

Fecal Excretion of Perfluoroalkyl and Polyfluoroalkyl Substances in Pets from New York State, United States

Jing Ma, Hongkai Zhu, and Kurunthachalam Kannan*

Cite This: https://dx.doi.org/10.1021/acs.estlett.9b00786



ACCESS	III Metrics & More	Article Recommendations	s Supporting Information

ABSTRACT: Human exposure to per- and polyfluoroalkyl substances (PFASs) continues to be a concern. Little is known about their toxicokinetics, particularly with regard to fecal excretion of PFASs. Because pets are sentinels of human exposure to environmental contaminants, analysis of PFASs in pet feces can provide information about rates of excretion of these chemicals. In this study, 15 PFASs were measured in cat and dog feces collected from the Albany area of New York State. All PFASs except perfluorodecanesulfonate and perfluoroheptanoic acid were found in cat and dog feces. The sum concentrations of 13 PFASs (Σ PFAS) varied between 21.6 and 474 (mean: 85.4 ± 94.5) ng/g dry weight for dogs, which were slightly higher than those found for cats (range: 18.0–165 ng/g dry weight, mean: 54.7 ± 26.9 ng/g dry weight). Long-chain perfluorodecanoic acid, perfluoroundecanoic acid, and perfluorododecanoic acid) were predominant



in pet feces. Perfluorooctanesulfonate and its precursors were found at low concentrations. Fecal excretion rates of PFASs in cats and dogs were found to be similar. The estimated daily fecal excretion suggested that both dogs and cats are exposed to some PFASs at doses above the provisional minimum risk level recommended for humans.

1. INTRODUCTION

Per- and polyfluoroalkyl substances (PFASs) are compounds that consist of a highly fluorinated hydrophobic alkyl chain of varying lengths and a hydrophilic end group.¹ Due to their chemical and thermal stability, high surface activity, and hydrophobic/lipophobic properties,² PFASs have been extensively produced and used in a wide variety of domestic and industrial applications. Since 2001, several studies have reported ubiquitous occurrence of a wide range of PFASs in the global environment.^{3,4} Toxicological studies of laboratory animals showed that PFASs, especially perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS), elicit hepatotoxicity, neurotoxicity, immunotoxicity, genotoxicity, and reproductive and developmental effects. 5-11 Although several PFAS producers have committed to a stewardship program to reduce environmental emissions, human exposure to PFASs continues to be a concern due to their persistence, high level of production, and usage of more than 4600 compounds.^{3,12}

The biomonitoring studies of human exposure to PFASs showed relatively higher concentrations in serum than in other tissues and fluids.^{13–15} In mammals, PFASs accumulate in the liver, kidneys, and blood.¹⁶ Some PFASs were reported to follow renal re-absorption and enterohepatic circulation that contributes to longer half-lives of these chemicals in humans.^{17–22} Animal studies have shown that PFASs may be eliminated through urine or feces.^{3,15,23–28} Whereas a few studies reported that urinary excretion of PFASs is slow, little is

known about fecal excretion of PFASs. Considering that PFAS concentrations are elevated in bile,^{24,29,30} it is postulated that fecal elimination may be an important route of excretion of these chemicals. As collection and analysis of human feces can be demanding, feces from pets can be used as a proxy. Pets such as dogs and cats share a common living environment with humans and have been used as sentinels of human exposure to environmental contaminants, including PFASs.³¹ Measurements of PFASs in feces can provide information about the extent and pattern of fecal elimination of this class of chemicals. Thus, the objectives of this study were to determine the occurrence and profile of PFASs in pet feces and to delineate the fecal excretion rates of these chemicals in pets.

2. MATERIALS AND METHODS

Samples. A total of 41 cat and 37 dog fecal samples (N = 78) were collected from the Albany area of New York State from January to March 2019. Cat and dog feces were collected from individual pet owners (14 cats and 12 dogs) and an animal shelter (27 cats and 25 dogs). All fecal samples were

Received: December 24, 2019 Revised: January 13, 2020 Accepted: January 15, 2020



Table 1. Area of I	Concen New You	trations rk State	(nanog , United	rams po States	er gram a	of dry	weight) c	of 13 PFA	Ss in C	Cat and 1	Dog Fe	ces Colle	ected from th	ie Albany
	PFBA	PFPeA	PFHxA	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFBS	PFHxS	PFOS	PFOSA	N-MeFOSAA	$\sum PFASs^{b}$
Cat(n = 41)														

														-
							Cat (n	= 41)						
DF (%)	59	90	76	85	54	80	73	71	44	34	27	63	37	_
mean	2.11	2.91	5.48	2.98	7.41	7.86	9.06	9.89	2.22	0.11	2.67	0.70	1.30	54.7
SD	2.34	1.23	5.02	2.18	13.5	7.87	13.2	6.79	2.54	0.25	5.70	0.64	1.95	26.9
median	1.95	2.90	4.89	2.48	2.76	7.67	6.50	12.0	ND	ND	ND	0.71	ND	49.7
min	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	18.0
max	8.70	5.27	22.2	11.0	81.3	37.2	79.5	21.6	5.50	1.39	27.7	2.06	7.55	165
							Dog (n	= 37)						
DF (%)	57	97	65	92	57	84	81	92	57	27	81	84	27	-
mean	1.74	4.08	3.77	2.96	31.4	15.9	6.11	11.8	2.84	0.20	3.34	0.70	0.54	85.4
SD	1.78	1.83	4.16	1.83	81.0	50.1	4.43	4.02	2.51	0.41	1.97	0.48	0.93	94.5
median	1.76	3.40	3.56	2.55	2.76	5.37	5.65	12.2	4.88	ND	3.50	0.70	ND	55.8
min	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	21.6
max	7.20	8.77	18.3	8.87	412	307	17.6	17.5	5.45	1.61	9.10	2.37	2.63	474
a 1 1 · .	DE	J	C		- t		ND		J 37-1	1 1			I T	00/2 - 1

Abbreviations: DF, detection frequency; SD, standard deviation; ND, not detected. Values below the LOQ were estimated using LOQ/2, and nondetects were set to zero for statistical analysis. ^bSum of 13 PFASs.

collected directly into a polypropylene (PP) container immediately after excretion. Information with regard to age, gender, and breed of the pets was obtained (Tables S1 and S2). Fecal samples were lyophilized in a freeze-drier (Free-Zone, Labconco, Kansas City, MO). To prevent potential extraneous contamination during sampling, we removed the surface layer of the feces after lyophilization. All samples were homogenized, ground (in a porcelain pestle and mortar), sieved through a 2.4 mm stainless steel sieve, and stored at -20°C until further analysis.

Standards. Native standards as well as isotope-labeled standards of perfluorobutanoic acid (PFBA), perfluoro-npentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorobutanesulfonate (PFBS), perfluorohexanesulfonate (PFHxS), perfluorooctanesulfonate (PFOS), perfluorodecanesulfonate (PFDS), perfluorooctane sulfonamide (PFOSA), and *n*-methyl perfluoro-1octanesulfonamidoacetic acid (N-MeFOSAA) were purchased from Wellington Laboratories (Guelph, ON). All reagents and chemicals were of analytical grade.

Analysis. Extraction of 15 PFASs from feces was accomplished by a modified ion-pair method, as described previously.^{24,32} Briefly, 0.1 g [dry weight (dw)] of feces was placed into a 15 mL PP tube and fortified with 10 ng each of labeled internal standards of all target PFASs, except for PFBS and PFDS. After the addition of 1 mL of tetrabutylammonium hydrogen sulfate (TBAHS, 0.5 M) and 2 mL of sodium carbonate (0.25 M) buffer, the mixture was vortexed for 1 min. To the mixture was added 5 mL of methyl-tert-butyl ether (MTBE), which was followed by shaking in an orbital shaker for 40 min and ultrasonication for 30 min. The organic layer was separated from the aqueous layer by centrifugation at 4500g for 10 min and transferred into another PP tube. The extraction was repeated with 3 mL of MTBE two more times, and the extracts were combined. The supernatant (i.e., MTBE extract) was evaporated under a gentle N2 stream to near dryness and reconstituted with 500 μ L of methanol. The extract was kept frozen at -20 °C for 2 h and then centrifuged in a microcentrifuge tube (Costar, Coring Inc., Salt Lake City,

UT), and 200 μ L of the supernatant was transferred into a liquid chromatographic vial for instrumental analysis.

The analysis was performed using a Shimadzu LC-20 AD Series high-performance liquid chromatograph (Shimadzu Corp., Kyoto, Japan), coupled to an API 3200 triplequadrupole mass spectrometric system (MS/MS, Applied Biosystems, Foster City, CA). The extract was injected onto a Betasil C₁₈ column (100 mm \times 2.1 mm, 5 μ m; Thermo, Waltham, MA), serially connected to a Betasil C_{18} guard column (20 mm \times 2.1 mm, 5 μ m; Thermo). The mobile phase consisted of methanol (A) and 20 mM ammonium acetate in high-performance liquid chromatography-grade water (B), eluted at a flow rate of 300 μ L/min. The gradient flow was set as follows: 90% B from 0.0 to 0.1 min, 90% to 70% B from 0.1 to 1.0 min, 70% to 1% B from 1.0 to 8.0 min, 1% B from 8.0 to 12.0 min, 1% to 90% B from 12.0 to 12.5 min, and 90% B from 12.5 to 17.5 min. Quantification of PFASs was based on an isotopic dilution method. Target analytes were monitored by multiple-reaction monitoring mode under negative ionization. Typical chromatograms of standard and real fecal sample are shown in Figure S1; further details of the MS parameters are listed in Table S3.

Quality Assurance/Quality Control (QA/QC). All experimental steps were performed in a clean fume hood. Procedural blanks were analyzed with every batch of 20 samples to check for background levels of contamination. An 11-point calibration curve was constructed with standard solutions of the target analytes over a concentration range of 0.1-200 ng/mL, which yielded a regression coefficient of >0.99. Duplicate injections of samples and midpoint calibration standards were performed after every 10 samples to ensure the precision and accuracy of each analytical run. Matrix spikes were prepared by fortifying known amounts of 15 target PFAS standards (5 and 50 ng of each) into four randomly selected fecal samples and subjected to the entire analytical procedure. The matrix spike recoveries ranged from 63% to 115% for individual PFASs. The absolute recoveries of labeled internal standards spiked into each sample prior to extraction ranged from 40 \pm 6% for $[^{13}C_8]PFOSA$ to 108 \pm 28% for $[{}^{13}C_4]$ PFHpA. Procedural blanks contained trace levels of PFHxS, PFOSA, PFOA, PFNA, PFDA, and PFPeA at concentrations that ranged from $0.43 \pm 0.95 \text{ ng/g}$ dw for

PFPeA to 4.69 \pm 2.28 ng/g dw for PFOA. The background values of these compounds were subtracted from reported sample concentrations. The limit of detection (LOD) and limit of quantitation (LOQ) were defined as the minimum amount of analyte that yielded signal:noise ratios of 3:1 and 10:1, respectively. The LODs and LOQs ranged from 0.03 to 0.89 ng/g and from 0.10 to 2.98 ng/g, respectively. Further details of the QA/QC data are listed in Table S4. Statistical significance was set at the p < 0.05 level.

3. RESULTS AND DISCUSSION

Fecal Concentrations of PFASs in Cats and Dogs. The measured concentrations of PFASs in cat and dog feces are listed in Table 1. All target chemicals, except PFDS and PFHpA, were found in cat and dog feces, with detection frequencies that ranged from 27% to 90% for cats and from 27% to 97% for dogs, suggesting widespread exposure of pets to PFASs.

The sum concentrations of 13 PFASs (\sum PFAS) in feces ranged from 18.0 to 165 ng/g dw, with a mean (\pm SD) value of 54.7 (\pm 26.9) ng/g dw for cats. Among 13 PFASs, the median concentration of PFDoDA (12.0 ng/g dw) was the highest in cat feces, followed by PFDA (7.67 ng/g dw) > PFUnDA (6.50 ng/g dw) > PFHxA (4.89 ng/g dw) > PFPeA (2.90 ng/g dw) > PFOA (2.48 ng/g dw) > PFBA (1.95 ng/g dw) > PFOSA (0.71 ng/g dw). Interestingly, longer-chain perfluorocarboxylic acids (PFCAs) with 9-12 carbons, (i.e., PFNA, PFDA, PFUnDA, and PFUoDA) were the most abundant compounds, collectively accounting for >60% of \sum PFAS measured in cat feces. PFPeA and PFOA were found in cat feces at detection rates of 90% and 85%, respectively, although they accounted for a smaller (13%) fraction of Σ PFAS. PFHxS, PFOSA, and N-MeFOSAA accounted for <4% of \sum PFAS with low detection frequencies (<50%) (Figure 1). In contrast to the



Figure 1. Profiles (percent of total concentrations) of PFASs in dog and cat feces.

highest abundance of PFOS in blood samples,¹³ this compound accounted for a small (4%) fraction of \sum PFAS (ranging from nondetectable to 27.7 ng/g dw, mean of 2.67 ng/g dw) with a low detection rate (27%) in cat feces. This may suggest that PFOS is not efficiently eliminated in cat feces as are other PFASs.

 Σ PFAS concentrations in dog feces varied between 21.6 and 474 ng/g dw, with a mean (±SD) value of 85.4 (±94.5) ng/g dw, which was slightly higher than those found in cat feces; however, the measured Σ PFAS concentrations in dog

and cat feces were not significantly different (p > 0.05). In dog feces, the median concentration of PFDoDA (12.2 ng/g dw) was the highest, followed by PFUnDA (5.65 ng/g dw) > PFDA (5.37 ng/g dw) > PFBS (4.88 ng/g dw) > PFHxA (3.56 ng/g dw) > PFOS (3.50 ng/g dw) > PFPeA (3.40 ng/g dw) > PFNA (2.76 ng/g dw) > PFOA (2.55 ng/g dw) > PFBA (1.76 ng/g dw) > PFOSA (0.70 ng/g dw). Similar to those in cats, long-chain PFCAs (PFNA, PFDA, PFUnDA, and PFUoDA) were the predominant compounds, collectively accounting for 63% of \sum PFAS measured in dog feces (Figure 1). It is worth noting that the detection frequency of PFOS was 81% in dog feces compared to 27% in cats.

Spearman rank correlation analysis was used to examine the relationships among the concentrations of PFASs in pet feces (Figure 2). The concentrations of PFDoDA, PFUnDA, and *N*-MeFOSAA were significantly correlated in pet feces (p < 0.05), indicating a common source/concurrent exposure to these compounds. It is probable that the long-chain PFCAs are derived from the biotransformation of 8:2, 10:2, and 12:2 fluorotelomer alcohols (FTOHs). Further studies are needed to track the sources of PFASs, especially long-chain PFCAs in pets.

Following oral ingestion, inhalation, and dermal exposures, PFASs are distributed in the body, with the highest concentrations found in the liver, kidneys, and blood.³³ Whereas the precursors of PFASs such as FTOHs and N-MeFOSAA undergo metabolite transformation, perfluorinated acids are expected to be excreted without further metabolism.³³⁻³⁷ Few studies have suggested that PFASs are eliminated in urine, feces, bile, breast milk, and menstrual fluid.^{26,34,38-41} Harada et al. estimated serum-to-urine and serum-to-bile clearance rates of PFOA and PFOS in humans.⁴¹ Fujii et al. reported that biliary clearance rates of long-chain PFCAs (PFNA, PFDA, PFUnDA, and PFDoDA) were higher than those of other PFASs.^{24,30} The abundance of PFNA, PFDA, PFUnDA, and PFDoDA in cat and dog feces is consistent with what was modeled for humans in previous studies. It is probable that long-chain PFCAs are bound to biliary proteins/lipids and excreted in feces.^{42,43} A greater number of long-chain PFCAs also may be attributed to the elevated level of exposure of pets to these compounds or their precursors.

In cattle, [¹⁴C]PFOA was fully absorbed and excreted in urine within 9 days of exposure, and $\begin{bmatrix} {}^{14}C \end{bmatrix}$ PFOA elimination in feces was reported to be minimal.⁴⁴ In comparison to longchain PFCAs (i.e., PFNA, PFDA, PFUnDA, and PFDoDA), PFOA accounted for only 3–5% of \sum PFAS concentrations in both cat and dog feces. The small proportion of PFOA found in cat and dog feces may be due to re-absorption of this compound in the kidneys, in which specific organic aniontransporting polypeptides and organic anion transporters facilitate elimination through urine. $^{43-45}$ In particular, the detection frequency of PFOS in cat feces was only 27%, whereas that in dog feces was 81%, indicating that fecal excretion of PFOS in cats was limited or that cats are less exposed to PFOS relative to long-chain PFCAs. Several studies conducted in non-human primates and rodents provided evidence that urine was the major route of excretion of PFOS.⁴⁶⁻⁴⁸ Nevertheless, in cattle, the major route of PFOS excretion was feces.²⁴ These results suggest physiological and species-specific differences in the absorption, distribution, and excretion of PFASs in mammals.



Figure 2. Heat map showing the Spearman correlation matrix of PFASs in pet feces. The Spearman correlation was calculated for each quantifiable compound and their total concentrations. Significance was set to 0.05.

Fecal PFAS Concentrations in Relation to the Age and Gender of Pets. The age- and gender-related differences in PFAS concentrations in pet feces were described only for those compounds that were detected in more than 60% of the samples (Table 2). We categorized dogs and cats into three different age groups for the comparison of concentrations [(i) young, ≤ 2 years; (ii) adult, $\geq 2-5$ years; (iii) old, ≥ 5 years], according to a previous study.⁴⁹ There were no significant differences in fecal PFAS concentrations among the three age groups. With regard to gender, the median concentration of PFDA was higher in female (9.79 ng/g dw) than in male (4.82 ng/g dw) cats, whereas it was lower in female (5.24 ng/g dw) than in male (7.57 ng/g dw) dogs. Nevertheless, these differences were not statistically significant, which suggests that age and gender do not have an effect on the concentrations of PFASs in the feces of cats and dogs.

Fecal Excretion Rates of PFASs in Pets. Cumulative daily excretion (CDX; nanograms per kilogram of body weight per day) of PFASs in pets via feces was calculated on the basis of measured concentrations in feces and excretion rates, using the following equation:

$$CDX = \frac{\text{fecal concentration } (ng/g) \times \text{feces excretion rate } (g/day)}{\text{average body weight } (kg)}$$

Average feces excretion rates in cats and dogs were 19.4 g/ day (range of 10.2-52.4) and 254 g/day (range of 21-1074), respectively.⁵⁰ The average body weights of cats and dogs were assumed to be 4.2 kg (range of 1.6-9.9) and 20.6 kg (range of 1.72-90.7), respectively.^{51,52} Considering that animals' fecal excretion rates vary by size, uncertainty associated with CDX calculations was calculated on the basis of the range of values measured for these two parameters.⁵³ The moisture content of feces analyzed in this study ranged from 10% to 71% for cats and from 50% to 75% for dogs (Tables S1 and S2). The wet weight-based concentrations of PFASs in pet feces were used in the calculation of CDX (Table S5). It should be pointed out that the presence of some long-chain PFCAs may be attributed to the exposure of pets to precursors (e.g., FTOHs), and this was not considered in our calculations. The estimated CDX of \sum PFAS via feces ranged from 31.1 to 351 ng (kg of body weight)⁻¹ day⁻¹, with a mean (\pm uncertainty) value of 118 (± 20) ng (kg of body weight)⁻¹ day⁻¹ for cats and from 51.0 to 2660 ng (kg of body weight)⁻¹ day⁻¹, with a mean (±uncertainty) value of 357 (±25) ng (kg of body weight)⁻¹ day⁻¹ for dogs. Although paired data on the intake and excretion (via urine/feces) are not available to delineate rates of accumulation of PFASs in pets, the measured CDX values provide some important information pertaining to approximate daily exposure doses. The Agency for Toxic Substances and Disease Registry's (ATSDR) provisional minimal risk levels (MRLs) for PFAS were 2.0 ng $kg^{-1} day^{-1}$ for PFOS, 3.0 ng $kg^{-1} day^{-1}$ for PFOA, 20.0 ng $kg^{-1} day^{-1}$ for PFHxS, and 3.0 ng kg⁻¹ day⁻¹ for PFNA.³³ The calculated CDX values for PFOA, PFNA, and \sum PFAS were 1-3 orders of magnitude above the MRLs. Considering that fecal elimination is not the only route of excretion of these chemicals in pets or humans, our results indicate that pets are highly exposed to PFASs and may be at risk from current exposure doses. These results also indicate that exposure to several precursor PFASs is significant and worthy of future investigations. It should be noted, however, that above the MRL values were recommended for humans, which were derived from laboratory animal data, and then adjusted for by a set of uncertainty factors. It is expected that MRLs in pets may be different from those of the humans due to differences in sensitivity. Thus, these results should be interpreted within those confines (Figure 3).

In summary, this study provides evidence that PFASs are present at measurable concentrations in feces of cats and dogs. PFAS profiles in pet feces are unique in that long-chain PFCAs with 9–12 carbons were the predominant compounds. PFOS

pu	
ats a	
of Ca	
ies (
egor	
Cat	
Age	
and	
Sex	
rent	
Diffe	
I gu	
amo	
ght)	
weig	
dry	
n of	
grai	
s per	
rams	
nog	
l; na	
erva	
int	
denc	
onfi	
5% c	
s (9	
FAS	
of F	
ions	
ntrat	
ncei	
n Co	
edia	
ф	
son (
paris	
Com	
2. (a
Γabl€	Jogs
	I



Figure 3. Cumulative daily fecal excretion (CDX) of nine PFASs in (A) cats and (B) dogs collected from the Albany area of New York State. Only analytes with detection frequencies of >50% were included in this calculation. The black horizontal line inside each box represents the median. The boxes represent 25th and 75th percentiles. The whiskers represent a value of $1.5 \times SD$. Dots represent outliers.

and its precursors were found at low levels in pet feces. The age and gender of pets did not affect concentrations of PFASs in cats and dogs. The concentrations and fecal clearance rates of PFASs in cats and dogs were similar. The daily fecal excretion rates of PFOA, PFNA, and PFOS were above the MRL for intake doses suggested by the ATSDR for humans, which indicate that pets are exposed to these PFASs at levels above the provisional MRLs. Further studies are needed to evaluate the sources and health effects of PFASs in pets.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.9b00786.

Tables showing information about cat and dog feces (Tables S1 and S2, respectively), MS/MS parameters of target PFAS compounds (Table S3), information about instrument performance (Table S4), calculations of cumulative daily excretion rates (Table S5), and typical chromatograms of PFASs in standard and real fecal sample (Figure S1) (PDF)

AUTHOR INFORMATION

Corresponding Author

Kurunthachalam Kannan – Wadsworth Center, New York State Department of Health, Albany, New York 12201, United States; Orcid.org/0000-0002-1926-7456; Phone: 518-474-0015; Email: kurunthachalam.kannan@health.ny.gov; Fax: 518-473-2895

Other Authors

- Jing Ma Wadsworth Center, New York State Department of Health, Albany, New York 12201, United States; School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, China
- Hongkai Zhu Wadsworth Center, New York State Department of Health, Albany, New York 12201, United States

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.estlett.9b00786

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Ms. Sunmi Lee, Ms. Michelle Morrissette, and Drs. Rajendiran Karthikraj and Christopher Palmer for help with collection of pet feces and Mr. Junjie Zhang for help with freeze-drying the samples.

REFERENCES

(1) Buck, R. C.; Franklin, J.; Berger, U.; Conder, J. M.; Cousins, I. T.; de Voogt, P.; Jensen, A. A.; Kannan, K.; Mabury, S. A.; van Leeuwen, S. P. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. *Integr. Environ. Assess. Manage.* **2011**, *7*, 513–541.

(2) Kannan, K. Perfluoroalkyl and polyfluoroalkyl substances: Current and future perspectives. *Environ. Chem.* 2011, 8, 333-338.

(3) Perez, F.; Nadal, M.; Navarro-Ortega, A.; Fabrega, F.; Domingo, J. L.; Barcelo, D.; Farre, M. Accumulation of perfluoroalkyl substances in human tissues. *Environ. Int.* **2013**, *59*, 354–362.

(4) Zhu, H. K.; Kannan, K. Distribution and partitioning of perfluoroalkyl carboxylic acids in surface soil, plants, and earthworms at a contaminated site. *Sci. Total Environ.* **2019**, *647*, 954–961.

(5) Ren, H.; Vallanat, B.; Nelson, D. M.; Yeung, L. W. Y.; Guruge, K. S.; Lam, P. K. S.; Lehman-McKeeman, L. D.; Corton, J. C. Evidence for the involvement of xenobiotic-responsive nuclear receptors in transcriptional effects upon perfluoroalkyl acid exposure in diverse species. *Reprod. Toxicol.* **2009**, *27*, 266–277.

(6) Guruge, K. S.; Yeung, L. W.; Yamanaka, N.; Miyazaki, S.; Lam, P. K.; Giesy, J. P.; Jones, P. D.; Yamashita, N. Gene expression profiles in rat liver treated with perfluorooctanoic acid (PFOA). *Toxicol. Sci.* **2006**, *89*, 93–107.

(7) Lau, C.; Butenhoff, J. L.; Rogers, J. M. The developmental toxicity of perfluoroalkyl acids and their derivatives. *Toxicol. Appl. Pharmacol.* **2004**, *198*, 231–241.

(8) Kennedy, G. L., Jr.; Butenhoff, J. L.; Olsen, G. W.; O'Connor, J. C.; Seacat, A. M.; Perkins, R. G.; Biegel, L. B.; Murphy, S. R.; Farrar, D. G. The toxicology of perfluorooctanoate. *Crit. Rev. Toxicol.* **2004**, *34*, 351–384.

(9) Austin, M. E.; Kasturi, B. S.; Barber, M.; Kannan, K.; MohanKumar, P. S.; MohanKumar, S. M. Neuroendocrine effects of perfluorooctane sulfonate in rats. *Environ. Health Perspect.* **2003**, *111*, 1485–1489.

(10) Butenhoff, J.; Costa, G.; Elcombe, C.; Farrar, D.; Hansen, K.; Iwai, H.; Jung, R.; Kennedy, G., Jr.; Lieder, P.; Olsen, G.; et al. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicol. Sci.* **2002**, *69*, 244–257.

(11) Biegel, L. B.; Hurtt, M. E.; Frame, S. R.; O'Connor, J. C.; Cook, J. C. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicol. Sci.* 2001, *60*, 44–55.

(12) Lindstrom, A. B.; Strynar, M. J.; Libelo, E. L. Polyfluorinated compounds: Past, present, and future. *Environ. Sci. Technol.* **2011**, *45*, 7954–7961.

(13) Kannan, K.; Corsolini, S.; Falandysz, J.; Fillmann, G.; Kumar, K. S.; Loganathan, B. G.; Mohd, M. A.; Olivero, J.; Van Wouwe, N.; Yang, J. H.; Aldous, K. M. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. *Environ. Sci. Technol.* **2004**, *38*, 4489–4495.

(14) Houde, M.; Martin, J. W.; Letcher, R. J.; Solomon, K. R.; Muir, D. C. G. Biological monitoring of polyfluoroalkyl substances: A review. *Environ. Sci. Technol.* **2006**, *40*, 3463–3473.

(15) Cui, L.; Liao, C. Y.; Zhou, Q. F.; Xia, T. M.; Yun, Z. J.; Jiang, G. B. Excretion of PFOA and PFOS in male rats during a subchronic exposure. *Arch. Environ. Contam. Toxicol.* **2010**, *58*, 205–213.

(16) Aas, C. B.; Fuglei, E.; Herzke, D.; Yoccoz, N. G.; Routti, H. Effect of body condition on tissue distribution of perfluoroalkyl substances (PFASs) in Arctic fox (*Vulpes lagopus*). *Environ. Sci. Technol.* **2014**, *48*, 11654–11661.

(17) Li, Y.; Fletcher, T.; Mucs, D.; Scott, K.; Lindh, C. H.; Tallving, P.; Jakobsson, K. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup. Environ. Med.* **2018**, 75, 46–51.

(18) Olsen, G. W.; Burris, J. M.; Ehresman, D. J.; Froehlich, J. W.; Seacat, A. M.; Butenhoff, J. L.; Zobel, L. R. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ. Health Perspect.* **2007**, *115*, 1298–1305.

(19) Brede, E.; Wilhelm, M.; Göen, T.; Müller, J.; Rauchfuss, K.; Kraft, M.; Hölzer, J. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. *Int. J. Hyg. Environ. Health* **2010**, *213*, 217–223.

(20) Worley, R. R.; Moore, S. M.; Tierney, B. C.; Ye, X. Y.; Calafat, A. M.; Campbell, S.; Woudneh, M. B.; Fisher, J. Per- and polyfluoroalkyl substances in human serum and urine samples from a residentially exposed community. *Environ. Int.* **2017**, *106*, 135–143.

(21) Bartell, S. M.; Calafat, A. M.; Lyu, C.; Kato, K.; Ryan, P. B.; Steenland, K. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. *Environ. Health Perspect.* **2010**, *118*, 222– 228.

(22) Gomis, M. I.; Vestergren, R.; Nilsson, H.; Cousins, I. T. Contribution of direct and indirect exposure to human serum concentrations of perfluorooctanoic acid in an occupationally exposed group of ski waxers. *Environ. Sci. Technol.* **2016**, *50*, 7037–7046.

(23) Zhong, W. J.; Zhang, L. Y.; Cui, Y. N.; Chen, M.; Zhu, L. Y. Probing mechanisms for bioaccumulation of perfluoroalkyl acids in carp (*Cyprinus carpio*): Impacts of protein binding affinities and elimination pathways. *Sci. Total Environ.* **2019**, *647*, 992–999.

(24) Lupton, S. J.; Huwe, J. K.; Smith, D. J.; Dearfield, K. L.; Johnston, J. J. Distribution and excretion of perfluorooctane Sulfonate (PFOS) in beef cattle (*Bos taurus*). *J. Agric. Food Chem.* **2014**, *62*, 1167–1173.

(25) Sundström, M.; Chang, S. C.; Noker, P. E.; Gorman, G. S.; Hart, J. A.; Ehresman, D. J.; Bergman, Å.; Butenhoff, J. L. Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. *Reprod. Toxicol.* **2012**, *33*, 441–451.

(26) Kudo, N.; Kawashima, Y. Toxicity and toxicokinetics of perfluorooctanoic acid in humans and animals. *J. Toxicol. Sci.* 2003, 28, 49–57.

(27) Kowalczyk, J.; Ehlers, S.; Fürst, P.; Schafft, H.; Lahrssen-Wiederholt, M. Transfer of perfluorooctanoic acid (PFOA) and

perfluorooctane sulfonate (PFOS) from contaminated feed into milk and meat of sheep: pilot study. *Arch. Environ. Contam. Toxicol.* **2012**, *63*, 288–298.

(28) Olsen, G. W.; Chang, S.-C.; Noker, P. E.; Gorman, G. S.; Ehresman, D. J.; Lieder, P. H.; Butenhoff, J. L. A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans. *Toxicology* **2009**, *256*, 65–74.

(29) Kannan, K.; Franson, J. C.; Bowerman, W. W.; Hansen, K. J.; Jones, J. D.; Giesy, J. P. Perfluorooctane sulfonate in fish-eating water birds including bald eagles and albatrosses. *Environ. Sci. Technol.* **2001**, 35, 3065–3070.

(30) Fujii, Y.; Niisoe, T.; Harada, K. H.; Uemoto, S.; Ogura, Y.; Takenaka, K.; Koizumi, A. Toxicokinetics of perfluoroalkyl carboxylic acids with different carbon chain lengths in mice and humans. *J. Occup. Health* **2015**, 57, 1–12.

(31) Sévère, S.; Marchand, P.; Guiffard, I.; Morio, F.; Venisseau, A.; Veyrand, B.; Le Bizec, B.; Antignac, J.-P.; Abadie, J. Pollutants in pet dogs: A model for environmental links to breast cancer. *SpringerPlus* **2015**, *4*, 27.

(32) Zhang, T.; Zhang, B.; Bai, X. Y.; Yao, Y. M.; Wang, L.; Shu, Y. Y.; Kannan, K.; Huang, X. F.; Sun, H. W. Health status of elderly people living near e-waste recycling sites: Association of e-waste dismantling activities with legacy perfluoroalkyl substances (PFASs). *Environ. Sci. Technol. Lett.* **2019**, *6*, 133–140.

(33) Agency for Toxic Substances and Disease Registry. Toxicological Profile for Perfluoroalkyls Draft for Public Comment. https:// www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237, 2018.

(34) Kemper, R. A.; Nabb, D. L. In vitro studies in microsomes from rat and human liver, kidney, and intestine suggest that perfluorooctanoic acid is not a substrate for microsomal UDP-glucuronosyltransferases. *Drug Chem. Toxicol.* **2005**, *28*, 281–287.

(35) Vanden Heuvel, J. P.; Kuslikis, B. I.; Van Rafelghem, M. J.; Peterson, R. E. Tissue distribution, metabolism, and elimination of perfluorooctanoic acid in male and female rats. *J. Biochem. Toxicol.* **1991**, *6*, 83–92.

(36) Goecke, C. M.; Jarnot, B. M.; Reo, N. V. A comparative toxicological investigation of perfluorocarboxylic acids in rats by fluorine-19 NMR spectroscopy. *Chem. Res. Toxicol.* **1992**, *5*, 512–519.

(37) Vanden Heuvel, J. P.; Kuslikis, B. I.; Van Rafelghem, M. J.; Peterson, R. E. Disposition of perfluorodecanoic acid in male and female rats. *Toxicol. Appl. Pharmacol.* **1991**, *107*, 450–459.

(38) Wang, Y. X.; Zhong, Y. X.; Li, J. G.; Zhang, J. Q.; Lyu, B.; Zhao, Y. F.; Wu, Y. N. Occurrence of perfluoroalkyl substances in matched human serum, urine, hair and nail. *J. Environ. Sci.* (*Beijing, China*) **2018**, *67*, 191–197.

(39) Tao, L.; Kannan, K.; Wong, C. M.; Arcaro, K. F.; Butenhoff, J. L. Perfluorinated compounds in human milk from Massachusetts, USA. *Environ. Sci. Technol.* **2008**, *42*, 3096–3101.

(40) Wong, F.; MacLeod, M.; Mueller, J. F.; Cousins, I. T. Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: Evidence from population-based pharmacokinetic modeling. *Environ. Sci. Technol.* **2014**, *48*, 8807–8814.

(41) Harada, K. H.; Hashida, S.; Kaneko, T.; Takenaka, K.; Minata, M.; Inoue, K.; Saito, N.; Koizumi, A. Biliary excretion and cerebrospinal fluid partition of perfluorooctanoate and perfluorooctane sulfonate in humans. *Environ. Toxicol. Pharmacol.* **2007**, *24*, 134–139.

(42) Bogdanska, J.; Borg, D.; Sundström, M.; Bergström, U.; Halldin, K.; Abedi-Valugerdi, M.; Bergman, Å.; Nelson, B.; DePierre, J.; Nobel, S. Tissue distribution of ³⁵S-labelled perfluorooctane sulfonate in adult mice after oral exposure to a low environmentally relevant dose or a high experimental dose. *Toxicology* **2011**, *284*, 54– 62.

(43) Hagenbuch, B.; Meier, P. J. The superfamily of organic anion transporting polypeptides. *Biochim. Biophys. Acta, Biomembr.* 2003, 1609, 1–18.

(44) Lupton, S. J.; Huwe, J. K.; Smith, D. J.; Dearfield, K. L.; Johnston, J. J. Absorption and excretion of C-14-perfluorooctanoic acid (PFOA) in angus cattle (Bos taurus). J. Agric. Food Chem. 2012, 60, 1128–1134.

(45) Han, X.; Nabb, D. L.; Russell, M. H.; Kennedy, G. L.; Rickard, R. W. Renal elimination of perfluorocarboxylates (PFCAs). *Chem. Res. Toxicol.* **2012**, *25*, 35–46.

(46) Benskin, J. P.; De Silva, A. O.; Martin, L. J.; Arsenault, G.; McCrindle, R.; Riddell, N.; Mabury, S. A.; Martin, J. W. Disposition of perfluorinated acid isomers in Sprague-Dawley rats; Part 1: Single dose. *Environ. Toxicol. Chem.* **2009**, *28*, 542–554.

(47) Butenhoff, J. L.; Kennedy, G. L., Jr.; Hinderliter, P. M.; Lieder, P. H.; Jung, R.; Hansen, K. J.; Gorman, G. S.; Noker, P. E.; Thomford, P. J. Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. *Toxicol. Sci.* **2004**, *82*, 394–406.

(48) Chang, S. C.; Noker, P. E.; Gorman, G. S.; Gibson, S. J.; Hart, J. A.; Ehresman, D. J.; Butenhoff, J. L. Comparative pharmacokinetics of perfluorooctanesulfonate (PFOS) in rats, mice, and monkeys. *Reprod. Toxicol.* **2012**, *33*, 428–440.

(49) Karthikraj, R.; Borkar, S.; Lee, S.; Kannan, K. Parabens and their metabolites in pet food and urine from New York State, United States. *Environ. Sci. Technol.* **2018**, *52*, 3727–3737.

(50) Nijsse, R.; Mughini-Gras, L.; Wagenaar, J. A.; Franssen, F.; Ploeger, H. W. Environmental contamination with Toxocara eggs: A quantitative approach to estimate the relative contributions of dogs, cats and foxes, and to assess the efficacy of advised interventions in dogs. *Parasites Vectors* **2015**, *8*, 397.

(51) Freeman, L. M.; Lachaud, M. P.; Matthews, S.; Rhodes, L.; Zollers, B. Evaluation of eeight loss over time in cats with chronic kidney disease. *J. Vet. Intern. Med.* **2016**, *30*, 1661–1666.

(52) Lavan, R. P.; Tunceli, K.; Zhang, D. M.; Normile, D.; Armstrong, R. Assessment of dog owner adherence to veterinarians' flea and tick prevention recommendations in the United States using a cross-sectional survey. *Parasites Vectors* **2017**, *10*, 284.

(53) https://physics.unc.edu/files/2018/07/Measurement-and-Uncertainty-Techniques.pdf (accessed January 13, 2020).