Revisiting the Board's PFMOAA Recommendation

NC Secretaries' Science Advisory Board

December 4, 2024

Frannie Nilsen, PhD

PFMOAA History with NC SSAB

During the August 1, October 3, and December 5, 2022, Secretaries' Science Advisory Board (Board) meetings, the Board discussed two PFMOAA peer-reviewed publications (Yao et al. 2020 and Woodlief et al. 2021) to determine if the existing data is of high enough quality and presents adequate results to derive a reference dose. The questions posed by the NC Department of Environmental Quality (NCDEQ) and the Board's summarized discussions are provided below. The DEQ conducted two literature reviews (summer 2022 and winter 2023) to retrieve any PFMOAA studies which might inform a reference dose; these searches yielded only the two papers brought to the Board for review.

The questions posed to the Board by NCDEQ during the June 6, 2022, meeting were:

1- Review the PFMOAA studies in detail.

- *assess the quality of the studies (low, moderate, high)*
- *based on sample sizes, dose regimes, endpoints measured*

2- Do the studies provide sufficient scientific information to determine a point of departure to derive a reference dose in June 2022?

PFMOAA – Toxicology Studies as of June 2022

Overall Summary:

Human serum measurements

- PFMOAA accumulates more than expected based on very low K_{ow} value (measure of adsorption)
- PFMOAA serum concentrations increased with age in humans
- PFMOAA in serum was not associated with changes in liver and kidney function biomarkers or lipid metabolism

Mice PFMOAA dosing

- Increased splenic T cells and NK cells and thymic helper and cytotoxic T cells in males
- A peroxisome proliferation response of palmitoyl-CoA changes in females
- Sex-specific differences in peroxisome proliferation (not statistically significant)

Overall Conclusion:

This is evidence to support public health concerns for PFMOAA as even with a low bioaccumulation potential in humans, high, chronic environmental doses could still lead to adverse health outcomes

PFMOAA History with NC SSAB

The Board's response *(abridged):*

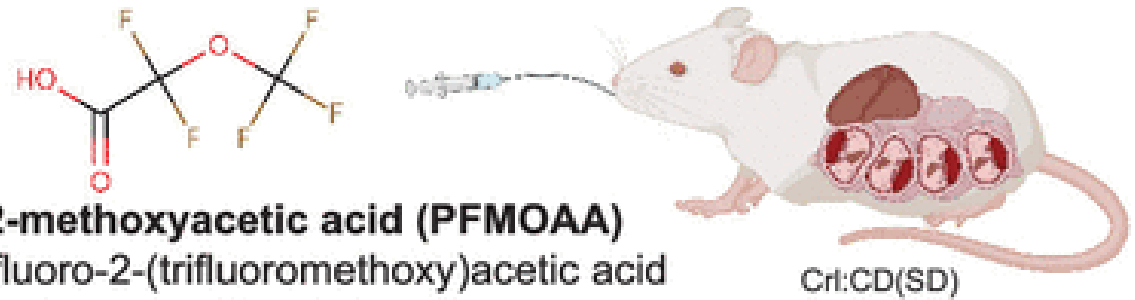
The two studies were of high quality but had limitations that would preclude their use to derive a reference dose.

The Board recommends that NCDEQ pause derivation of a reference dose until the referenced manuscript in preparation is published and available for review. (Refers to *DeWitt et al. In Prep*)

In the interim, the Board encourages NCDEQ to periodically refresh their PFMOAA literature search for other relevant papers for inclusion in a toxicological synthesis with the expected new information.

The recordings of the three Board discussions of the topic are here:
NC DEQ and DHHS Secretaries' Science Advisory Board 08/01/2022 (at 1:28:00),
NC DEQ and DHHS Secretaries' Science Advisory Board 10/03/2022 (at 0:22:50),
NC DEQ and DHHS Secretaries' Science Advisory Board 12/05/2022 - (at 00:47:33)

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat

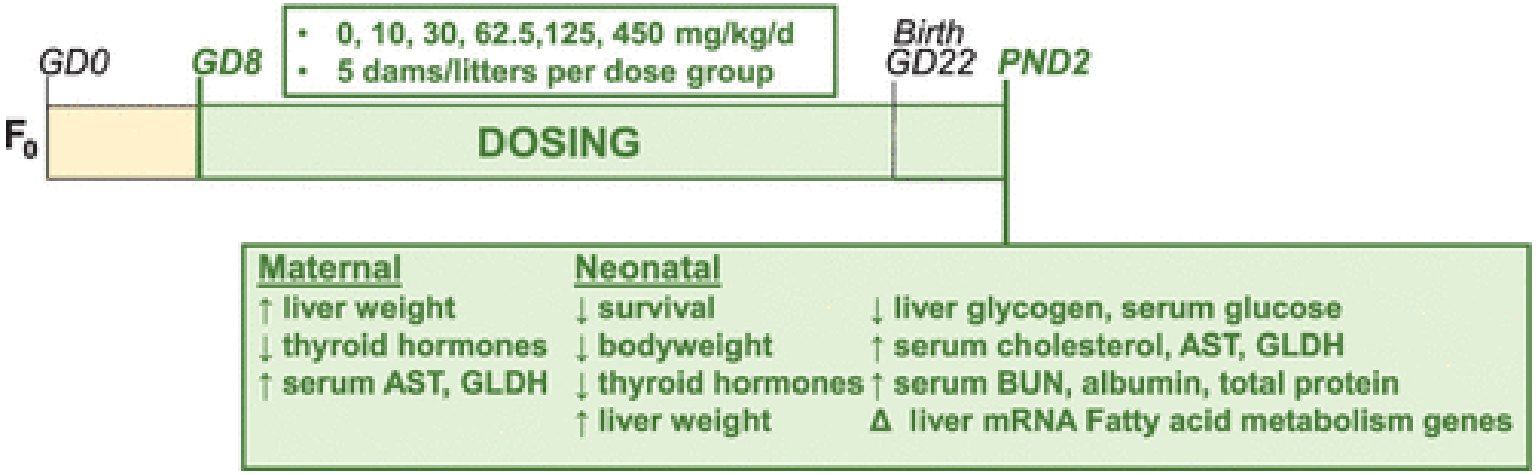


Perfluoro-2-methoxyacetic acid (PFMOAA)

IUPAC: 2,2-difluoro-2-(trifluoromethoxy)acetic acid

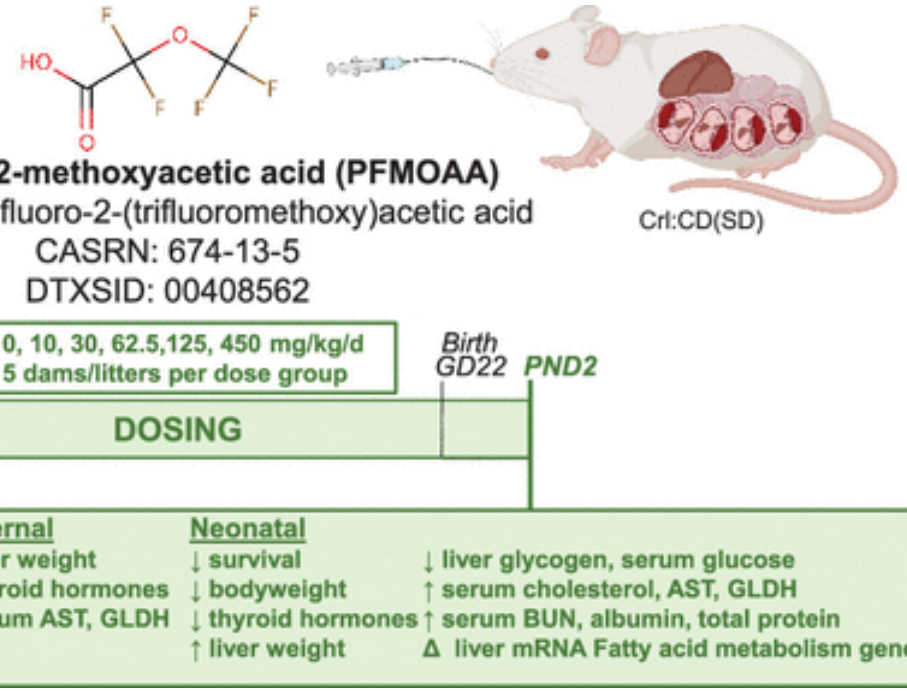
CASRN: 674-13-5

DTXSID: 00408562



[Conley et al. 2024, ES&T]

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat



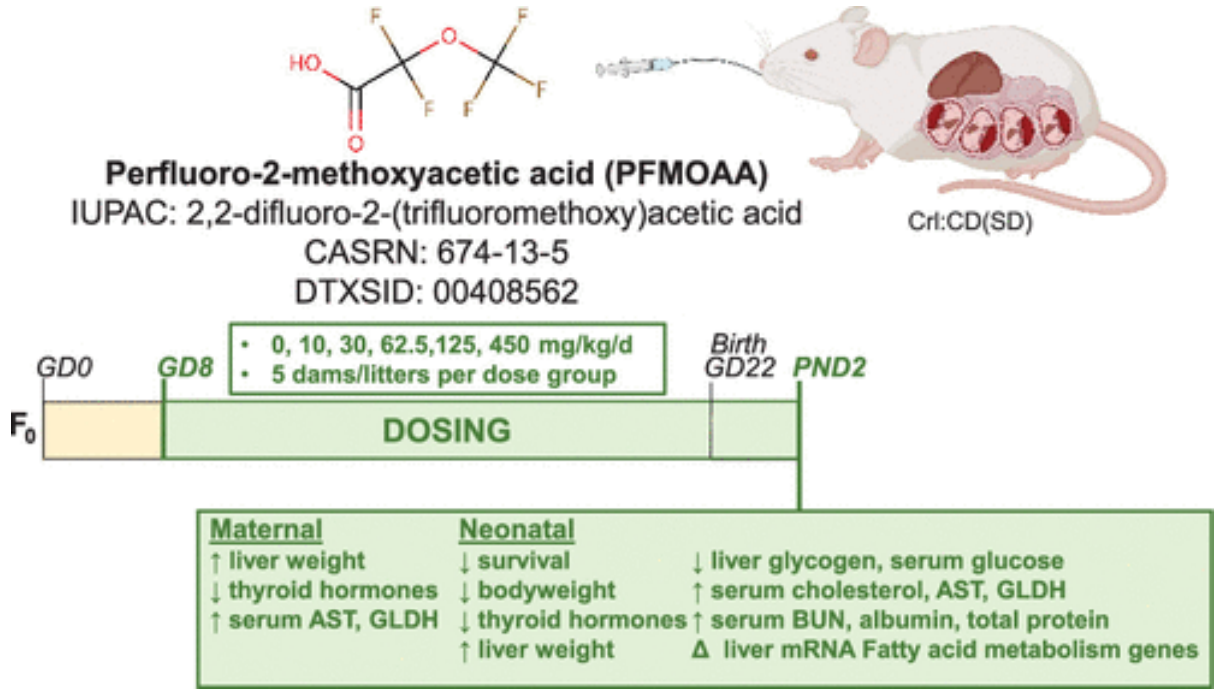
Methods:

1. Pregnant Sprague–Dawley rats to a range of PFMOAA doses (10–450 mg/kg/d) via oral gavage from gestation day (GD) 8 to postnatal day (PND) 2.

2. Results were compared to results previously reported for PFOA and HFPO–DA (GenX).

Conley et al. 2024, ES&T

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat



Results:

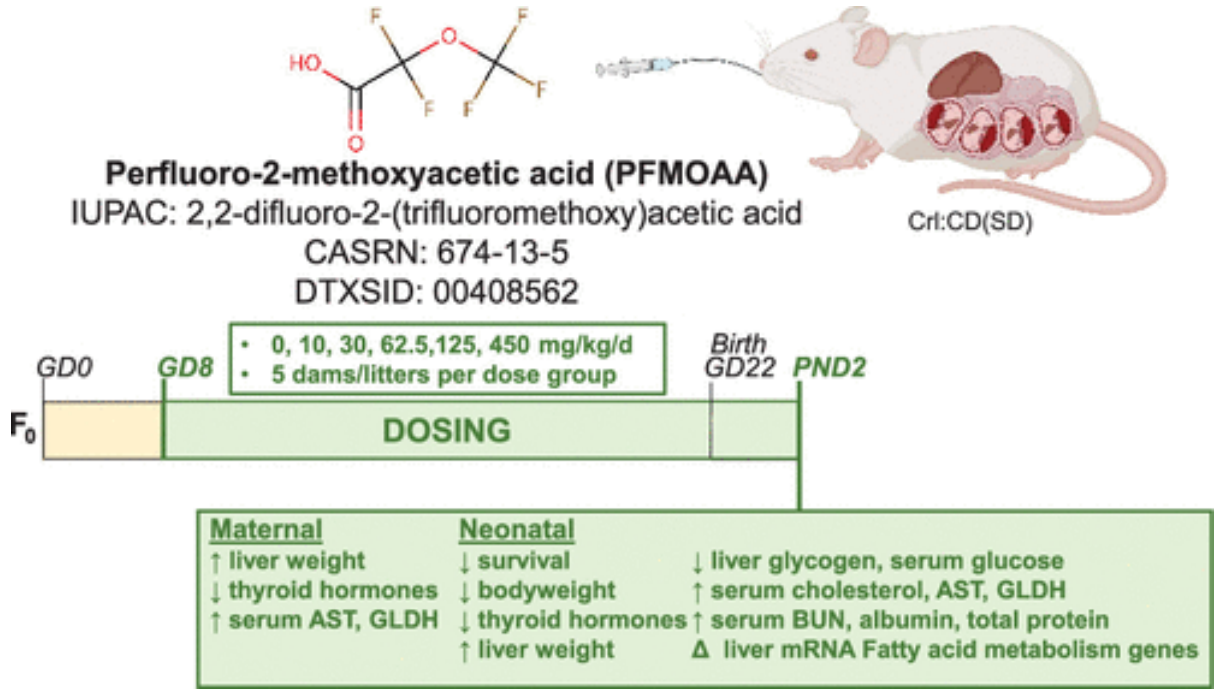
Newborn pups displayed:

1. reduced birthweight (≥30 mg/kg),
2. depleted liver glycogen concentrations (all doses), hypoglycemia (≥125 mg/kg), and
3. numerous significantly altered genes in the liver associated with fatty acid and glucose metabolism ***similar to*** gene changes produced by ***GenX***.

Conley et al. 2024, ES&T

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat

[*Conley et al. 2024, ES&T*]



Results:

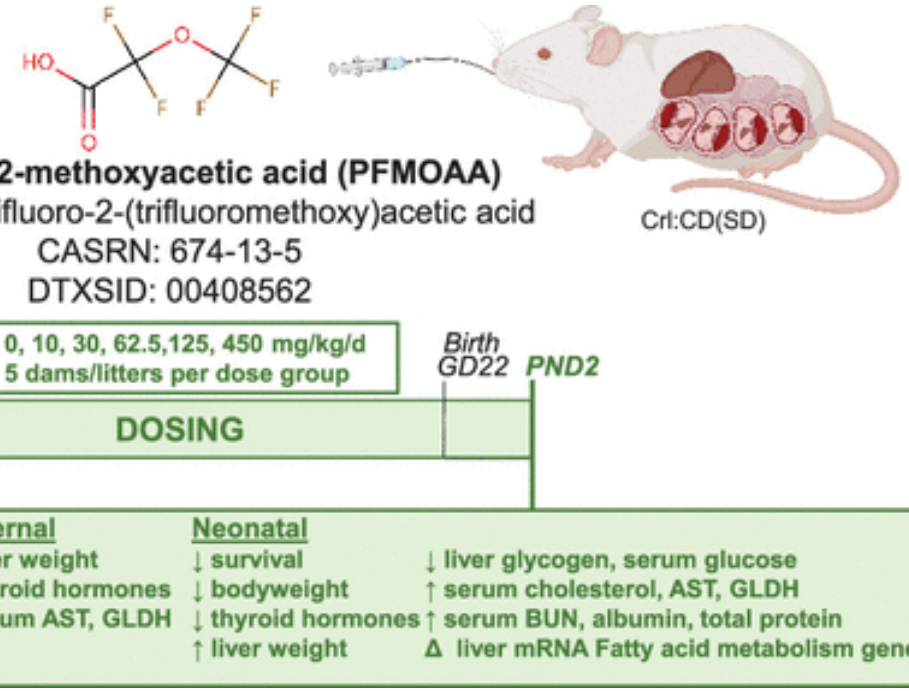
Pup survival was significantly reduced at the ≥125 mg/kg doses.

At necropsy both maternal and neonatal animals displayed:

1. increased liver weights,
2. increased serum aspartate aminotransferase (AST),
3. and reduced serum thyroid hormones ***at all doses*** (≥10 mg/kg).

Pups also displayed highly elevated serum cholesterol at all doses.

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat



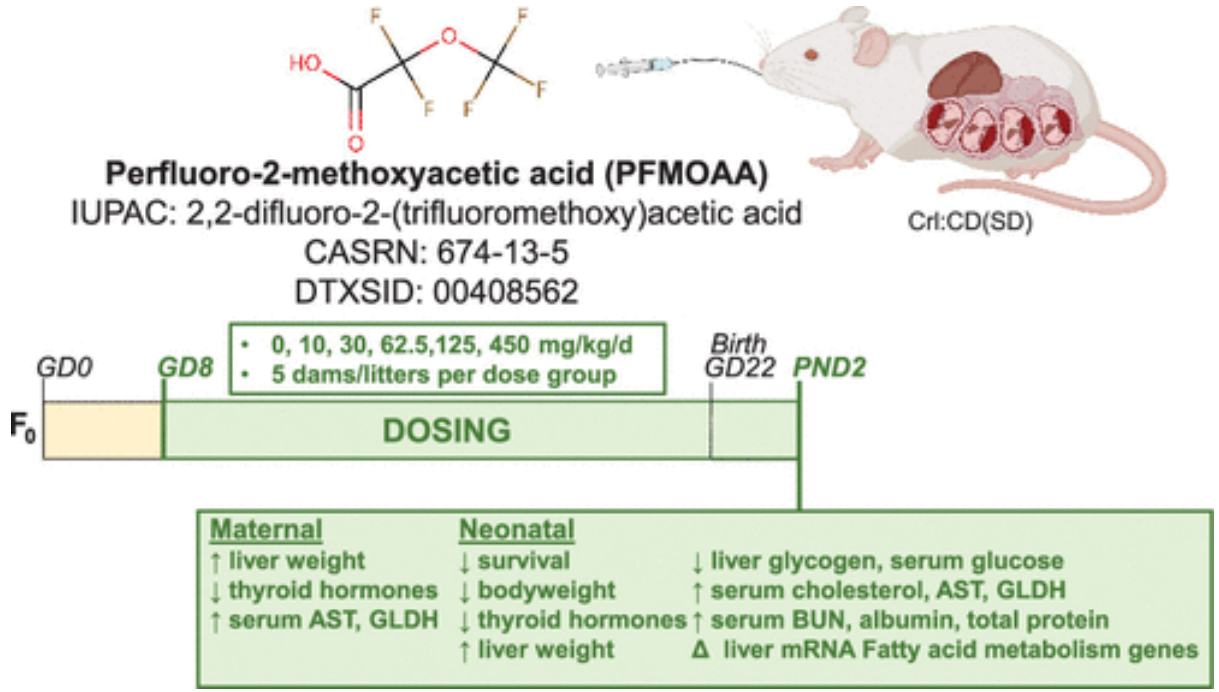
Results compared to PFOA and GenX:

PFMOAA concentrations in serum and liver increased with maternal oral dose in both maternal and newborn animals and were similar to those that were reported for PFOA but considerably higher than HFPO–DA.

Conley et al. 2024, ES&T

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat

[*Conley et al. 2024, ES&T*]



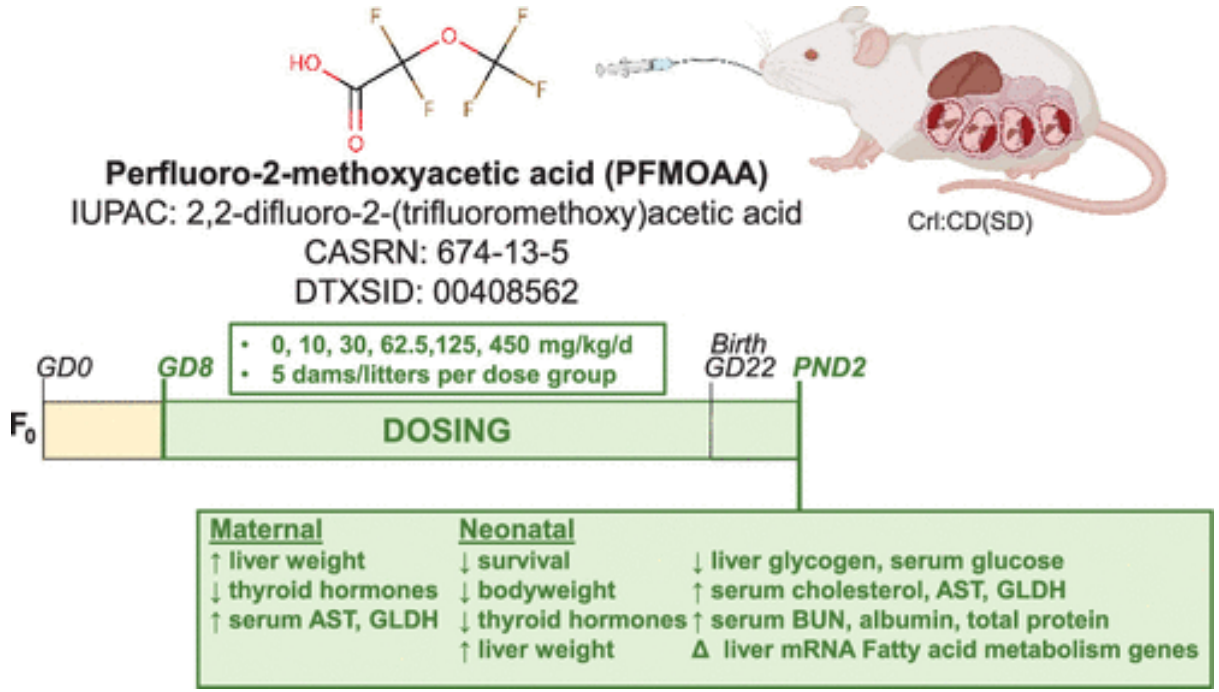
Results compared to PFOA and GenX:

The authors calculated 10% effect levels (ED10 or EC10) and relative potency factors (RPF; PFOA = index chemical) among the three compounds based on maternal oral dose and maternal serum concentration (μM).

Reduced pup liver glycogen, increased liver weights and reduced thyroid hormone levels (maternal and pup) were the most sensitive end points modeled.

Maternal and Neonatal Effects of Maternal Oral Exposure to PFMOAA during Pregnancy and Early Lactation in the SD Rat

[*Conley et al. 2024, ES&T*]



PFMOAA Potency compared to PFOA and GenX:

PFMOAA was ~3–7-fold less potent than PFOA for most end points based on maternal serum RPFs, but slightly more potent for increased maternal and pup liver weights.

PFMOAA is a maternal and developmental toxicant in the rat producing a constellation of adverse effects similar to PFOA and HFPO–DA.

PFMOAA Updated Literature Base

PFMOAA References:

1. Woodlief T, Vance S, Hu Q, DeWitt J. 2021. Immunotoxicity of per- and polyfluoroalkyl substances: Insights into short-chain PFAS exposure. *Toxics* 9(5):100.

2. Yao J, Pan Y, Sheng N, Su Z, Guo Y, Wang J, Dai J. 2020. Novel perfluoroalkyl ether carboxylic acids (PFECAs) and sulfonic acids (PFESAs): Occurrence and association with serum biochemical parameters in residents living near a fluorochemical plant in China. *Environmental Science & Technology* 54 (21): 13389-13398.

3. Justin M. Conley, Christy S. Lambright, Nicola Evans, Jacqueline Bangma, Jermaine Ford, Donna Hill, Elizabeth Medlock-Kakaley, and L. Earl Gray Jr. 2024. *Environmental Science & Technology* 58 (2), 1064-1075.

Request to the Science Advisory Board

DEQ is asking the Board to review the literature base for PFMOAA toxicity and determine if an RfD can be derived with the available scientific information.

Charge Question:

With the studies from Woodlief et al, Yao et al, and Conley et al, is there enough scientific support to identify a Point Of Departure for deriving a Reference Dose for PFMOAA?