Recent Animal Toxicity Findings on PFAS

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Legacy PFAS (PFAA) toxicity in Animal Studies

- Hepatic and Metabolic toxicity
  - hepatomegly; 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

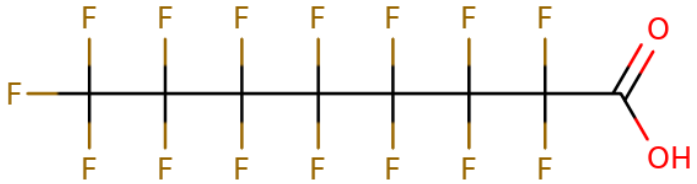
- Activation of nuclear receptors that regulate energy metabolism
  - *PPARα, PPARγ, CAR, PXR*
- Inhibition of gap junction at cell membrane to disrupt cell-cell communication
- Partition into membrane phospholipid bilayers
  - *lung surfactant?*
- Interference of protein binding to displace endogenous 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

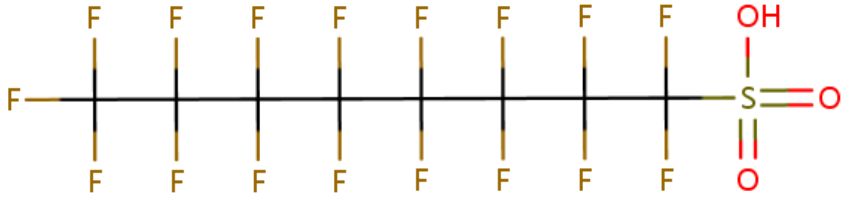
- Increasing use of zebrafish models in addition to rodents
- Comparative studies with multiple PFAA (functional groups, chain lengths)
- Findings are largely consistent with those already identified
  - Zebrafish model generally recapitulates rodent findings
- Very little significantly novel adverse 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

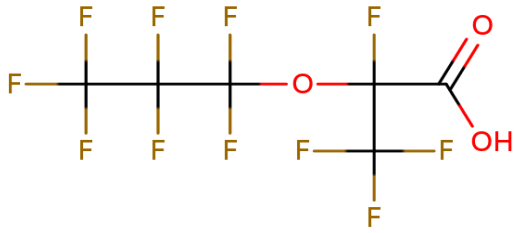
PFOA



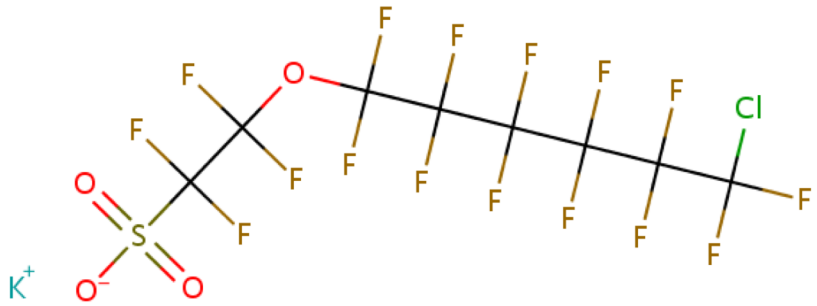
PFOS



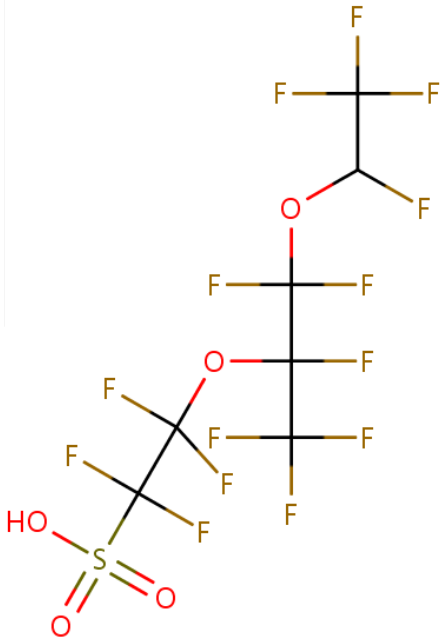
GenX



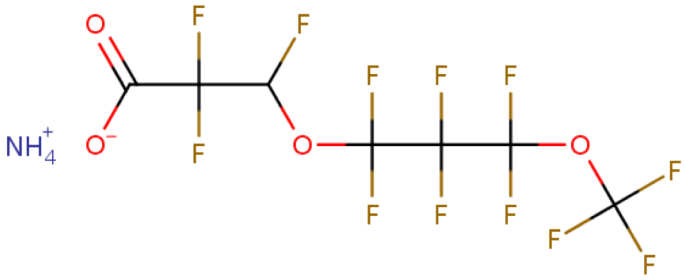
F-53B



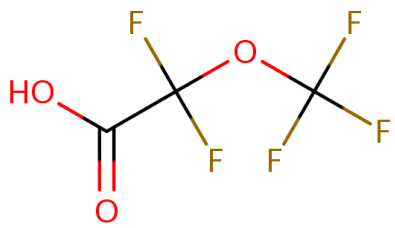
NBP-2



ADONA



PFMOAA



USEPA Chemical Dashboard

Perfluoroalkyl Ether Carboxylates

- **ADONA**: *ammonium 4,8-dioxa-3H perfluorononanoate*
  - Apparently short half-life in rat, detectable but not accumulated in 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*
  - Hepatomegly, fatty liver: does not activate PPARα (mice)
  - Developmental toxicity: neonatal mortality (rats)

Questions?