Per- and polyfluoroalkyl substances: using comparative medicine to understand exposure and adverse health outcomes in people and their pets

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ABSTRACT
One of the important human health benefits of keeping pets may be to serve as an early warning system for indoor childhood exposure to toxic chemicals such as per- and polyfluoroalkyl substances (PFAS). The stain-resistant properties and environmental stability of PFAS make them a preferred choice for protective coatings and lubricants, and they have been used for years in various manufacturing and industrial processes around the world. Although the use of PFAS has arguably improved many commercial products, they have been linked to adverse health outcomes such as developmental delays, liver damage, immune suppression, disruption of endocrine and reproductive systems, and some cancers. The current body of literature suggests that serum PFAS levels in dogs and cats are analogous to their human counterparts and that household pets experience similar changes in blood chemistry markers. The proximity of small children and household pets to PFAS-treated carpets and floors, in addition to their tendency to put things into their mouths, potentially allows pets to serve as sentinels for household PFAS exposure. To assess the suitability of pets as indicators for exposure, researchers need to understand the most likely sources of PFAS exposure for household pets and identify the biomarkers of biological effects in those animals. Understanding these parameters may alert veterinary clinicians to potential sources of contamination in the home and ultimately protect the lives of the children and animals who live there.

As described in the companion Currents in One Health by Brake et al, JAVMA, July 2023, the discovery of per- and polyfluoroalkyl substances (PFAS) was by accident. Roy Plunkett1 was working to develop safer chemical refrigerants when he discovered polytetrafluoroethylene (PTFE) lining a metal cylinder he and his assistant were using. PTFE appeared as a waxy white powder and was initially thought to be a useless inert polymer. The unique structure of the polymer, a carbon-fluorine chain, was stable at high temperatures, resistant to degradation, and able to repel oil and water.

PTFE was the first of many in the family of PFAS. PFAS are organic fluorinated polymers, which means that they are a material made up of large numbers of carbon-fluorine subunits chained together (Figure 1) typically with a polar “head.” The individual species of PFAS are differentiated from one another by the number of carbons in their chain and the type of head group. Historically PFAS polymers were formed through an electrochemical fluorination process2 where the alkyl chains are joined together and cross-linked in the presence of electricity. As time and technology progressed, additional methods have been developed for manufacturing PFAS. The Environmental Protection Agency’s (EPA’s) CompTox Chemicals Dashboard3 currently reports over 14,000 types of PFAS in their database.

PFAS was first used by the US military to protect metal from radioisotopes in the atomic bomb.4 Following World War II, the chemical’s use greatly expanded. Manufacturers began using the chemical and its derivatives to coat wires, reduce friction on gears, seals, and gaskets, protect fabrics, and as a component of ski bindings. One of the most notable uses of PFAS is as the principal component of non-stick surfaces for cookware. Perfluorooctanoic acid (PFOA) was introduced to help smooth out the coatings. Another common use of PFAS is as a surfactant in aqueous fire-fighting foams (AFFF). From the point of its development until 2001, perfluorooctane sulphonate (PFOS) was a major component of AFFF.5,6 PFOS served as a surfactant, allowing...
the foams to spread and effectively cover and put out fires. PFOS-containing foams have been, and in some places continue to be, used in military bases and airports for training exercises. Frequent use of AFFF on these facilities is responsible for some of the highest levels of PFAS contamination found in drinking water systems today7 and is the recent focus of Agency for Toxic Substances and Disease Registry (ATSDR) human exposure studies.7,8

Prevedouros et al2 estimated that the amount of long-chain perfluoroalkyl carboxylic acids (PFCA) produced and emitted into the environment between 1951 and 2004 is between 3,200 and 6,900 tons with a smaller amount being residual impurities or degradation products.2 However, the 2 most commonly produced PFAS chemicals were PFOA and PFOS (Figure 2).

PFOA, PFOS, and a handful of others are referred to as “legacy PFAS.” Legacy PFAS have long carbon chains (≥ 8 carbons for perfluoroalkyl carboxylate acids such as PFOA and ≥ 6 carbons for perfluoroalkyl sulfonic acids such as PFOS). In the early 2000s, because of the risks to human and animal health, major chemical companies in the United States made a commitment to change the structure of PFAS,9 shortening the chain while still maintaining its desired properties. As a result, worldwide production of the long-chain legacy PFAS, PFOA, and PFOS decreased significantly. Epidemiological studies have shown a corresponding steady decline of the legacy PFAS in human and animal samples and an increase in the newer short-chain PFAS. Short-chain PFAS do not bioaccumulate as much as their long-chain counterparts but persist in the environment and still pose a risk to human and animal health.

Figure 1—PFOA and PFOS are 2 well-known species of PFAS that were used in the manufacture of nonstick pans and stain repellents, respectively. PFOA is a perfluorocarboxylic acid (PFCA) and PFOS is a type of perfluorosulfonic acid (PFSA). The molecules that make up the polar “head” of the PFAS structure lead to its classification. Note the sulfur molecule on PFOS.

Figure 2—Tetrafluoroethylene has 2 carbon atoms and 4 fluorine atoms. It binds together in chains and cross-links in a process called polymerization. The result is polytetrafluoroethylene (PTFE). a—Chemical structure of tetrafluoroethylene and its polymerized form, PTFE. b—Simplified schematic of PTFE cross-linked together.
that indirect exposure to PFAS through diet is also an emerging threat.

Due to indoor dogs and cats being exposed to the same environment as their owners, an argument could be made for their use as a sentinel species for PFAS contamination. However, there are gaps in the body of literature regarding primary routes of exposure, the biomarkers of exposure and biomarkers of biological effect, lowest observed adverse effect levels, and half-lives following PFAS exposure in companion animals. Understanding these parameters may alert veterinary clinicians to potential sources of contamination in the home and ultimately protect human and animal lives.

**Evaluation of Exposure**

**What are the primary sources of PFAS for dogs and cats?**

Sources of PFAS exposure can be direct, or indirect, meaning that pets and people can be exposed to PFAS precursors or their degradation products. Within a typical household, PFAS exposure most likely occurs through a combination of contaminated water, food, and dust for both humans and animals. Children, especially toddlers, are thought to be exposed primarily through mouthing behaviors, such as crawling on carpets and furniture and then putting their hands or toys into their mouths. The proximity of small children and household pets to PFAS-treated carpets and floors where dust accumulates, in addition to their mouthing behaviors, potentially places children and pets at similar exposure risk.

**Dust**—In studying samples from > 2,500 sites around the world, Brusseau et al. found that background levels of PFAS in soils ranged from 0.001 to 237 µg/kg in areas with no known contamination, whereas PFAS levels in soils from contaminated sites ranged from 0.4 to 460,000 µg/kg. Proximity to industrialized and urban areas factor into animal exposure to long-chain PFAS. In a study of outdoor air within Korea, Kim et al. found up to 500 times higher concentrations of volatile PFAS (fluorotelomer alcohols) compounds in urban and industrialized sites compared to their background site. A corresponding study investigating PFAS burdens in Oriental Magpies in Korea found that birds living in more urbanized areas had significantly higher PFAS in their livers compared to birds from suburban and rural locations.

Studies in Europe and North America have demonstrated that indoor air and dust have been a greater source of PFAS contamination than outdoor air. The companion Currents in One Health by Brake et al., *JAVMA*, July 2023, addresses the magnitude of differences between PFAS concentrations in indoor and outdoor air. Although PFAS can be detected outside, Shoeb et al. demonstrated PFAS concentrations inside could be 100 times greater. Similar findings were reported following a 2013 study of dust in homes across the United States, Canada, and the Czech Republic.

When considering dust exposure in pets or children, it may be better to measure whole house dust rather than vacuum individual pet beds or pieces of furniture. It would be challenging to correlate individual sample results with the many brands of furniture, carpets, or pet beds that are commercially available, much less the infinite combinations of fabric and flooring types. Trudel et al. have developed an estimated daily intake (EDI) formula for children, which may be appropriate for application to pets.

**Water**—Drinking water and food are considered the primary routes of exposure in adults, particularly when living in an area with known water contamination. Analyzing data from EPA’s third Unregulated Contaminant Monitoring Rule (UCMR) conducted between 2013 and 2015, Hu et al. estimated that the drinking water of approximately 6 million people serviced by public water systems within the United States was contaminated with PFAS above EPA’s 2016 health advisory recommendations of 70 ppt. PFAS levels were highest in public water systems located near military sites and airports that used AFFF in fire-fighting training exercises, manufacturing facilities that produced or used PFAS, and wastewater treatment plants.

Although most of the water systems denoted as having high PFAS concentrations during the third UCMR have been remediated, serum PFAS levels in the people living in those areas are still elevated. In 2022, ATSDR published the results of an exposure assessment conducted in 10 sites with high levels of contamination as reported by the third UCMR. The 10 sites chosen were located near current or former US military bases with known use of AFFF in military training exercises. ATSDR reported maximum PFAS in drinking water as high as 3,100 ppt of PFOS in Moose Creek, AK; 2,900 ppt of PFOA in Lubbock County, TX; and 1,500 ppt of perfluorohexanoic acid (PFHxA) in Airway Heights, WA, which correlated with serum PFAS levels of residents.

We know PFAS in drinking water is a risk for animals. PFAS runoff from facilities using AFFF in Australia had contaminated the drinking water of nearby farms and resulted in increased serum PFAS levels of the livestock raised there. Within the United States, at least 1 dairy farm has been depopulated due to exposure to PFAS-contaminated water directly linked to a nearby military base. It is important to look at the drinking water sources, as well as PFAS use in nearby facilities when considering drinking water exposure.

**Diet**—Untangling the potential exposures through diet is particularly challenging because of the variety of foods and sources of foods that are eaten by pets. In his assessment of the amount of PFAS produced and its disposition, Prevedouros et al. suggested that perfluorooctanoate accumulated in sediments and in the oceans, where currents transport PFAS around the world. Aquatic plants and animals near the bottom of the food chain absorb the substances and serve as sources of PFAS for higher trophic levels. Consequently,
concentrations of PFAS have been found in both marine mammals and fish.\textsuperscript{27,28} As addressed in the companion Currents in One Health by Brake et al, JAVMA, July 2023, PFAS was found in nearly 99% of commercial fishmeal with total concentrations ranging from 0.65 to 85.5 µg/kg.\textsuperscript{29} Fish and fish byproducts, such as fishmeal, are frequently used in animal feeds, which could put both our large and small veterinary patients at risk.\textsuperscript{30,31}

Run-off from contaminated ground, rain, and the injection of biosolids into the ground as fertilizer are all sources of PFAS for terrestrial flora.\textsuperscript{17} The uptake of PFAS in plants differs by chain length and plant species, but there is a direct correlation between the amount of contamination and plant uptake.\textsuperscript{3} In reviewing studies related to PFAS exposure from agricultural plants, Ghisi\textsuperscript{17} and Felizeter\textsuperscript{32} surmised that small-chain PFAS accumulate in leaves and fruits, whereas the longer chain PFAS seemed to concentrate in the roots. Blaine et al\textsuperscript{33} found this to be true when comparing PFAS distribution to various part compartments of edible crops exposed to PFAS. The highest concentrations of long-chain PFAS were found in radish roots, celery shoots, and in pea fruit, respectively. Stahl et al\textsuperscript{34} found that absorption of PFAS into plants decreased significantly with chain length and that PFAS tended to accumulate more in the stalks or “straw” of wheat, rye, barley, and canola rather than the kernels. Absorption of PFAS into plants is particularly important since these crops are critical components of silage fed to livestock and can make up a significant portion of commercial pet food ingredients.

The idea that animal feeds could be a contributor to PFAS exposure in cattle was demonstrated by Vesterøg
cen et al.\textsuperscript{35} In his study of a Swedish dairy farm with no known sources of PFAS contamination, the researchers found that of all the food and water the cattle consumed, silage made from crops grown on the farm was the primary route of PFAS exposure. In 2016, a dairy farm in Maine, US, was depopulated due to PFAS-contaminated feed. Although the producer had installed a water treatment system and purchased new cows after discovering PFAS contamination on his farm, PFAS turned up again in the milk and manure of his animals. The recurring presence of PFAS was attributed to feeding hay grown on soil contaminated by years of fertilizing with sewage sludge (biosolids).\textsuperscript{36} PFAS contamination of soil and crops is also responsible for shuttering a cattle company in Michigan. In January 2022, the Michigan Department of Agriculture and Rural Development issued a consumption advisory following discovery of PFOS in beef samples. The farm in question used biosolids from a waste treatment plant as fertilizer for their fields.\textsuperscript{36}

Fish, grains, meat, and dairy products are all important components of human and animal diets and may be a significant source of PFAS exposure.\textsuperscript{28,35,37,38} Dietary studies conducted within Europe, Canada, and the United States have determined that the amount of PFAS consumed through food was less than EPA’s reference dose for adults. In contrast, studies among Inuit people living in Nunavik, the northernmost region of Quebec, Canada, found long-chain PFAS levels at 4 to 7 times greater than the Canadian population.\textsuperscript{39} This corresponds directly to the PFAS levels found in “natural foods” of the population, marine mammals, and seafood.

Just as with human diets,\textsuperscript{24,38} the risks of PFAS exposure among pets consuming commercial pet foods are not well understood. An exploratory study\textsuperscript{40} conducted by Chinthakindi et al using 11 different brands of popular dog and cat food sold within the United States demonstrated that nearly 30% of the samples contained PFCAs with total PFCA concentrations ranging from less than the limit of detection to 3.67 ng/g. Four of the 9 PFCAs were measurable: perfluorobutanoic acid (PFBA), PFHxA, perfluorohexanoic acid (PFHxA), and PFOA. Of these, PFOA was found in the highest concentrations.

Chinthakindi et al\textsuperscript{40} then conducted oxidation studies on the pet foods to determine whether the presence of fluorotelomer alcohols (which are PFAS pre-cursors and used in pet food packaging) could degrade into the PFCAs of interest. After subjecting the samples to the total oxidizable precursor assay, the laboratory found detectable levels for 8 of the 9 PFCAs analyzed.

Chinthakindi et al\textsuperscript{40} used data before and after oxidation to calculate the EDI of PFAS that can be attributed to pet foods. Before oxidation, the EDI was 14.2 ng/kg body weight/day for cats and 14.1 ng/kg body weight/day for dogs.\textsuperscript{40} This value is lower than the EPA’s reference dose in humans (20 ng/kg body weight/day).\textsuperscript{24} However, when inputting the oxidized sample into the equation, the EDI of cats and dogs is 95.2 ng/kg body weight/day and 125 ng/kg body weight/day, respectively, which exceeds the human reference dose. There is no reference dose for PFAS in dogs and cats. Chinthakindi et al\textsuperscript{40} concluded that pet food itself may not be a significant risk in pets but that pet food packaging, which includes precursors to several PFCAs, may be a larger problem.

As addressed in the companion Currents in One Health by Brake et al, JAVMA, July 2023, PFAS has been authorized by FDA for use in food contact surfaces since the 1960s. It is a well-known coating for the inside of microwave popcorn bags, pizza boxes, and fast-food wrappers. Small amounts of PFAS do leak from coated food-contact surfaces into human-grade food, particularly into oils or emulsified foods like butter,\textsuperscript{41} and it is likely that coatings on pet food packaging do the same.

Maternal transfer—Evidence of maternal transfer of PFAS to the fetus and through lactation has been documented in humans and animals. Kim et al\textsuperscript{42} collected maternal blood, umbilical cord serum, and breast milk from 20 volunteers in Seoul, Korea in 2007. Six PFCAs were detected in all maternal and cord serum samples, while 3 were found in breast milk. Of all the PFCAs, PFOS was found in highest concentration across the 3 tissues sampled—making up 94% of the total PFCA concentration in breast milk. Kim et al concluded that the transfer of
PFCAs between maternal serum and umbilical cord depended on the length of the carbon chain and the type of PFAS. Regardless of which type of PFAS was found, breast milk concentrations were several orders of magnitude less than maternal serum. Hinderliter et al. discovered a similar phenomenon when conducting pharmacokinetic studies of PFOA on pregnant rats. After dividing the rats into subgroups, Hinderliter et al. administered a daily dose of 3, 10, or 30 mg/kg/day starting on gestation day 4. PFOA was found in the amniotic fluid, placentas, fetuses, and milk of the rats at rates proportional to the dose. The concentration of PFAS in milk was steady state throughout the lactation period and represented about 10% of the concentration found in maternal plasma. Maternal transfer of PFAS has been documented in multiple other species including birds, fish, cattle, and marine mammals. Based on these observations, maternal transfer likely occurs in pets as well and could be an area of future study.

Dermal exposure—Dermal exposure in pets has not been well described. Besides contact with floors and furniture treated with PFAS-containing products, dogs and cats may also be at risk from popular flea and tick prevention. The environmental watchdog, Public Employees for Environmental Responsibility (PEER), commissioned laboratory analysis of a flea and tick collar and a topical flea and tick preventative. Four types of PFAS, PFHxA, PFHpA, perfluorooctane sulfonate (PFOS), and hexafluoropropylene oxide dimer acid (GenX), were measured in the topical product for a total of 2,390 ng/L. The collar contained 0.25 ng/g perfluorododecane sulfonate.

In addition to the flea and tick products mentioned, researchers have found that when increasing concentrations of PFOA are applied to the skin of mice, there was a corresponding increase in serum PFOA levels. Whitehead et al. evaluated 231 human cosmetic products purchased in the United States and Canada and found that foundations, mascaras, and lip products had the highest proportion of total fluorine. PFAS concentrations ranged from 22 to 10,500 ng/g product weight with the highest amounts of PFAS found in foundation and lip products. Investigators are still working out the risks of using PFAS-containing cosmetics. In the same way, more work should be done to investigate the risk of topical flea and tick preventatives in animals.

Can dog and cat exposure to PFAS be diagnosed from blood chemistry or clinical signs?

Human epidemiological and laboratory animal studies have demonstrated that PFAS exposure can impact the health of individuals. The C8 study conducted among people working in and around a Teflon manufacturing facility in West Virginia, found probable associations between exposure to high levels of PFOA and kidney cancer, testicular cancer, pregnancy-induced hypertension, thyroid disease, high cholesterol, and ulcerative colitis. Though the geometric mean of serum PFOA concentrations found in the C8 was an order of magnitude higher than documented in the dog and cat studies cited here. There is mounting evidence that animals experience similar adverse events following exposure to PFAS. PFAS exposure in companion animals may impact future study.
body condition scores, blood chemistry levels, fetal development, as well as multiple body systems (hepatic, respiratory, immunological, amongst others). To date, PFAS has been significantly linked to changes in kidney and liver function in both dogs and cats and has been positively associated with obesity, pleural effusion, and altered thyroid function in cats (Figure 3).

Liver enzymes and cholesterol—In human and laboratory animal studies, PFAS exposure is associated with liver changes. As covered in the companion Currents in One Health by Brake et al., PFAS activates the peroxisome proliferator-activated receptor-α in hepatocytes, which ultimately leads to liver enlargement due to accumulation of cholesterol in the liver and hypertrophy of hepatocytes. In reviewing data from the general population gathered by the NHANES studies in 1999–2000, 2003–2004, and 2007–2010, researchers found consistent associations between serum liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transferase [GGT] ) and PFAS levels and increased liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transferase [GGT]) . Laboratory rodent and nonhuman primate studies also demonstrated links between exposure to certain types of PFAS and increases in liver weight, altered serum lipid levels, and elevated liver enzymes.

Outside of the laboratory, the findings are different. You et al. explored PFAS's influence on liver enzymes in police dogs and laboratory beagles by analyzing individual blood chemistry components with several different types of PFAS. The results indicated that different species of PFAS could significantly alter blood chemistry parameters in different ways. For example, PFNA and perfluorodecanoic acid (PFDA) were both significantly associated with an increase in cholesterol while PFOA and PFOS were significantly associated with a decrease in cholesterol. Only 2 of the species measured, 6:2 chlorinated polyfluorinated ether sulfonate and PFDA, were associated with significant differences.
in alkaline phosphatase in their study. In analyzing sera of cats in Swedish households, Weiss et al\textsuperscript{54} could not find a significant association between cholesterol levels and PFOA or PFOS but did find a significant increase in cholesterol associated with total PFAS levels. In the C8 project participants, there were also discrepancies in the biochemistry results. Some researchers\textsuperscript{18} found associations between serum PFOA levels and ALT and bilirubin while others did not.

**Thyroid hormones**—In their 2021 PFAS Toxicological Profile,\textsuperscript{18} ATSDR concluded that there is a relationship between PFAS exposure and altered thyroid function but cautions that results are not consistent across human or animal studies. As with liver enzymes, the findings on PFAS and thyroid hormone seem to differ based on the type of PFAS and the study conducted. As Winquist et al\textsuperscript{52} found, sometimes a single study reveals different results. In their retrospective cohort study of C8 participants, they found positive associations between PFOA exposures and both hypothyroidism and hyperthyroidism among women participants in the C8 study,\textsuperscript{50} whereas only hypothyroidism was seen in men.

No data have been reported for thyroid function disruption in dogs, although studies conducted by Wang et al,\textsuperscript{50} Bost et al,\textsuperscript{20} and Weiss et al\textsuperscript{54} have pointed to some disruption in cats. In a study of 72 cats in North Carolina, Bost et al\textsuperscript{20} discovered that PFAS was detectable in all but 1 of their cat samples with PFOS and PFHxS being the most common compounds measured. Bost reported a significant association between hyperthyroidism and serum PFOA levels and a weaker association between hyperthyroidism and total PFAS.\textsuperscript{20} These findings correspond with a similar study conducted by Wang et al\textsuperscript{50} in California. In studying hyperthyroidism in cats living in the San Francisco Bay area, Wang et al\textsuperscript{50} found that PFOA and PFHxS levels were significantly higher in hyperthyroid cats compared to nonhyperthyroid cats. Swedish researchers found that all of their feline sera of cats in Swedish households, Weiss et al\textsuperscript{54} could not find a significant association between cholesterol levels and PFOA or PFOS but did find a significant increase in cholesterol associated with total PFAS levels. In the C8 project participants, there were also discrepancies in the biochemistry results. Some researchers\textsuperscript{18} found associations between serum PFOA levels and ALT and bilirubin while others did not.

In companion animals, the data on obesity and exposure are scarce. Bost et al\textsuperscript{20} found a significant relationship between PFAS concentration and body weight among cats in North Carolina, US. Statistical analysis revealed a strong association with body weight in PFOS and PFHxS but not PFOA or C9. Laboratory animal findings are the opposite. The 2021 PFAS Toxicological Profile reports that exposures to PFAS “have consistently shown decreases in body weight or decreases in body weight gain.”\textsuperscript{18}

**Body mass**—The question of whether PFAS exposure contributes to obesity largely remains unanswered. In a systematic review of 19 maternal studies evaluating the association between prenatal persistent organic pollutants exposure and childhood obesity, Stratakis et al\textsuperscript{63} found no associations between PFAS exposure in utero and childhood obesity. In a retrospective cohort study of nearly 9,000 adults living in the Mid-Ohio Valley region, Barry et al\textsuperscript{64} also could not find significant correlations between PFAS exposure in early childhood and body mass. Alternatively, in a study of 803 children enrolled in a National Institute of Child Health and Human Development Fetal Growth Study, Bloom et al\textsuperscript{65} found gestational exposure to PFUnDA in some women was positively associated with childhood adiposity. Similarly, in a study of 940 adolescents, Averina et al\textsuperscript{18} reported that PFHxS and PFHpS concentrations were positively associated with obesity.

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**Respiratory effusion**—To date, there have been very few studies evaluating respiratory endpoints in humans exposed to PFAS. Epidemiological studies of humans with known exposure to PFOA have mixed results. Workers at the Washington Works Plant, who presumably would have high levels of exposure, did not seem to be affected. Conversely, residents living near the plant reported a significant increase in chronic bronchitis and shortness of breath.\textsuperscript{18} Respiratory disease has been documented in both laboratory animals and cats for PFOA, PFOS, and PFHxS. Bost et al\textsuperscript{20} divided cats into 4 distinct quartiles according to their serum PFAS concentrations in their study. Three of the cats in their study suffered respiratory effusion, and significantly greater PFHxS levels were demonstrated in all 3 cats with respiratory disease. The authors hypothesized that since PFAS is known to embed in lipid bilayers, it may disrupt the surface tension of a particular lung surfactant common in cats, dipalmitylphosphatidylcholine. A similar finding was reported in laboratory animals.
Inhalation exposure of very high concentrations of PFOS and PFOA dust induced wheezing and nasal discharge.\textsuperscript{18} Prolonged exposure to the sodium salt of PFHxA resulted in a reversible degeneration of the nasal olfactory epithelium in rats.\textsuperscript{64}

**Pharmacokinetics of PFAS**

Although exposure and absorption of PFAS across species are comparable, there are still some unique differences between humans and companion animals, which may prevent a direct comparison. To address the question of whether PFAS levels in pets can be compared to that of their owners, we first need to learn whether or not proteins that bind and transport PFAS throughout the body are different between animal species and humans; differences may affect how long and where PFAS can circulate.

**Distribution**—During exposure, PFAS is rapidly absorbed into the bloodstream and binds quickly to transport proteins. High concentrations of both PFOS and PFOA have been found in serum, liver, and kidneys of laboratory animals exposed to the chemicals with smaller amounts found in the skin, spleen, and reproductive organs (Figure 3).\textsuperscript{67} Distribution of PFAS is related to the dose: at smaller doses, a larger proportion of PFAS concentrates in the liver compared to larger doses where concentrations are more evenly distributed between organs.\textsuperscript{68}

The protein-binding properties and level of resorption (i.e., enterohepatic recirculation) of PFAS in the body increases with the number of carbon atoms. In the same way, transporter proteins and carbon-chain length also influence how PFAS are eliminated from the body.\textsuperscript{53} PFAS can be eliminated via urine or feces, lactation, pregnancy, and menstruation. However, depending on the specific chemical, sex, and animal species-specific properties, elimination rates differ and influence the half-lives of PFAS.\textsuperscript{14,18,22,53}

For example, the half-life of PFOS in mice ranges from days to weeks, while in pigs it is almost 2 years (634 days).\textsuperscript{14,69} For PFOA, the half-life could be as short as 2 hours in mice, while in pigs the half-life of the same compound was 236 days.\textsuperscript{69} In dogs, the half-life of PFOA ranged between 8 and 30 days.\textsuperscript{70} At the time of this writing, there was no report for half-lives in cats. When analyzing data from retired fluorochemical production workers, Olsen et al\textsuperscript{71} recorded mean half-lives of PFOS, PFHxS, and PFOA as 5.4 years (95% CI, 3.9 to 6.9), 8.5 years (95% CI, 6.4 to 10.6), and 3.8 years (95% CI, 3.1 to 4.4), respectively.

**Sex and species differences**—In oral and inhalation studies, researchers found a difference in the absorption and excretion of PFAS by species and sex. When a single oral dose of radiolabeled ammonium perfluorooctanate was administered to male and female mice, rats, hamsters, and rabbits, Hundley et al\textsuperscript{67} found that the male and female rabbits, the female rat, and the male hamsters all excreted more than 99% of the original dosing within 120 hours, while the male rat and the female hamster excreted 39% and 60% of the dose within the same time frame. When exposing rats to aerosolized PFOA, Hinderliter et al\textsuperscript{72} found the time to maximum plasma concentrations took much longer in male rats than in female rats. A similar trend occurred when the plasma PFOA concentrations returned to baseline. Species and sex differences found in inhalation and gastrointestinal studies may also apply to dermal absorption.

**Conclusion**

In 2022, the National Academies of Science, Engineering, and Medicine published a report\textsuperscript{73} suggesting that the ATSDR recommend biomonitoring as part of their clinical guidance for human patients exposed to PFAS. Although some of the recommended screening is routine, the tests chosen and frequency of monitoring are based on the level of serum PFAS concentrations found in the patient.

There are many aspects to consider before making this recommendation. Clinicians will have to identify people who are exposed; determine the length of time biomonitoring should be conducted; decide if additional, sometimes invasive, procedures should be conducted; and find the funds to pay for it all. Another consideration is the challenge of finding facilities and tests that can analyze PFAS. There are several laboratories across the country that are certified to test PFAS. However, testing is expensive and often limited to water samples. In addition, private testing of dust and foods may not be offered, unless it is part of a larger study. Unless a patient was living in an area with documented contamination, they may never know if they have been exposed.

Scientific research suggests that we may soon have the tools to effectively use dogs and cats as predictors of human exposure. Researchers have demonstrated that PFAS can be detected in cats and dogs and that levels of individual types of PFAS positively correlate with those found in human samples.\textsuperscript{50} Because of the limited half-life of PFAS in dogs, it can be predicted that changes in body systems and the overall health of pets exposed to toxic substances may appear months or even years before their human counterparts. This could mean that like canaries who stood watch over miners in days of old, dogs and cats may be able indicators of harmful exposures in the household.

Despite the efforts of many to try to reduce or prohibit the use and manufacture of certain types of PFAS, the chemical is here to stay. Indoor dogs and cats largely live on the same flooring and furniture, breathe in the same air, and drink the same water as their human counterparts. Using dogs and cats as sentinels for human exposure in the household will be an important component in identifying risks and preserving healthy outcomes for the people who live there.

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