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

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

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
  - PFOS/PFNA as effectors of lipid metabolism
- Possible Approach for PFAS Hazard Assessment

PFAS Hazard Assessment Challenges

PFAS Hazard Data are Most Comprehensive

PFOS and PFOA

<table>
<thead>
<tr>
<th>Compound</th>
<th>Common Name</th>
<th>Carbon #</th>
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</thead>
<tbody>
<tr>
<td>PFBA</td>
<td>Perfluorobutyric acid</td>
<td>C3-4</td>
</tr>
<tr>
<td>PFBS</td>
<td>Perfluorobutanesulfonic acid</td>
<td>C4</td>
</tr>
<tr>
<td>PFHxA</td>
<td>Perfluorohexanoic acid</td>
<td>C5-6</td>
</tr>
<tr>
<td>PFHxS</td>
<td>Perfluorohexane sulfonic acid</td>
<td>C6</td>
</tr>
<tr>
<td>PFOA</td>
<td>Perfluorooctanoic acid</td>
<td>C7-8</td>
</tr>
<tr>
<td>PFOS</td>
<td>Perfluorooctane sulfonic acid</td>
<td>C8</td>
</tr>
<tr>
<td>PFNA</td>
<td>Perfluorononanoic acid</td>
<td>C9</td>
</tr>
</tbody>
</table>

PFOS Hazard Status

In Vitro (inc Tox 21)
Animal Studies (mice, rat)
Human Studies

Evidence for Health Effects

- Not Classifiable/Suspected/Presumed/Known
  - Low/Inadequate
  - Moderate
  - High

2006 National Toxicology Program Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate

Hazard Assessment: Disparate Data Streams

Table 1. PFAS Main Immune Effects Summary Table

<table>
<thead>
<tr>
<th>Category of Immune Response</th>
<th>Immune Outcome</th>
<th>Immunosuppression</th>
<th>Hypersensitivity</th>
<th>Level of Immune Response</th>
<th>Level of Evidence</th>
<th>Endocrine Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Human</td>
<td>Animal</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Autimmune</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Asthma</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
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

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

Peroxisome Proliferator Activated Receptors (PPAR)

Phthalates
Organotins
OPFRs & PFOA
Triiodothyronine (T3)

• TR regulates metabolism and thermogenesis. Important role in development.

• Thyroid hormones come in two forms: T4 is most abundant; T3 is most active

PBDEs, PCBs
PFOA

Dayan and Panicker. 2009. Nat. Rev. Endocrinol. 5'
(A/G)GGTCAnnnn
(A/G)GGTCA
-3'

PBDEs, PCBs, PFOA

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 offspring 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.

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. PFAs may disrupt fatty acid binding and lipid regulation

Obesity
Adipocytes and the Brain - generating insulin resistance, glucose intolerance, dyslipidemia

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

Endocrine Physiology & Communication Between Systems

Neurotoxicity
Clinical Disease target = neurons
Seizures, Paralysis, Numbness, Headache

Thyroid hormone important for brain maturation and development
Thyroid disruption is a potential mediator for neurodevelopmental toxicity
Thyroid Regulates:
- Metabolism & lipid homeostasis
- Respiratory, cardiovascular, nervous, & reproductive systems (Choksi, 2003)
- Growth/neurodevelopment (de Escobar, 2004)

The Thyroid as Example

Clinical Disease
- Hypothyroidism: $\text{Thyroid Hormones} \downarrow$ $\text{T}_{3}$, $\text{T}_{4}$, $\text{TSH}$
  - Fatigue, weight gain, depression
- Hyperthyroidism: $\text{Thyroid Hormones} \uparrow$ $\text{T}_{3}$, $\text{T}_{4}$, $\text{TSH}$
  - Weight loss, anxiety, tachycardia

Subclinical Disease
- Fatigue, Fetal Growth & Neurodevelopment
- Reproduction, Cognition

Thyroid-mediated Endpoints

Positive association of PFOS and Thyroid Stimulating Hormone

Controls on Thyroid Hormone Release and Response

The pathophysiology of nonalcoholic fatty liver disease progression.
Are humans the same as mice when it comes to PPARs?

While PPARα 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...

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)

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

Conclusions

The PFAS Hazard Assessment Puzzle

Impact of This Work

Liver

Immune

Memory

Metabolic Dysregulation

Brain

Complete set of chemicals - how many?

“There is disagreement among studies.” Look at the whole puzzle.

Conclusions

The PFAS Hazard Assessment Puzzle

Impact of This Work

- Liver birth weights following PFAS exposure
  - Kortas et al., 2016, Environ. Health Perspect.
  - Severson et al., 2016, Environ. Health Perspect.

- Immune
  - Increased neutrophil counts in exposed children, 2016, Environ. Health Perspect.

- Memory

- Metabolic dysregulation
  - Increased cholesterol, 2016, Environ. Health Perspect.

- Brain
  - Increased neurodegeneration, 2016, Environ. Health Perspect.

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

Extras

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

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

Increases in Infant PFOA Serum Levels after Birth

NJ DWQI, 2016