EPA Health Advisory for PFOA and PFOS Drinking Water

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Outline

• PFOA Background

• How did the advisory come about?

• Animal Studies
  • Skeletal Variations
  • Testicular Cancer
  • Persistent Liver Damage
  • Mammary Gland Development
Perfluorinated Compounds

• Entirely manmade products including in non-stick coatings, fire fighting foams and stain resistance materials.
• Composed of an acid group (carboxylic or sulfonic) and a carbon chain tail with F instead of H.
• Resistant to chemical reactions, persists indefinitely, and water soluble.
• Slow elimination (half life of years in humans).

Perfluorooctanoic acid (PFOA, C₈)

Perfluorinated Compounds: Reproductive Toxicity

• Pregnant/breastfeeding mothers are the primary sensitive populations.
  • Detected in breastmilk, umbilical cord blood, and amniotic fluid.

• At birth, infants have roughly the same serum levels of PFOA as mother.
  • But will surpass mom during the first few months due to breastmilk exposure (or water from formulae)!

• USEPA set for 70ppt for PFOA + PFOS exposure.
How did this advisory come about?

**RfD = NOAEL / (UF x MF)**

Reference Dose (RfD): estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime. (mg/kg/day)

NOAEL: No observed adverse effect level. If NOAEL isn’t established, LOAEL (lowest) is sometimes used. (mg/kg/day).

UF: Uncertainty factor to err for safety in relating animal studies to sensitive human populations.

MF: Modifying factor to be determined based on professional judgement

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**Animal Study Endpoints**

- Skeletal Variations
- Testicular Cancer
- Persistent Liver Effects
- Mammary Gland Development

NOAEL

Dismissed by USEPA

Primary endpoint for NJ DWQI

USEPA Determine Safe Levels for Humans
How did this advisory come about?

RfD (non-cancerous): 20ng/kg/day

LOAEL 1mg/kg/day based on Lau et al 2006 (skeletal variations and accelerated puberty in males) and then applied additional UF of 10 for NOAEL extrapolation.

Then pharmacokinetic modeling was used to relate serum level in mice to humans to generate human equivalent doses.

Animal Models for PFAS Toxicity

• Strengths:
  • Ethically carry out controlled studies.
  • Establish mechanism.
  • Provide preliminary data to inform human studies.

• Weaknesses
  • Animals are not people.
    • Especially so in reproduction (puberty timeline, testicular cancer).
  • Half-life varies a bunch by species.
    • Humans 3.5 years
    • Cynomolgus Monkey: ~28.5 weeks
    • Mouse: 15-18 days
    • Male rat: 6-10 days
    • Female rat: 3-4 hours

  Cost prohibitive

Maternal half-life too short for daily dosing.
Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse (Lau et al 2006 Tox Sci)

Timeline

Pregnancy

Gavaged Daily

Birth

skeletal examination

After birth

Breastfed

Start of puberty evaluated

"developmental effects to fetuses during pregnancy or to breastfed infants (e.g., low birth weight, accelerated puberty, skeletal variations)."

Skeletal Variations

Lau et al 2006

Effect was significant at 1mg/kg dose (LOAEL 1)
Fetal birth weight

Birth weight was significant at 20mg/kg dose (NOAEL of 10)

Accelerated Puberty (males)

Developmental landmarks of mouse pups exposed to PFOA in utero. Data represent means ± S.E. of numbers of litters (for eye opening) or individual pups (for vaginal opening, first estrus and preputial separation) examined as indicated. For eye opening, N = litter, for other landmarks, N = individual animal, numbers in parenthesis indicate litters represented. ANOVA indicate significant treatment effect in all parameters examined (p < 0.05). Significant differences (p < 0.05) between each dose group were determined by Duncan's multiple range test and are depicted by different letters (a, b, c and d).

Sign of puberty for females

Sign of puberty for males
Chronic Dietary Toxicity and Carcinogenicity Study with Ammonium Perfluorooctanoate in Sprague-Dawley Rats (Butenhoff et al 2012) Toxicology

Cited for testicular cancer effects.

Rats were given 0, 30 and 300ppm PFOA fed via diet for 1 or 2 years.
Hepatic mitochondrial alteration in CD1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA) (Quist et al 2015) Toxicol Pathol

• Design: Pregnant CD-1 mice were exposed to 0, 0.01, 0.1, 0.3, and 1mg/kg PFOA by gavage daily from GD1-17.
Figure 3.
Liver weight and relative liver weight of PND 21CD-1 mice. Mean liver weights (g) and relative liver weights (liver:body weight ratio) in female offspring following prenatal exposure to PFOA. All pups consumed Purina 5001 diet at this life stage. Data presented as mean ± SEM. n =10/dose group. Significant treatment effect compared with controls (*p≤0.05, **p≤0.01).

Dose-related Chronic Inflammation and Hypertrophy

Chronic inflammation (cancer risk)

Increase cell size (classic sign of stress, usually reversible)
The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure (Tucker et al 2015) Repro Tox

Pregnant CD-1 and C57Bl/6 mice were exposed to 0, 0.01, 0.1, 0.3, 1.0mg/kg PFOA for GD1-17. Female offspring were analyzed for mammary gland development.

Day after breeding
Gavaged Daily

Sexual maturity is between 6-8 weeks (PD36-48)

Mammary Gland Development

Control | 0.01mg/kg | 0.1mg/kg | 0.3mg/kg | 1.0mg/kg

PD: 21

A | B | C | D | E

PD: 35

F | G | H | I | J

PD: 56

K | L | M | N | O
Mammary Gland Development

Relation to humans and toxicity are controversial.

Animal Study Conclusions

- **Skeletal Variations**
  - Nonmonotonic dose response.
  - Not permanent.

- **Testicular Cancer**
  - Based on Leydig cell tumors in rats.
  - Tumor is not common in humans.

- **Persistent Liver Effects**
  - Increase in liver weight (in utero).
  - Signs of chronic stress well into adulthood.

- **Mammary Gland Development**
  - Possible sensitive endpoint for endocrine issues.
  - Adverse effect and human relevance unclear.

USEPA Determine Safe Levels for Humans
Summary

• Mouse represent a decent animal model for PFAS exposure due to longer elimination.

• Animal studies claiming toxicity from low dose PFOA in utero exposure is based on several endpoints
  • skeletal variations, low birth weight, accelerated puberty development (Lau et al), testicular cancer (Leydig cell tumor, Butenhoff et al), lasting liver effects (Quist et al) and other effects.

• The impact of in utero PFOA exposure on mouse mammary gland development (Tucker et al) remains controversial.
  • Accepted by NJDWQI but not USEPA

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4. Tucker DK, Macon MB, Strynar MJ, Dagnino S, Andersen E, Fenton SE. "The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure." Reprod Toxicol. 2015 Jul;54:26-36