Recent Animal Toxicity Findings on PFAS

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Legacy PFAS (PFAA) toxicity in Animal Studies

• Hepatic and Metabolic toxicity
  • hepatomegaly; aberrant histology; fatty liver; decreased serum cholesterol/TG; changes of liver enzymes less consistent

• Reproductive and Developmental Toxicity
  • weak reproductive effects; few and transient birth defects: neonatal mortality; low birth weight; growth deficits and developmental delays

• Immunotoxicity
  • thymic and splenic atrophy; reduced acquired and innate immune responses

• Tumor Induction
  • liver, pancreas, testes

• Endocrine Disruption
  • reduced serum T4, no change in TSH

• Neurotoxicity
  • Few reports of neuronal deficits and behavioral abnormalities
Some Proposed MOA for PFAS

• Activation of nuclear receptors that regulate energy metabolism
  • PPARα, PPARγ, CAR, PXR
• Inhibition of gap junction at cell membrane to disrupt cell-cell communication
• Partition into membrane phospholipid bilayers
  • lung surfactant?
• Interference of protein binding to displace endogenous ligands
• Induction of oxidative stress
• Induction of mitochondrial dysfunction
• Inappropriate actions on cellular or molecular signals that regulate cell functions
Recent Animal Toxicity Findings of PFAA

• Increasing use of zebrafish models in addition to rodents
• Comparative studies with multiple PFAA (functional groups, chain lengths)
• Findings are largely consistent with those already identified
  • Zebrafish model generally recapitulates rodent findings
• Very little significantly novel adverse effects reported
• Mechanistic findings begin to fill data gaps
  • Cellular and molecular pathways to elaborate effects on energy metabolism and oxidative stress
Some Emerging PFAA Alternatives

- **PFOA**
- **PFOS**
- **GenX**
- **F-53B**
- **NBP-2**
- **ADONA**
- **PFMOOA**

USEPA Chemical Dashboard
Perfluoroalkyl Ether Carboxylates

• **ADONA:** *ammonium 4,8-dioxo-3H perfluorononanoate*
  - Apparently short half-life in rat, detectable but not accumulated in liver
  - Increased liver weight, hepatocellular hypertrophy
  - Activation of PPARα in liver
  - No developmental toxicity detected

• **GenX:** *ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate*
  - Short half-life: 5h in rats, 20h in mice, detectable but not accumulated in liver
  - Increased liver weight (hypertrophy), necrosis, elevated serum ALT, AST, activation of PPARα
  - Liver, pancreatic, Leydig cell tumors
  - Developmental mortality, low birth weight, growth deficit (potency << PFOA)
  - Immunomodulatory effects (< immunosuppression)

• **PFMOAA:** *difluoro(perfluoromethoxy) acetic acid*
  - Below detection limit in serum or liver 24 h after administration (mice)
  - Little developmental toxicity (in rat), <<< GenX << PFOA
Perfluoroalkyl Ether Sulfonates

• **F-53B**: *chlorinated polyfluoroalkyl ether sulfonate*
  • Mice: Enlarged and fatty liver, induced apoptosis, dysregulation of hepatic PPARα and PXR (effects > PFOS); Inflammation of GI tract
  • Zebrafish: bioaccumulated in liver/gonads, hepatotoxicity (hepatocellular vacuoles and oxidative stress); uninflated swim bladder in larvae
  • Chick: enlarged liver in embryo

• **Nafion Byproduct-2**: *perfluoro-2-[[perfluoro-3-(perfluoroethoxy)-2-propanyl]oxy]ethanesulfonic acid*
  • Hepatomegaly, fatty liver: does not activate PPARα (mice)
  • Developmental toxicity: neonatal mortality (rats)
Questions?