3,3',4,4',5-Pentachlorobiphenyl (PCB 126) decreased the ratios of epoxide metabolites of unsaturated fatty acids to their corresponding diols in male rodents

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Background

- 3,3',4,4',5-Pentachlorobiphenyl (PCB 126): Dioxin-like pollutant.
- PCB 126 exposure may affect the global metabolome, including oxygenated metabolites of unsaturated fatty acids (oxylipins).
- Oxylipins: Regulatory lipid mediators implicated in metabolic syndrome.

**Polyunsaturated fatty acids**
- **Cyclooxygenase pathway**
- **Lipoxygenase pathway**
- **Cytochrome P450 epoxygenase pathway**
- **Epoxide metabolites**
- **Soluble epoxide hydrolase (sEH)**
- **Prostanoids**
- **Diols**
Hypothesis

Chronic exposure to PCB 126 alters the levels of regulatory lipid mediators (oxylipins) in rats.
Experiment design

- Five week old male Sprague-Dawley rats (n=8~10/group, 147 ± 8 g)
- Biweekly I.P. injections of PCB 126 in corn oil for 3 months.
- Cumulative doses: 0, 0.06, 0.3 and 1.2 µmol/kg b.w.

- Tissue (e.g., liver, lung and thymus) were collected
Experimental part

• General toxicity: Body and organ weight
• GC-ECD: PCB 126 levels
• LC/MS/MS: Oxylipin levels
• Determination of epoxide hydrolase activity: Cytosol, peroxisomes, and microsomes
• Statistical analysis: One way AVOVA and Tukey's Studentized Range (HSD) Test. Comparisons are significant at 0.05 level.
General toxicity

- Decreased:
  - Growth
  - Relative thymus weight

- Increased relative organ weights:
  - Liver
  - Lung
  - Spleen

* Significant different from control (p<0.05)
PCB 126 tissue levels

- **Liver:** Dose-dependent increase
- **Plasma:** < Limit of Detection (5.0 ng/mL)
Oxylipins profiling in plasma

Levels of 24 oxylipins changed:

- Eleven epoxide/diol ratios decreased (epoxide ↓ and diol ↑)
- Leukotriene B4 ↑, 6-keto-PGF1α ↑
Oxylipins profiling in liver

Levels of 27 oxylipins changed:

- Eleven diols ↑, 1 epoxide ↓ (most epoxides unchanged)
- Five epoxide/diol ratios decreased
- Increase: 8-Hydroxyeicosatetraenoic acid (HETE), 5-oxo-ETE, lipoxin A4, leukotriene B3
- Decrease: 15-deoxy-PGJ2
Activities of soluble epoxide hydrolase slightly increased

- tDPPO (trans-diphenylpropene oxide), substrate for sEH
- Incubation tDPPO (50 µM), 15 min at 30 °C
- *Significant different from control (p<0.05)
Conclusions

- Fatty liver
- Activities of soluble epoxide hydrolase (sEH)
- The ratios of epoxide metabolites to diols
- PCB 126
Future directions

Test whether sEH inhibition can attenuate PCB 126–induced hepatic steatosis by reduced systemic inflammatory status in rat.
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