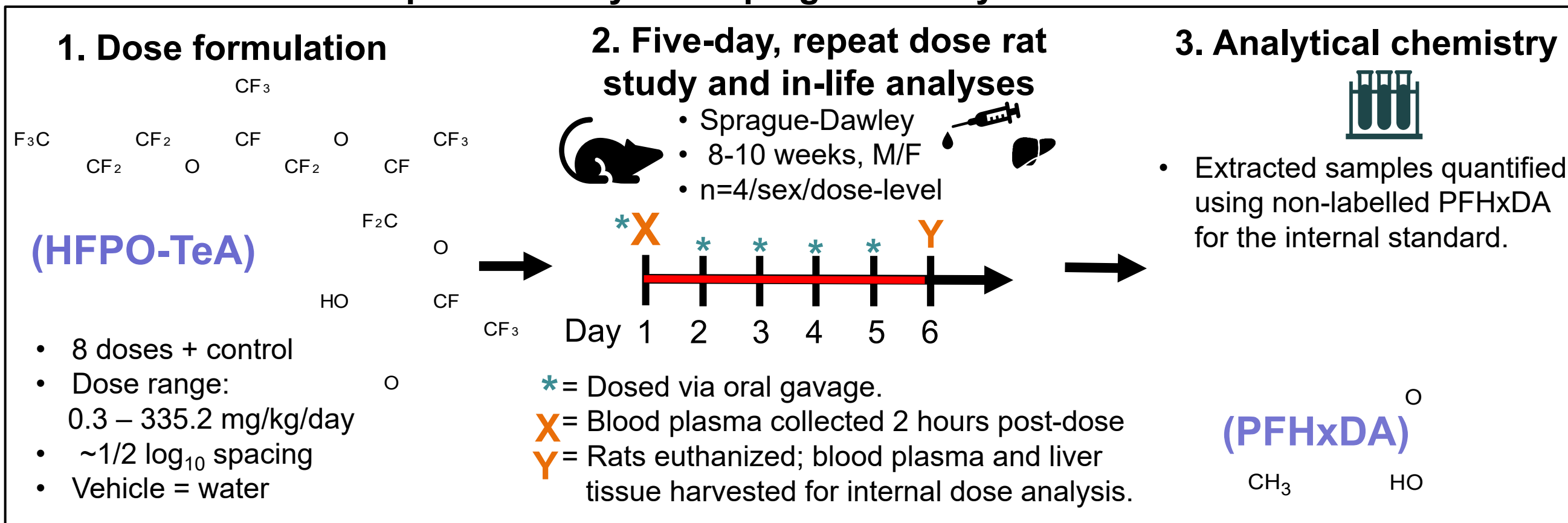


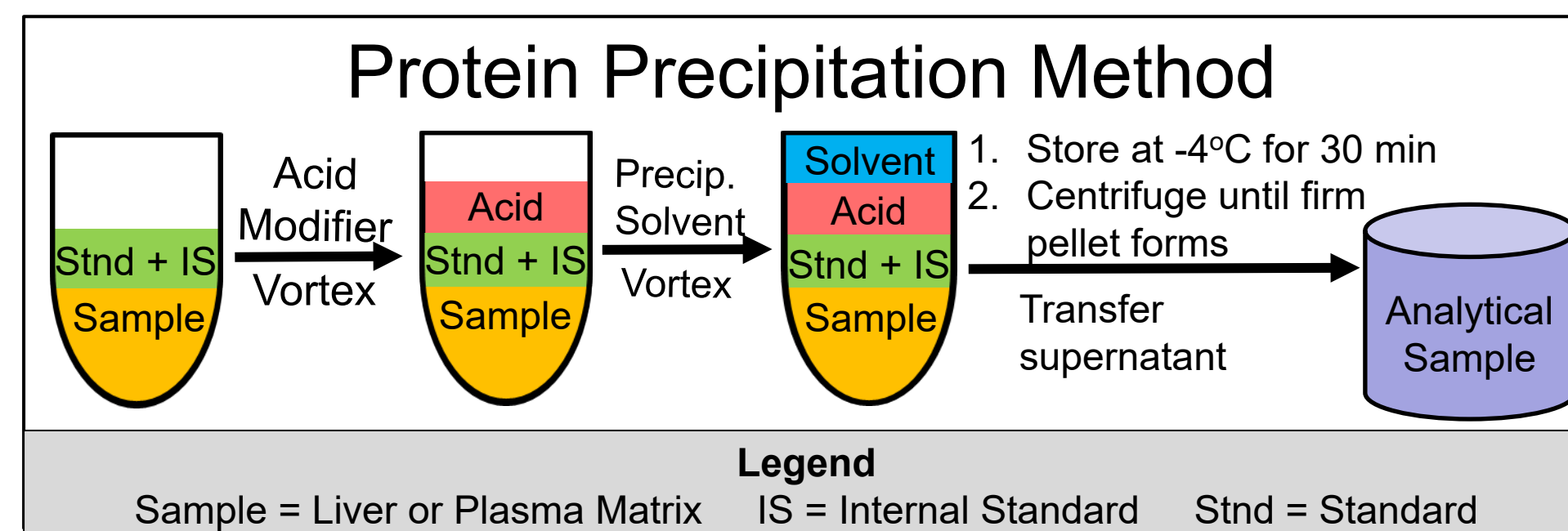
## Introduction and Approach

- Environmentally persistent, legacy, straight-chain per- and polyfluoroalkyl substances (**PFAS**) are being replaced worldwide with ether-linked carboxylic acid (**PFECA**) fluorochemicals intended to break down more easily and potentially have less toxicity.
- PFECA, including **GenX** (2,2,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid), are now widespread in consumer product use, and of concern and interest to regulatory agencies, researchers, and consumers.
- Perfluoro-(2,5,8-trimethyl-3,6,9-trioxadodecanoic) acid (**HFPO-TeA**) is an oligomer of GenX that is increasing in industrial use and has little available toxicological data.
- Here we present dosimetry results for HFPO-TeA and the potential for bioaccumulation from a short term exposure study with Sprague-Dawley rats.**



## Sample Preparation and Analysis

- A protein precipitation method was used for HFPO-TeA extraction from liver and plasma.
- Perfluorohexadecanoic acid (PFHxDA) was the internal standard for quantitation.
- A range of dilutions of an acid modifier and precipitation solvent was used based upon initial range-finding concentrations of HFPO-TeA within each matrix.
- Limits of detection were 1.76 ng/mg tissue in liver and 8.9 ng/mL in plasma.**



- Liquid chromatography coupled with time-of-flight mass spectrometry in negative ion polarity with electrospray ionization was used for quantitation of HFPO-TeA.

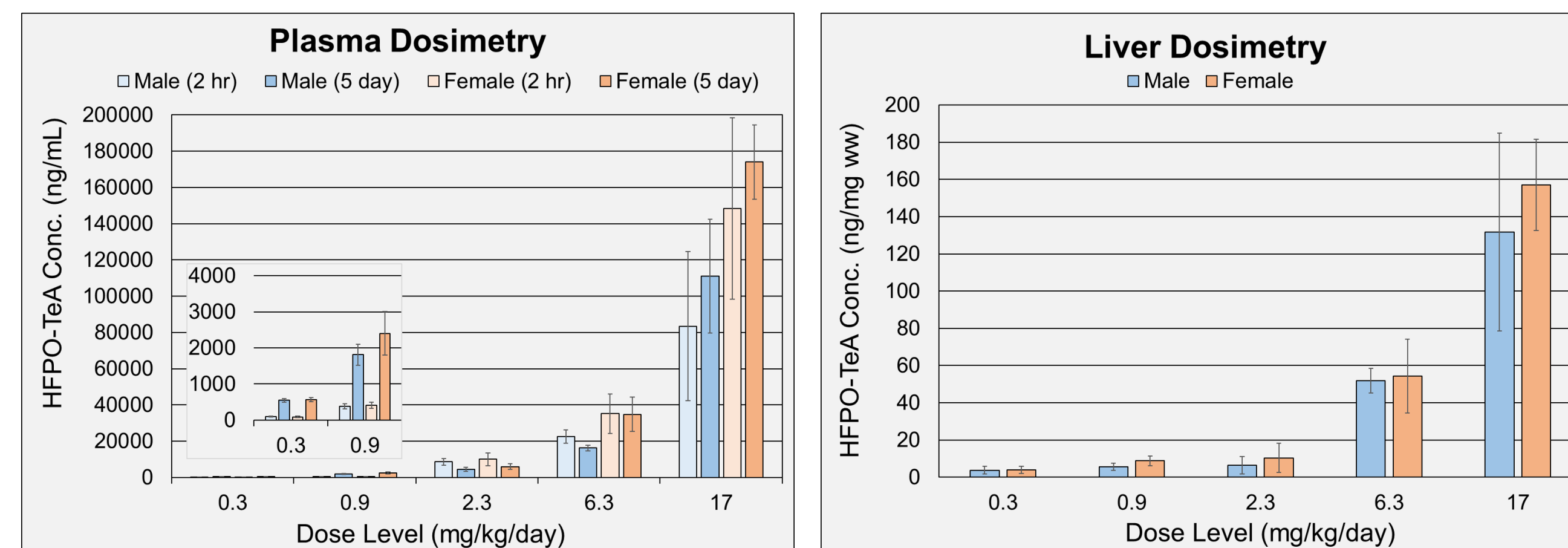
## In-Life Observations

- Rats from the 3 highest dose groups (45.9, 124, and 335.2 mg/kg/day) did not survive to scheduled termination.
- Weight losses were observed for females at 6.3 mg/kg/day and for both sexes at 17 mg/kg/day.

Weight Changes in Male and Female Sprague-Dawley Rats Throughout 5 Days of HFPO-TeA Exposure				
Dose Level (mg/kg/day)	Male Avg. Weight Change (g) (mean ± SD)	Female Avg. Weight Change (g) (mean ± SD)	Relative Male Avg. Liver (g) (mean ± SD)	Relative Female Avg. Liver (g) (mean ± SD)
Vehicle	31.33 ± 3.33	3.73 ± 5.65	4.58 ± 0.24	4.19 ± 0.19
0.3	37.20 ± 9.02	6.48 ± 4.44	4.70 ± 0.22	4.49 ± 0.06
0.9	39.60 ± 4.32	12.18 ± 4.30	5.29 ± 0.20	5.09 ± 0.22
2.3	39.30 ± 4.78	12.30 ± 6.25	5.92 ± 0.30	5.30 ± 0.07
6.3	31.78 ± 8.14	-17.75 ± 14.28	6.98 ± 0.53	5.33 ± 0.63
17	-51.48 ± 10.93	-55.18 ± 5.73	5.89 ± 0.23	5.80 ± 0.22

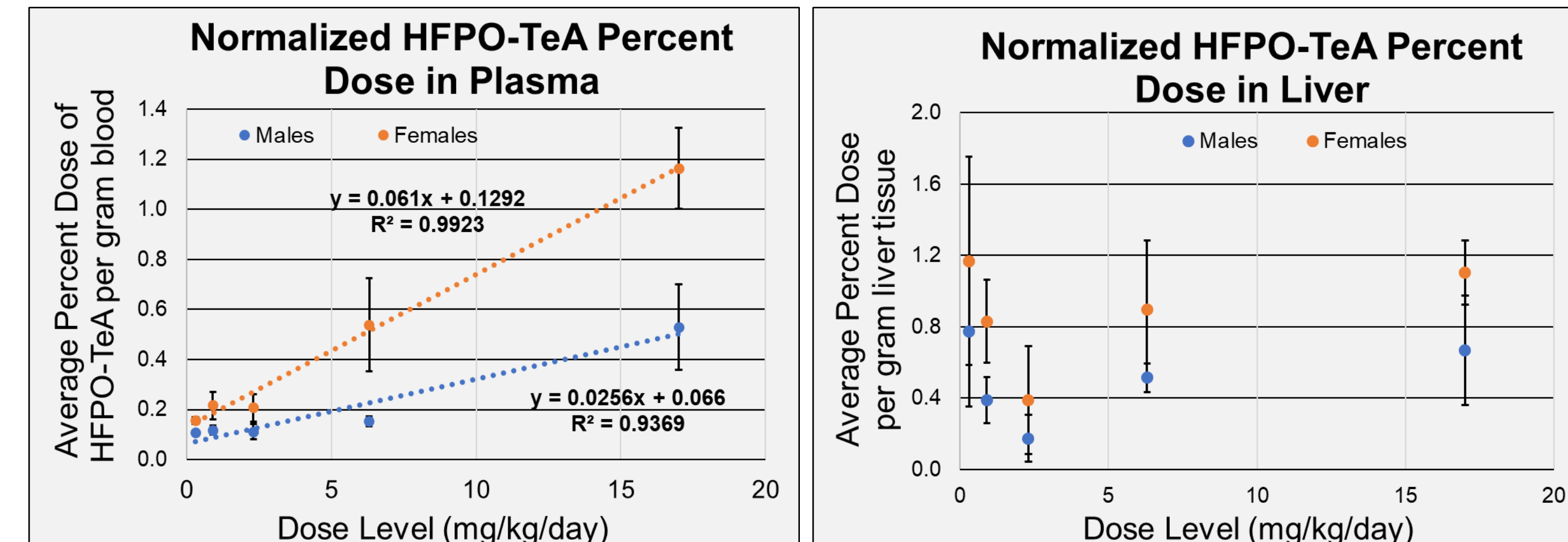
- Signs of toxicity observed with doses from 6.3 – 45.9 mg/kg/day (males) and 6.3 – 124 mg/kg/day (females) include: thinning of hair, piloerection, cold to touch, hunched, abnormal breathing, and lethargy.

## Dosimetry Results



- Higher HFPO-TeA plasma concentrations (left) were observed for females than males at 2 hours and 5 days for doses ≥ 0.9 mg/kg/day.
- Sex-related differences observed in plasma after 5 days were statistically significant at 17 mg/kg/day.**
- HFPO-TeA liver concentration differences (right) between the sexes were not statistically significant.

## Bioaccumulation Potential



- Normalized % dose observed in the liver (right) decreased across the first three doses and then leveled out for the last two, possibly **suggesting initial enzymatic induction followed by saturation of clearance mechanisms and toxic stress.**
- Normalized % dose in blood (left) supports the induction followed by saturation hypothesis suggested for liver. The results for the lowest three doses appear to plateau, before increasing to an approximately constant amount at the upper two doses.
- Combined, the data for liver and plasma suggest the potential for HFPO-TeA to bioaccumulate in rats.**

## Discussion and Conclusions

- We observed higher concentrations of HFPO-TeA in female rat plasma than males following 5 days of dosing at 17 mg/kg/day.**
- For an earlier pilot study dosing Sprague-Dawley rats with a shorter chain PFECA, perfluoro-3-methoxypropanoic acid (PF-MOPA), we observed higher internal dose concentrations in male rats compared to females.<sup>1</sup>
- The contrasting results from these two studies suggest that further interrogation of the sex-related effects of PFAS is needed. We are not aware of any published PFAS dosimetry studies that include results comparing the sexes.
- Both plasma and liver dosimetry data support the potential for bioaccumulation of HFPO-TeA in rats after 5 days of exposure.**
- On-going investigations of transcriptomic response may provide insights into HFPO-TeA dose disposition in rat.

## References

1. Renyer A., MacMillan, D.K., et.al. Presented at the 61st Annual Society of Toxicology Meeting and ToxExpo, San Diego, CA March 27-31, 2022. Poster 3087