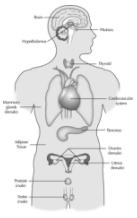
Obesity
Adipocytes and the Brain – generating insulin resistance, glucose intolerance, dyspidemia

Diabetes
PFOS directly affects the islet of Langerhans and increase/decrease normal insulin biosynthesis and release, generating hyper- or hypoglycemia. An excess of insulin signaling, as well as insulin resistance, can result in metabolic syndrome

.....Excess Insulin
Induces insulin resistance, glucose intolerance, fatty liver, and dyslipidemia, liver, and skeletal muscle

Extracted from Gore et al., 2016; Yan et al., 2015; Kim et al., 2016; Cheng et al., 2016).

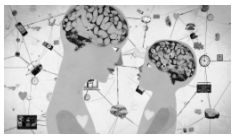
Endocrine Physiology & Communication Between Systems



Neurotoxicity

Clinical Disease
target = neurons

Seizures
Paralysis
Numbness
Headache



Subclinical Disease – NOT MEASURED IN TRADITIONAL HIGH DOSE, TOXICITY OR REGULATORY GUIDELINE STUDIES.
Neurocognition, neurodevelopment.

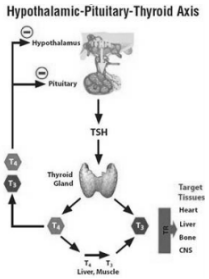
Thyroid hormone important for brain maturation and development

Thyroid disruption is a potential mediator for neurodevelopmental toxicity

The Thyroid as Example

Thyroid Regulates:

- Metabolism & lipid homeostasis
- Respiratory, cardiovascular, nervous, & reproductive systems (Choksi, 2003)
- Growth/neurodevelopment (de Escobar, 2004)



Thyroid-mediated Endpoints

Clinical Disease
Hypothyroidism: ⇩T4 ⇧TSH
Fatigue, weight gain, depression

Hyperthyroidism: ⇧T4 ⇩TSH
Weight loss, anxiety, tachycardia

Subclinical Disease
Fertility
Fetal Growth & Neurodevelopment
Reproduction
Cognition

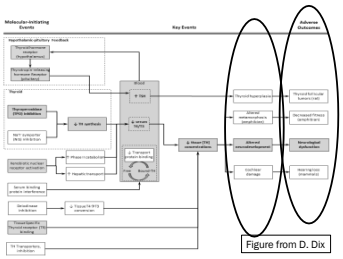
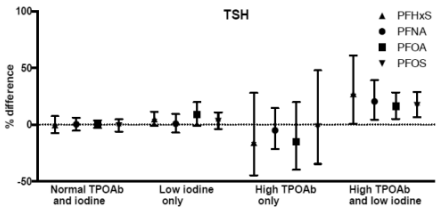


Figure from D. Dix

Positive association of PFOS and Thyroid Stimulating Hormone

(TPOAb is a marker of autoimmune hypothyroidism)



Webster et al Environ Health Perspect (2015)

Controls on Thyroid Hormone Release and Response

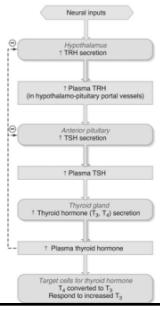
Hypothalamus

↓

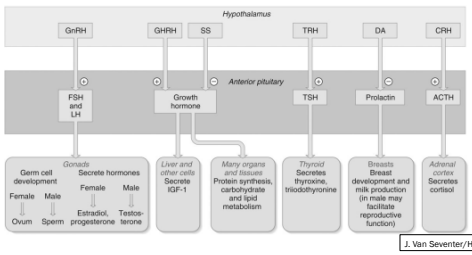
Pituitary

↓

Target Endocrine Gland
adrenal gland
thyroid gland
gonads

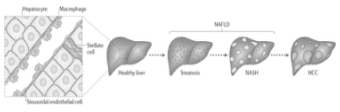


Relationships between Brain & Target-Endocrine Gland Hormones or Other Targets



J. Van Seventer/Hill-McGraw

The pathophysiology of nonalcoholic fatty liver disease progression.

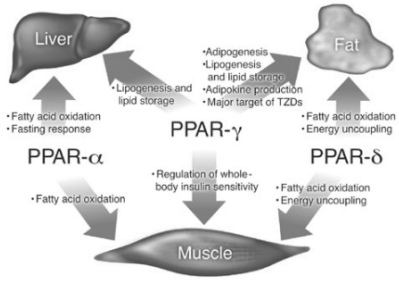


Foulds, C. E. *et al.* (2017) Endocrine-disrupting chemicals and fatty liver disease *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2017.42

Clinical Outcomes
Fatty Liver
Irreversible fibrosis
life-threatening cirrhosis
hepatocellular carcinoma (HCC)

Subclinical Outcomes
⇧ LDL or total cholesterol
Changes in liver enzyme levels

⇧ Susceptibility to obesity & diabetes



PPAR- alpha = master regulator of hepatic intermediary metabolism
PPAR- gamma = master regulator of lipid metabolism

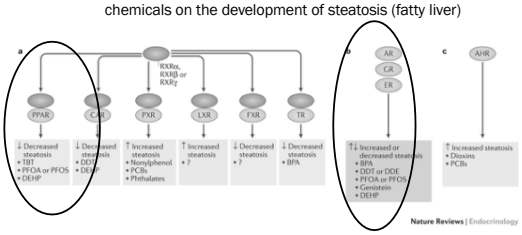
From: Nature Medicine 10, 355 - 361 (2004)

Are humans the same as mice when it comes to PPARs?

While PPARa agonists cause peroxisome proliferation and hepatocarcinogenesis in rodents, this does not occur in humans because of differences in both the PPAR itself and the genes that it regulates. BUT other effects DO occur…
…..lipid dysregulation

Fibrate-based drugs used to control high triglyceride levels in blood.

Nuclear hormone receptor-mediated effects of endocrine- disrupting chemicals on the development of steatosis (fatty liver)



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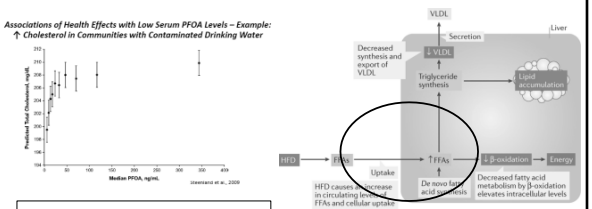
Altered hepatic metabolic pathways that lead to nonalcoholic fatty liver disease (NAFLD)



Longer Chain PFAS
Elevated LDL or total cholesterol
Increase of TG levels and induce steatosis
PFOA induces lipid dysregulation in rodent liver;
Involved in dysregulation of Fatty Acid trafficking.

Zeng XW et al. 2015; Hui et al., 2017; Das etal., 2017

Foulds, C. E. *et al.* (2017)
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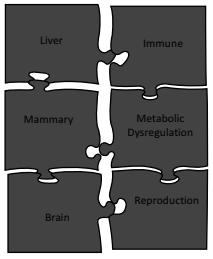
Conclusions
The PFAS Hazard Assessment Puzzle



Complex set of chemicals - how many?

"There is disagreement among studies."
---------- Look at the whole puzzle ----------

Human studies, animal studies, in vitro & mechanistic

NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

L. Birnbaum, Northeastern
https://pfasproject.com/pfas-conference-presentations/

Impact of This Work

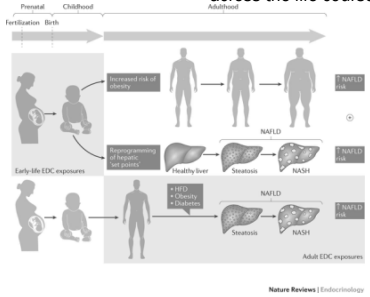
- Lower birth weights following PFOA exposure
  - Koustas *et al.*, 2014 *Environ Health Perspect* – Navigation Guide – sufficient evidence for link between prenatal PFOA exposure and birthweight deficits in mice
  - 5/8 papers used in meta-analysis were by Fenton *et al.*
- Overweight supported in epidemiological studies
  - Increased gestational weight gain in Danish women; 2016 *Int J Environ Res Public Health*
  - Overweight in 20-yr old Danish daughters exposed in utero; 2012 *Environ Health Perspect*
- Decreased breastfeeding duration in humans
  - Women who had highest levels of serum PFAS lactated shorter time or could not continue as long as they wished.
  - Timmerman *et al.*, 2016 *Reprod Toxicol*; Romano *et al.*, 2016 *Environ Res*
- Use of mammary data in risk evaluation
  - Tucker *et al.* 2015, Macon *et al.* 2011, White *et al.* 2011
  - German EPA; NJ, NC, MN, and NY environmental protection departments
- Liver data proves human relevant mechanism of action
  - Data also used in N.J Department of Environmental Protection risk evaluation

Possible Approach for PFAS Hazard Evaluation

- Review all individual hazard studies;
- Identify endpoints but recognize connections between them;
- Use the molecular/cellular data as "glue-like" to support connections;
- Assess confidence in the literature
  - *Consider approach recommended by NTP (2015) & compiled by NAS (2017)*

Extras

Exposure to EDCs & the risk of nonalcoholic fatty liver disease across the life course.



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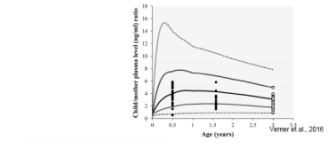
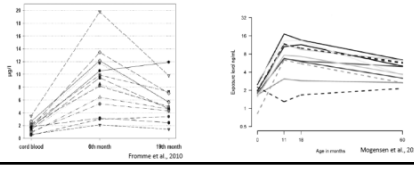
Nature Reviews | Endocrinology

Foulds, C. E. et al. (2017) Endocrine-disrupting chemicals and fatty liver disease. Nat. Rev. Endocrinol. doi:10.1038/nrendo.2017.47

Increases in Infant PFOA Serum Levels after Birth





NJ DWQI, 2016