TRANSCRIPTIONAL EFFECTS OF DIFFERENT PFCS IN RAT HEPATOMA CELLS
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Outline

- History and Background
- Rationale for Study
- Methods
- Results
- Conclusions
PFC History and Background

- Large scale production and usage began in the 1950’s
- Thought to be chemically stable and biologically inert in the environment
- Globally distributed in a wide variety of environmental matrices
- Most work has focused on only the two most widely produced and detected chemicals (PFOS and PFOA)
- The causative biochemical events leading to toxicity as a result of PFC exposure are largely unknown
PFC History and Background

- PFOS has been shown to cause reduced body weight, increased liver weight, reduced cholesterol and steep dose response curves for mortality in vertebrates including non-human primates.

- PFOS has been shown to be an incomplete peroxisome proliferator.

- PFOA has been shown to be a potent and complete peroxisome proliferator, and causes liver and pancreatic tumours.

- But most research so far has focused only on PFOS and PFOA, with emphasis on distribution and transport.
Rationale

- Due to these toxicological concerns PFOS production was phased out in 2000.

- Shorter chain-length replacement chemicals such as PFBS and PFBA were chosen because of studies showing them to have reduced half-lives and fewer biological effects.

- There are few mechanistic and toxicological studies of PFCs other than PFOS and PFOA but in general these replacement chemicals have been shown to work through similar mechanisms, but with reduced toxicity.
Rationale

- PFCs have been shown to alter biochemical process such as fatty acid metabolism, cholesterol synthesis, peroxisome proliferation, cellular communication and thyroid hormone function

- Specific genes were chosen based on previous research showing alterations in mRNA abundance as a result of PFOS exposure
Objectives

- To compare the potential effects of 10 widely distributed and frequently identified PFCs on 7 important genes related to processes potentially altered by PFCs.

- Describe potential affects PFCs have on key biochemical pathways and evaluate relative potencies for altering these important processes.
Genes Related to the Thyroid

- **Paired box gene 8 (PAX8)**
  - Related to thyroid follicular cell development

- **Homeobox (HEX)**
  - Related to thyroid cell differentiation
Genes Related to Fatty Acid and Cholesterol Synthesis

- **Apolipoprotein A-IV (ApoA4)**
  - Related to fatty acid synthesis
- **Squalene synthase (SqSyn)**
  - Important in the synthesis of sterols
- **Peroxisome 3-ketoacyl-CoA thiolase (Per Keto A)**
  - Involved in FA beta-oxidation
- **Mitochondria 3-ketoacyl-CoA thiolase (Mito Keto A)**
  - Involved in FA beta-oxidation
- **Mitochondria 3-ketoacyl-CoA thiolase (Mito Keto B)**
  - Involved in FA beta-oxidation
# Chemicals Tested

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<thead>
<tr>
<th>Chemical Name</th>
<th>Acronym</th>
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<tbody>
<tr>
<td>Perfurobutane sulfonate</td>
<td>PFBS</td>
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<td>Perfurohexane sulfonate</td>
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<td>Perflurooctane sulfonate</td>
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Methods

- Cell culture and exposure
- RNA Extraction
- cDNA Synthesis
- Q-PCR
Sulphonates

Fold Change at 100 uM

Chemicals

PFBS  PFHS  PFOS

MKA  APOA 4  PKA  MKB  SQSYN  HEX  PAX 8
Specific Conclusions

- Both processes were affected by PFC exposure
- All of the sulphonates and all but one of the carboxylates caused up-regulation in the two genes related to the thyroid
- The response for the 5 genes related to fatty acid and cholesterol processes were much more variable, but significant changes were seen for 35% of the chemicals
General Conclusions

- mRNA expressions studies provide a useful tool for identifying potentially effected pathways, and allows for quick comparisons between chemicals.

- Not all PFCs cause the same affects on mRNA expression and differences could not simply be attributed to chain-length or head group.

- Further studies are needed to determine if these differences are expressed at more toxicologically relevant endpoints, such as at the protein level.
Thank You!