Review

Per- and polyfluoroalkyl substances (PFAS) in livestock and game species: A review

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HIGHLIGHTS

- There are a limited number of small studies investigating PFAS in livestock and game.
- Tissue distribution and elimination of PFAAs varies markedly between animal species.
- PFAA concentrations in meat samples are consistently lower than offal such as liver.
- PFAAs are transferred from exposed animals to offspring, milk and eggs.
- Concentrations of PFAAs in edible animal products decline after exposure ceases.

GRAPHICAL ABSTRACT
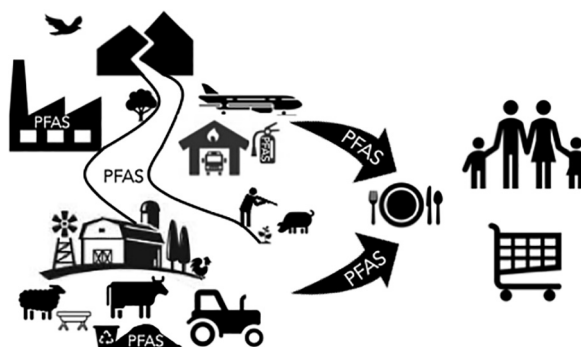
ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are synthetic, organic chemicals that resist environmental breakdown. The properties that made PFAS into an industrial success also led to their persistence and bioaccumulation. As PFAS were widely used for many decades their presence is evident globally, and their persistence and potential for toxicity create concern for human, animal and environmental health. Following the precautionary principle, a reduction in human exposure is generally recommended.

The most significant source of human exposure to PFAS is dietary intake (food and water) with additional exposure via dust. As PFAS concentrations have been more frequently studied in aquatic food sources, there is less understanding of exposure via terrestrial animals. To further define human exposure via animal products, it is necessary to determine PFAS concentrations and persistence in terrestrial livestock and game species. Studies assessing ambient concentrations of PFAS have noted that, aside from point sources of contamination, there is generally low input of PFAS into terrestrial agricultural food chains. However, livestock and game species may be exposed to PFAS via contaminated water, soil, substrate, air or food, and the contribution of these exposures to PFAS concentrations in food products is less well studied.

This review focuses on perfluoroalkyl substances (PFAAs) and compiles information from terrestrial livestock and game species as a source of dietary exposure in humans, and discusses toxicokinetics and health effects in animals, while identifying future focus areas. Publications describing the transfer of PFAAs to farmed and hunted animals are scarce, and demonstrate large variability in distribution and elimination. We outline several relatively small, short-term studies in cattle, sheep, pigs and poultry. While negative effects have not been noted, the poultry investigations were the only studies to explicitly assess health effects. Comparative information is presented on PFAA concentrations in livestock products and edible tissues of game animals.

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Contents

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a family of >4000 synthetic chemicals, used extensively throughout the world from the mid-twentieth century (Buck et al., 2011, Sunderland et al., 2019). PFAS are highly fluorinated aliphatic compounds, which differ in their functional groups and carbon chain length (Buck et al., 2011). Many PFAS can reduce surface tension, are resistant to degradation at high temperatures, and are water, oil and dirt repellent (OECD, 2013). These properties mean they have been widely used, for example in metal plating and coating agents, greases, lubricants, adhesives, paints, polishes, cleaning products, surfactants, photographic products, packaging, herbicides and insecticides, textile and leather products, and fire-fighting foams (OECD, 2013). PFAS resist biodegradation, photo-oxidation, and hydrolysis due to the strength of the carbon-fluorine bond (Sznajder-Katarzyńska et al., 2019). This review focuses on perfluoroalkyl acids (PFAAs) and, in particular, on the most frequently studied PFAAs: perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). The majority of PFAS research and regulatory attention has been focused on PFOS and PFOA due to their frequent occurrence in the environment, known persistence, and bioaccumulative properties (CRC CARE, 2016).

PFOS and PFOA belong to the group of long perfluorocarbon chain PFAS and they can be the chemical breakdown product of other PFAS (Buck et al., 2011). There are less data available on the toxicity of PFAS other than PFOS and PFOA (ATSDR, 2018), nevertheless in the studies that are available the toxicity of shorter chain PFAS has been lower (e.g. Newsted et al., 2008; Lieder et al., 2009a, 2009b; Butenhoff et al., 2012a). Due to their widespread use, mobility, and persistence in the environment, PFAS are found in soil, surface water and groundwater in urban areas at low concentrations, and have been measured globally in a wide variety of marine and terrestrial animals, and humans (Buck et al., 2011, OECD, 2013). Globally, PFOS is the most prevalent PFAS found (Reiner and Place, 2015). Ecological studies in North America,

Europe, Asia and remote polar regions have found PFOS in tissues of polar bears, river otters, albatrosses, bald eagles, fish, dolphins, penguins, and Arctic and Antarctic seals (e.g. Giesy and Kannan, 2001, Houde et al., 2011, Reiner and Place, 2015, Muir et al., 2019). Concentrations of PFOS in wild animals from relatively more populated and industrialised regions, such as the North American Great Lakes, Baltic Sea, and Mediterranean Sea, were greater than those in animals from remote marine locations (Giesy and Kannan, 2001). Honey samples originating from an industrial region of Poland showed 20% higher concentrations of perfluoroheptanoic acid (PFHpA) compared to those from non-industrial regions (Surma et al., 2016).

In 2009, PFOS and PFOA were listed under the *Stockholm Convention on Persistent Organic Pollutants* 'due to their demonstrated toxicity, bioaccumulation, persistence in the environment and ability to travel long distances from the point of release or application' (SC, 2019). This requires participating countries to eliminate or reduce the release of these chemicals into the environment. Manufacturing of other PFAS has continued, with a shift in manufacturing to short-chain PFAS (e.g GenX), which has led to more frequent measurement of these chemicals in the environment, some of which also appear to be environmentally persistent (Sunderland et al., 2019). However, human serum concentrations of PFOS and PFOA have shown a downward trend worldwide since the 2000's (Kato et al., 2015).

In a recent global survey of inhalation, dietary and drinking water sources of PFAS exposures, Jian et al. (2017) noted that food and drinking water are still the main routes of human exposure. This followed assessment of PFAS profiles in indoor air and dust samples collected from home, office, and vehicles, in addition to food (vegetables, dairy products, beverages, eggs, meat products, fish, and shellfish) and drinking water. Dietary exposure to PFAS in fish and shellfish remain the most significant dietary source (Domingo and Nadal, 2017). However, one Canadian study showed that beef contributed around 90% of the total dietary intake of PFOS, with fish being of lower importance (Tittlemier et al., 2007). In a 2016 Australian report, which recorded the occurrence

of PFAS in animal products sourced near contaminated sites, PFOS concentrations were highest in rabbit meat, finfish livers, cattle meat and mammalian offal (FSANZ, 2016). PFOA was below reporting limits in most samples, but where measurable it was highest in molluscs and freshwater fish (FSANZ, 2016). There are currently no specific regulatory limits for PFAS in food in any country (FSANZ, 2017), but Tolerable Weekly Intakes (TWI) have been set in Europe (EFSA, 2020), there are guidelines for selected PFAS in drinking water (US EPA, 2016; US EPA, 2017; NHMRC, 2018), and some countries like Australia have also set 'trigger levels' for investigation of PFAS in food products and environmental media (FSANZ, 2017; HEPA, 2020).

PFAS have the potential to bioaccumulate and biomagnify in food webs (Kelly et al., 2009; Houde et al., 2011; Reiner and Place, 2015; Xiao, 2017). The rate of bioaccumulation has been shown to increase as the carbon chain length increases (Houde et al., 2011), supported by studies where bioaccumulation of PFOA is lower than for PFOS (Conder et al., 2008). For example in sheep (Kowalczyk et al., 2012), similar to rats (Cui et al., 2010), PFOA had a higher elimination rate than PFOS. In addition, it has been shown that perfluoroalkyl sulfonic acids (PFSAs) (as compared to perfluoroalkyl carboxylic acids, PFCAs, of the same perfluorinated chain length (see **Table S1** for description of chemical grouping)) accumulate in organisms to a higher degree due to their differing functional groups (Zhao et al., 2012; Conder et al., 2008). Müller et al. (2011) studied a lichen-caribou-wolf terrestrial food web and found that trophic magnification factors were highest for PFAS with nine to eleven carbons, that PFOA did not significantly biomagnify, and that magnification factors were around two times lower than in the marine environment.

Studies have shown large variability in PFAS elimination half-lives between species and chemical type (Kudo, 2015). As these compounds are proteinophilic, PFAS concentrations are generally highest in blood and liver, followed by varying concentrations in bile, kidney, lung, skin, muscle, fat and brain, which vary with species and chemical (Pizzurro et al., 2019; Kudo, 2015). Some PFAS are transferred via the placenta, milk (Kato et al., 2015; Pizzurro et al., 2019) and eggs (Wilson et al., 2020), which reflect direct pathways of PFAS into animal products for human consumption.

While this review includes publicly available PFAS data from terrestrial livestock and game species, most studies have focused exclusively on PFAAs. The term PFAS is used here to be inclusive of PFAAs and other *per*- and polyfluoroalkyl substances. The available studies are outlined by species, and a summary of PFAS concentrations in retail samples of livestock products or edible tissues of game animals (e.g. wild boar, deer, quail and ducks) is provided.

2. Sources of PFAS in livestock and game species

2.1. Contaminated air and water

PFAS can be transported long distances in dust (OECD, 2002; US EPA, 2017). In general, concentrations of PFAS in indoor air and dust samples significantly exceed those found outdoors when an industrial point source is absent, for example home and office PFOS concentrations in Europe, South Korea and North America ranged between <1.0–400 pg/m^3 and outdoor concentrations ranged between <1.0–150 pg/m^3 (Goosey and Harrad, 2012). Nonetheless, studies in China have shown that total PFAS concentrations in monkey blood samples near urbanised areas (i.e. zoo animals) were one order of magnitude higher than the concentrations in wild monkeys (i.e. nature reserve animals) and that tree leaves accounted for the highest percentage of daily intake (Cui et al., 2019), likely due to airborne deposition. This suggests that food-producing animals in peri-urban areas may also have higher airborne PFAS exposure when compared to those from remote areas, due to a higher density of sources such as landfills and industry.

In relation to exposure via water, reviews of the range of ambient PFOS concentrations in drinking water in Japan (Guruge et al., 2008), Australia (Thompson et al., 2011) and Europe (EFSA, 2018) have reported concentrations varying from <0.1–51 ng/L. Global drinking water PFAS concentrations have been reviewed recently by Rahman et al. (2014) and Domingo and Nadal (2019). PFAS have been measured in sediments in bays, lakes and rivers, and in effluents from sewage treatment plants (OECD, 2002; Ahrens et al., 2009; Möller et al., 2010). An example of surface water PFOS concentrations downstream from wastewater treatment facilities includes concentrations in Japan up to 157 ng/L (Guruge et al., 2008). Increased water concentrations occur downstream of PFAS production sites (Boiteux et al., 2017) and sites where historical use of aqueous film forming foams (AFFF) occurred for fire-fighting purposes (D'Agostino and Mabury, 2017), as well as downstream of landfills (for example, concentrations in leachate from an Australian study were PFOA max. 48 ng/L, and PFOS max. 240 ng/L; Gallen et al., 2017). PFOS and PFOA have surface water half-lives of 41 years and 92 years respectively (DoER, 2016) and nanofiltration may be required to remove PFAS from treated water (Domingo and Nadal, 2019). In Australia, the principal source of PFAS contamination in livestock has been due to stock drinking water contaminated via stormwater runoff from historic use of AFFF at neighbouring sites (Australian Government, 2020).

2.2. Contaminated soil, pasture or substrate

Globally, many regions are continuing to discover PFAS contaminated sites from AFFF use, particularly next to airports, fire training areas and military bases (Sunderland et al., 2019; DoD, 2020). Background PFAS concentrations in soil versus concentrations seen at contaminated sites globally have recently been reviewed by Brusseau et al. (2020). Concentrations reported for PFAS-contaminated sites were generally orders-of-magnitude greater than background concentrations, particularly for PFOS, which ranged upwards of several hundred mg/kg (Brusseau et al., 2020). Among other PFAS, PFOA and PFOS are found in sludge or biosolids from wastewater treatment plants with 80–100% detection frequency, thus application to pastures raises concern about accumulation in the edible tissues of food animals (Lupton et al., 2011, 2014, Venkatesan and Halden, 2013). PFAS concentrations in biosolids have been found to range from 1 to 244 µg/kg dry weight (dw) PFOA and 5–3120 µg/kg dw PFOS in the USA (Lupton et al., 2011, 2014), from 4.3 to 89 µg/kg dw PFOS in Italy (Brambilla et al., 2016) and between 4.7 and 86 µg/kg dw PFOS in Australia (Sleep and Juhasz, 2020). Concentrations of PFOS in soils of biosolid-amended fields have been measured up to 483 µg/kg dw (Sepulvado et al., 2011).

Animals consume soil while they are grazing and plants also uptake PFAS from soils; multiple studies have demonstrated that the amount of PFAS in plants is directly proportional to soil concentrations (e.g. Stahl et al., 2009), but uptake occurs to different extents according to their concentrations, chain lengths, functional group, plant species and variety, growth media (hydroponics vs. soil), and soil characteristics, primarily soil organic matter (Ghisi et al., 2019). Example concentrations in potential livestock feed products grown in soil spiked with 1 mg/kg of each compound include rye grass: PFOA 408–7250 µg/kg dw and PFOS 92–470 µg/kg dw, and wheat straw: PFOA 1900 and PFOS 270 µg/kg dw (Stahl et al., 2009). In forage grown on biosolid-amended soil, concentrations of PFOS and PFOA have been measured at 1–20 µg/kg and 10–1200 µg/kg dw respectively (Yoo et al., 2011). Fernandes et al. (2019) found evidence of PFAS uptake into pig liver from biosolids exposure, and also demonstrated that PFAS concentrations in eggs showed evidence of uptake from chicken exposure to recycled cardboard, dried paper pulp and wood shavings used as substrate/bedding. This indicates that long-term exposure to PFAS from soil and forage is important to consider in livestock grazed on pastures with ongoing application of biosolids (Lupton et al., 2014), and that

care must be taken with use of recycled materials as substrates in the animal industries (Fernandes et al., 2019).

In 2018, the European Food Safety Authority (EFSA) reported modelling where forages represented 78% of PFAS exposure in ruminants, while soil accounted for >80% in outdoor poultry/eggs and pigs (Brambilla et al., 2015). This proportionality would clearly change depending on the PFAS concentrations in each exposure medium (water, soil, grass) at a particular location of interest, as well as with housing and rotation practices of livestock, and feeding habits. As an example of dietary PFAS exposure from processed animal feed other than fishmeal, a Turkish study of PFAS concentrations in commercial feed for layer hens, cattle and sheep found PFOA and PFOS concentrations up to 7.55 μg/kg ww and 0.88 μg/kg ww respectively (Onel et al., 2018).

2.3. High-energy rations and fishmeal

Some PFAS have been shown to bioconcentrate in fish (US EPA, 2017). Thus, mixed feeds for animals originating from fish may contribute to higher PFAS exposure in some farm animal species (Guruge et al., 2008). A study from Japan suggested that use of feeds with animal and fish products for fattening could explain accumulation of PFOS in beef cattle (Guruge et al., 2008). Li et al. (2019a) collected 92 commercial fishmeal samples from leading fishmeal-producing countries and found that the sum concentration of 16 common PFAAs ranged from 0.65 to 85.5 μg/kg (mean: 18.2 μg/kg, 12% moisture). PFOS predominated, with high detection of perfluoroundecanoic acid (PFUnDA), and wide occurrence of short-chain PFAS (e.g. PFBA, PFBS) (Li et al., 2019a). The total concentrations of PFAA in fishmeal were significantly higher in products originating from fish in the northern compared to the southern hemisphere (Li et al., 2019a), which correlates with modelled ocean PFAA concentrations (Muir et al., 2019).

2.4. Transplacental and lactational transfer

Studies of humans and laboratory animals demonstrate that both PFOA and PFOS in maternal plasma can cross the placenta and can also enter breast milk (Kato et al., 2015; Pizzurro et al., 2019; ATSDR, 2018) and that the ratio of PFOS concentrations between maternal serum:milk:cord blood are comparable across species (van Asselt et al., 2013). Guruge et al. (2008) found high concentrations of PFOS in cattle foetal livers, indicating that PFOS crosses the placental barrier to enter foetal circulation. Following birth, lactational transfer has been shown to occur in humans and mice (Lau, 2015) and studies in PFAS exposed cattle and sheep have demonstrated PFAS transfer from feed to milk (Kowalczyk et al., 2012, 2013), so this is likely to be the same in livestock and game species.

3. PFAS toxicokinetics

PFAAs are generally well absorbed from the gastrointestinal tract (e.g. >90% absorption of PFOA and PFOS in rats) and are not metabolised (Kudo, 2015, Pizzurro et al., 2019). As they are non-volatile and metabolically inert, body clearance of PFAAs depends on elimination into urine and faeces, and the enterohepatic circulation that occurs following excretion into bile may extend half-life (Kudo, 2015). In contrast to neutral hydrophobic organic contaminants (e.g. polychlorinated biphenyls or PCBs), which are primarily accumulated in adipose tissue (Conder et al., 2008), PFAAs are distributed mainly to the serum, liver, and kidneys (ATSDR, 2018, Kudo, 2015, Pizzurro et al., 2019) and their bioaccumulation potential cannot be predicted by traditional approaches (Conder et al., 2008). Toxicokinetic studies in rats demonstrated that different homologues of the two major groups of PFAA, PFCAs and PFSAs, have different urinary clearance rates (Ohmori et al., 2003). Renal elimination is the most critical process in determining total body clearance and biological half-lives of PFAS (Kudo, 2015).

Large differences in elimination rates of PFAS have been observed within and between different species (Lau, 2015, see Table 1), with the longest half-lives seen in humans (Pizzurro et al., 2019). Half-lives vary with chemical, and are longer for the eight-carbon versus four-carbon PFAS, and longer for the sulfonates compared to the carboxylates (Pizzurro et al., 2019). Human, mouse, rat and monkey studies show that half-lives decrease in the order of PFHxS > PFOS > PFOA > PFBS > PFBA but the longer half-life estimate for PFHxS may be related to uncertainty in the assumptions used to derive the estimate (Pizzurro et al., 2019). There have been relatively few studies in livestock. The variation in half-lives between species is large and ranges from hours e.g. PFOA in rabbits (Hundley et al., 2006), to days or weeks e.g. PFOS and PFOA in mice (Chang et al., 2012; Lou et al., 2009) and birds (Newsted et al., 2007; Wilson et al., 2020; Tarazona et al., 2015), then up to several months e.g. PFOS in monkeys (Chang et al., 2012; Seacat et al., 2002), and finally years for PFOS in pigs (Numata et al., 2014) and humans (Spliethoff et al., 2008; Glynn et al., 2012). Studies of PFAS in rats have also demonstrated differences in elimination half-lives between sexes (e.g. Chang et al., 2012) however further work is required to explain these gender differences.

Tissue to serum partition coefficients of PFAS vary by chemical type, and between species (**Table S2**). For example while PFOS and longer chain PFAS bioaccumulate and persist in protein-rich compartments (liver, blood) (Kelly et al., 2009), partitioning between the blood and the liver is highly specific to animal species (Guruge et al., 2008). The evidence in humans and experimental mammals suggests that PFOA, PFOS, and PFBS preferentially distribute to the liver, whereas PFBA and PFHxS appear to preferentially distribute to the serum (Pizzurro et al., 2019). While PFAS are proteinophilic and their concentrations exhibit positive correlation with protein content of tissues, rather than fat content (Kelly et al., 2009), PFAS are found in fat tissue to varying extents and cannot all be thought of as being lipophobic (Numata et al., 2014). In humans, the long half-lives of PFOS and PFOA appear to arise from the processes of enterohepatic recycling and of saturable resorption from the kidney (Roberts, 2016). Overall, studies demonstrate varying levels of excretion and accumulation of PFAS, dependent on both the chemical and the animal species. Several studies have demonstrated that short chain PFAS compounds (such as PFBS), which show different elimination kinetics due to smaller molecular size, higher water solubility and reduced protein binding, have demonstrably shorter half-lives (e.g. Kowalczyk et al., 2013). Riebe et al. (2016) proposed that the low PFOA concentration in herbivorous and carnivorous species in their study, compared with the mean PFOA concentrations seen in wild

Table 1
Serum/plasma elimination half-lives of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) across experimental, game and livestock species. Modified from Lau (2015) and ToxConsult (2016 a,b).

	PFOS		PFOA	
	Female	Male	Female	Male
Rabbit	88 days[a]		7 h[b]	5.5 h[b]
Rat	14–83 days[c,d]	7.5–82 days[e,d]	2–16 h[f]	1.3–21 days[g,d]
Mallard duck		13.6 days[h]		
Quail		20.7 days[h]		
Chicken	3.5–160 days[i,j]			4.6 days[k]
Mouse	31–38 days[k]	36–43 days[l]	16 days[m]	22 days[m]
Dog			8–13 days[n]	20–30 days[n]
Cattle	39–106 days[o]	120 days[p]	1.3 days[o]	19.2 h[q]
Sheep	No data	No data	No data	No data
Monkey	110–200 days[k,r]	132–200 days[l,r]	33 days[s]	21 days[s]
Pig	1.7 years[t]		236 days[t]	

[a]Tarazona et al. (2016). [b]Hundley et al. (2006). [c]Wang et al. (2010a, 2010b). [d]De Silva et al. (2009). [e]Johnson and Ober (1979). [f]Kemper (2003). [g]Benskin et al. (2009). [h]Newsted et al. (2007). [i]Wilson et al. (2020) (laying hens). [j]Tarazona et al. (2015) (8-wk old males). [k]Yoo et al. (2009). [l]Chang et al. (2012). [m]Lou et al. (2009). [n]Hanhijärvi et al. (1988). [o]Vestergren et al. (2013). [p]Lupton et al. (2015). [q]Lupton et al. (2011). [r]Seacat et al. (2002). [s]Butenhoff et al. (2004). [t]Numata et al. (2014).

boar, suggests an omnivorous diet could play an important role in the uptake of PFAS, which may be a result of the affinity of PFAS for protein and therefore animal tissues.

4. Health effects of PFAS in animals

Although concern has been raised over the toxic effects seen in experimental animal studies at high PFAS doses, it is presently unclear whether these findings are relevant in livestock and game species at environmentally relevant exposure concentrations. The primary effects observed in laboratory animals exposed to perfluoroalkyl compounds (generally at doses higher than human exposure concentrations) are liver toxicity, developmental toxicity and immune toxicity (ATSDR, 2018). Experimental exposure to PFOS results in accumulation mostly in the serum and liver (OECD, 2002), with evidence of liver toxicity at high oral doses of PFOS (e.g. 0.75 mg/kg in monkeys) (Seacat et al., 2002) and PFOA (e.g. 5 mg/kg in mice) (Crebelli et al., 2019). Studies in monkeys and rats have shown a decrease in serum cholesterol concentrations, weight loss, and detrimental effects on glycogen metabolism (Seacat et al., 2002; Jiang et al., 2015). Also in rats, carcinogenicity (e.g. testicular, liver and pancreas tumours) has been demonstrated in some sub-acute and chronic PFOS and PFOA studies at high oral doses (e.g. 5-20 mg/kg in feed) (Biegel et al., 2001; Butenhoff et al., 2012b; NTP, 2020; Thomford, 2002). There is evidence of reproductive (Lu et al., 2019) and developmental toxicity in rats, mice and rabbits (OECD, 2002; Lau et al., 2003; Thibodeaux et al., 2003; Luebker et al., 2005a, 2005b; Wang et al., 2010a; Li et al., 2019b), and altered thyroid hormone concentrations in monkeys (Seacat et al., 2002). These types of health effects have not been investigated or reported in livestock or game species, and the variability seen in experimental animal species suggests a wide range of potential effects, over a range of exposure doses and time frames, need to be considered in future PFAS studies in food-producing animals. Due to the large differences in PFAS toxicokinetics between species, blood serum (or plasma) PFAS concentrations are a better indicator than external dose for comparing adverse effects between different species (Pizzurro et al., 2019).

From many experimental studies, it appears that animals can tolerate extremely high concentrations of PFAS. Recorded PFOS 'No Observable Adverse Effect Levels' (NOAELs) in experimental animals include blood concentrations of 67 mg/L in monkeys (Seacat et al., 2002) and 40 mg/L in rats (Luebker et al., 2005a, 2005b; ToxConsult, 2016a). In livestock, detrimental health effects were not reported, and are therefore assumed not to have been observed, in multiple short-term experimental studies at similarly high maximum observed blood plasma PFOS concentrations, including up to 0.24 mg/L in sheep (Kowalczyk et al., 2012), 0.25 mg/L in pigs (Kowalczyk, 2014) and between 2.46 mg/L (Kowalczyk et al., 2013) and 76.3 mg/L (Lupton et al., 2015) in cattle. For context, the average human blood PFOS concentration from various studies in the United States between 2005 and 2009 ranged from 13.2 to 17.1 ng/mL (Kato et al., 2015).

Several studies have discussed health effects in birds. Although bird eggs have been used in biomonitoring studies on PFAS, and there are some indications of eggshell thinning and reduced hatching success in wild birds, effects of environmental PFAS concentrations on avian reproduction remain largely unknown (Custer et al., 2014; Groffen et al., 2019). Some avian studies have demonstrated higher plasma oxidative damage and lowered plasma antioxidant defences secondary to longer-chain PFAS exposure, which has the potential to affect key fitness traits such as reproduction (Costantini et al., 2019). The acute and chronic effects of PFOS (Newsted et al., 2006, 2007) and PFBS (Newsted et al., 2008) in mallard ducks and northern bobwhite quail have been studied using high doses in experimental settings, in which adult health, body and liver weight, feed consumption, gross morphology and histology of body organs, and reproduction were examined (for half-life results see Table 1). These studies show that high doses can be tolerated in these birds, with effects not reported below the 10 mg/kg of PFOS

in feed dose (Newsted et al., 2007, 2008). Exposure concentrations of ≥10 mg/kg in feed showed decreased survivorship of quail offspring, a greater incidence of small testes length (Newsted et al., 2008) and an increase in quail, but not mallard, liver weight (Newsted et al., 2008). In the acute and chronic PFBS studies, the only detrimental effect was reduced body weight gains at doses >5620 mg/kg feed (Newsted et al., 2008). These studies appear to support the hypothesis that shorter chain PFAS, like PFBS, are of lower toxicity.

There were no published studies found that were specifically designed to investigate health effects in terrestrial livestock species; experimental studies to date have focused on chemical uptake and clearance after relatively short repeat exposures (approx. 3 weeks to 3 months e.g. Kowalczyk et al., 2012, 2013, Kowalczyk, 2014) or high bolus doses (e.g. Lupton et al., 2014, 2015), so the reported tissue concentrations, elimination rates and health observations are more relevant to acute rather than chronic exposure situations. The only livestock studies that have actively assessed health effects, in addition to reporting tissue PFAS concentrations and elimination times, are the three main studies discussed below in poultry (Yeung et al., 2009; Yoo et al., 2009; Wilson et al., 2020) in which no adverse effects were reported. In one of the two studies assessing domestic pigs reviewed below (Numata et al., 2014), general health was assessed by daily observation and there were no reports of adverse effects. There was no discussion of health effects in the cattle and sheep studies reviewed (Kowalczyk et al., 2012, 2013; Lupton et al., 2014, 2015; Vestergren et al., 2013), and the assumption is that no overt adverse effects were observed.

5. PFAS studies in livestock and game species

5.1. Overview

There have been relatively few investigations of PFAS in livestock and game species, which complicates management of farm animal health and food safety regulation. PFOS, PFHxS and PFOA are the predominant PFAS that have been described in livestock and game studies. Some studies have assessed livestock tissue concentrations due to ambient exposure to various PFAS (e.g. Guruge et al., 2008; Vestergren et al., 2013). The absolute concentrations of PFOS seen in Swedish cattle (Vestergren et al., 2013) were substantially lower compared with Japan (Guruge et al., 2008), emphasising regional differences in the magnitude of ambient PFAS exposure for farmed animals. Guruge et al. (2008) collected blood and liver samples from multiple farm animal species. PFOS was measurable in all samples and was the most prominent PFAS found in farm animals, with chicken livers containing the highest mean PFOS concentration, followed by livers from pigs and cattle (Guruge et al., 2008). The presence of other PFAS in livestock (such as PFOA, PFNA, PFDA, PFUnDA and PFDoDA) was insignificant (Guruge et al., 2008).

Some of the studies in livestock described below have taken advantage of "naturally contaminated" forage, for example, following a case of illegal mixing of industrial waste with fertiliser. The contaminated forage was subsequently used for two seminal pilot studies in cattle and sheep (Kowalczyk et al., 2012, 2013), with doses estimated to be 10- to 100-fold less than those used for toxicokinteic studies in chickens and rats. The majority of experimental studies are, however, less reflective of ambient exposure and have looked instead at tissue concentrations and elimination half-lives after a single, large bolus dose of PFAS (e.g. Lupton et al., 2014, 2015), with some investigating exposure over several months (e.g. Zafeiraki et al., 2016b; Wilson et al., 2020).

5.2. Cattle studies

Cattle have been the subject of more PFAS studies than other livestock species, and this work has demonstrated that PFAS concentrations in exposed animals will be highest in blood, liver and kidney, with some

accumulation in fat and muscle, and potential transfer to milk. Enterohepatic circulation of PFOS results in its prolonged presence in plasma, whereas PFOA is almost fully excreted (Lupton et al., 2014). In general, the shorter-chain PFAS like PFHxS and PFBS have lower accumulation potential in cattle compared to the long-chain compounds like PFOS (Lupton et al., 2011, 2014).

Vestergren et al. (2013) studied the bioaccumulation of PFAS in five dairy cows (<24 months of age) receiving feed and drinking water in Sweden with ambient concentrations of PFAS. Despite feed and water concentrations of PFOA being approximately double those of PFOS, tissue concentrations of PFOS were an order of magnitude higher (Vestergren et al., 2013). Mean PFOS concentrations were highest in whole blood, followed by liver and then muscle, and the authors concluded that long-chain PFAS have a relatively high potential for transfer to milk and beef from the diet of dairy cows (Vestergren et al., 2013).

Kowalczyk et al. (2013) investigated the transfer of perfluorobutanesulfonate (PFBS), PFHxS, PFOS and PFOA into tissue and milk of 6 Holstein dairy cows fed contaminated hay and silage. After 28 days, three cows were slaughtered while three underwent a 21-day depuration period prior to slaughter. Overall, PFBS, PFHxS, PFOS, and PFOA showed different kinetics, and different milk elimination patterns. In plasma, concentrations of PFBS and PFOA remained low, whereas PFHxS and PFOS continuously increased during the feeding period (Kowalczyk et al., 2013). After the dietary exposure had stopped, PFOS concentrations continued to increase in muscle, kidney, plasma and liver, whereas PFHxS decreased linearly during the depuration time (Kowalczyk et al., 2013). The highest PFHxS concentrations were detected in liver and kidney, with lowest total PFAS concentrations seen in muscle. At the end of the feeding study, cumulative secretion in milk was determined for PFOS ($14 \pm 3.6\%$) and PFHxS ($2.5 \pm 0.2\%$), whereas PBFS and PFOA were barely secreted into milk (Kowalczyk et al., 2013). Overall, the kinetics of PFOA were similar to those of PFBS and substantially differed from that of PFHxS and PFOS (Kowalczyk et al., 2013). The very low concentration of PFBS in plasma and milk, the relatively high urinary excretion, and only traces of PFBS in liver and kidney suggest that PFBS does not accumulate in the body of dairy cows (Kowalczyk et al., 2013). This study showed that the longer the carbon chain, the lower the elimination rate via urine and milk, corresponding to higher accumulation in tissue samples, however the kinetics of PFOA were more similar to the short chain PFBS, compared to PFOS and PFHxS (Kowalczyk et al., 2013).

van Asselt et al. (2013) developed a physiologically based pharmacokinetic (PBPK) model for transfer of PFOS from feed to milk using the data described above from Kowalczyck et al. (2013), and estimated the half-life of PFOS in milk (56 days). There was a high correlation between PFOS concentrations in blood and milk, and model calculations showed that once steady state is reached almost all ingested PFOS is excreted through the cows' milk, although parameter estimation was complicated as the experiments were shorter than the half-life (van Asselt et al., 2013).

Lupton et al. (2011, 2014, 2015) have performed multiple small trials in cattle using various doses of PFOS and PFOA. Lupton et al. (2011) studied the elimination of a single, high oral dose (1 mg/kg) of PFOA in four Angus steers in the USA and found that it was fully excreted in the urine within 9 days of dosing, with a plasma elimination half-life of <20 h. Although PFOA was rapidly absorbed, it was also rapidly excreted and did not persist in edible tissues (Lupton et al., 2011). This finding was supported by Kowalczyk et al. (2013), where negligible amounts of PFOA were observed in all tissue samples.

Following a single, high, oral dose (approx. 8 mg/kg) of PFOS in three Angus steers, Lupton et al. (2014) found that the major route for excretion was via faeces ($11 \pm 1.3\%$), with minimal excretion via urine ($0.5 \pm 0.07\%$) and tissue concentrations decreased in the order: liver > back fat > kidney > intraperitoneal fat > lung > spleen > muscle. The high PFOS concentrations in liver and bile, and the prolonged presence of PFOS in plasma, indicated the important role that enterohepatic

circulation plays in PFOS fate and distribution (Lupton et al., 2014). Fat samples had consistently higher concentrations than muscle (Lupton et al., 2014), but these results are not typical, as other animal studies have observed low accumulation of PFOS in fat tissues (Yoo et al., 2009; Bogdanska et al., 2011). A large concentration of the initial dose was still in blood at 28 days (36%), followed by the carcass remainder (6%) and muscle tissue (4%) (Lupton et al., 2014). Approximately 39% of the dose was not accounted for in the mass balance, therefore they hypothesized that large compartments such as skin and bone could be pools where PFOS is distributed in cattle (Lupton et al., 2014). Bogdanska et al. (2011) analyzed the skin and bone of mice and observed concentrations similar to those observed in blood, indicating that distribution to these tissues could be a source of the unaccounted PFOS, which is supported by a finding that concentrations of PFOS in duck skin were higher than those in muscle (Senversa, 2018).

Two Angus steers given a single oral bolus dose (capsule; 0.098 mg/kg bw) of PFOS and slaughtered on day 343 showed similar average PFOS concentrations in liver and plasma (0.15 μg/g ww and 0.15 μg/mL), whereas muscle concentrations (0.005 μg/g ww) were much lower (Lupton et al., 2015). Heifers in the same study were given a much higher oral bolus dose of PFOS (9.1 mg/kg bw) and tissue concentrations on Day 343 ($n = 2$) remained highest in plasma (8.3 μg/mL), followed by liver (4.7 μg/g) and then muscle (0.28 μg/g ww) (Lupton et al., 2015). Plasma depletion half-lives for the steers and heifers were 120 ± 4.1 and 106 ± 23.1 d, respectively (Lupton et al., 2015).

Guruge et al. (2008) found a positive correlation between serum PFOS concentration and age in lactating Holstein cows. In Australia, serum samples from cattle that resided adjacent to a site with historical use of firefighting foam showed much higher serum PFOS concentrations in bulls that had been resident for a longer period (i.e. several years) compared to the cows and calves, but PFHxS concentrations between the groups did not differ (Senversa, 2018).

5.3. Sheep studies

A pilot study by Kowalczyk et al. (2012) in Germany demonstrated the transfer of PFOS from contaminated feed (corn silage cultivated on cropland where illegal waste had contaminated farmland) into sheep milk and meat. Two East Friesian sheep were fed PFAS (PFOS: 90 μg/kg dry matter, PFOA: 33 μg/kg dry matter) contaminated corn silage for 21 days and PFOS was excreted in milk at higher concentrations (0.2–19.2 μg/L) than PFOA (<0.2–1.3 μg/L) (Kowalczyk et al., 2012). Although the transfer was low over this short period, PFOS could be measured in milk, liver, kidney and muscle tissue (Kowalczyk et al., 2012). PFOA was excreted in the urine, but PFOS excretion was primarily via the faeces (Kowalczyk et al., 2012).

Zafeiraki et al. (2016a) sampled livers from sheep fed with grass obtained from a river floodplain in the Netherlands, with PFOS concentrations up to 0.5 μg/kg, compared to those fed clean grass. Some sheep were fed for 112 days and PFOS concentrations in liver reached 10.9 ng/g w/w, whereas animals switched to clean grass after 56 days of exposure showed a decrease in liver concentrations from 9.2 to 4.7 ng/g w/w after 64 and 112 days respectively (Zafeiraki et al., 2016a). The percentage of PFOS ingested and retained in the liver was estimated to be 12% at day 56, which reduced to 6% after another 56 days on clean grass (Zafeiraki et al., 2016a).

5.4. Poultry studies

Yeung et al. (2009) dosed juvenile male domestic chickens with 0, 0.1 or 1 mg/kg combined PFOS, PFOA and perfluorodecanoate (PFDA) via gavage three times a week for three weeks. After three weeks of exposure, half of the chicks were sacrificed, and the other half underwent depuration for a further three weeks. No dose-dependent statistically significant differences in body/organ weights were observed among treatment and control groups for the duration of the study, and

histological and plasma biochemical parameters did not differ. The half-lives at the higher dose rate were 17 days for PFOS, 16 days for PFDA, and 3.9 days for PFOA (Yeung et al., 2009). The liver was the main target during exposure, and the blood was the main reservoir during depuration.

Yoo et al. (2009) exposed groups of six male chickens to two levels of PFOA (0.1 or 0.5 mg/mL) or PFOS (0.02 or 0.1 mg/mL) via subcutaneous osmotic pump for four weeks and then allowed them to depurate for an additional four weeks. This administration route is unusual and unlikely to reflect environmental exposures, however, these exposures did not cause any statistically significant changes in body index, clinical biochemistry or histology among treatments relative to the controls ($p = 0.05$), except that concentrations of total cholesterol and phospholipids were less in chickens exposed to PFOS. The elimination rate constant for PFOA was approximately six-fold greater than that of PFOS, and the greatest concentrations of PFOA and PFOS were found in kidney and liver, respectively (Yoo et al., 2009). In summary, in broilers, PFOS concentrations were higher in liver and blood compared to kidney, whereas PFOA concentrations were highest in kidney and it was eliminated faster (Yeung et al., 2009; Yoo et al., 2009).

A study in 119×30-week old layers dosed for two months with PFOS, PFOA, PFHxS and PFHxA (perfluorohexanoic acid) at up to 300 µg/L water did not demonstrate any negative health or productivity effects (Wilson et al., 2020). There was a linear correlation between the PFAS concentrations in the drinking water of hens and those detected in the egg (Wilson et al., 2020). The PFAS elimination half-life in eggs measured over the study period (collected every second day), calculated as the rate at which the PFAS concentrations in eggs decreased after PFAS exposure to the hen via drinking water ceased, also referred as the "clearance phase", was 7 d for PFHxS, 5.4 d for PFOA, 3.5 d for PFOS and 2 d for PFHxA (Wilson et al., 2020).

Some egg injection studies have shown that PFOS is embryotoxic to domestic chickens (*Gallus gallus domesticus*). In a study by O'Brien et al. (2009), in which chicken eggs were directly injected with 0.1, 5, or 100 µg PFOS/egg into the air cell prior to incubation, the embryo median lethal dose (LD50) was 93 µg/g, however egg injection studies have limited applicability to how embryos are exposed in the environment. Briels et al. (2018) demonstrated that when PFOS was injected into chicken eggs prior to incubation, embryonic survival was not affected, nor were there any effects detected on hatchling weight or oxidative stress parameters.

The poultry studies described above have explicitly assessed and reported health effects in exposed animals, in addition to PFAS tissue concentrations, and are the only livestock studies to have taken this approach.

5.5. Domestic pig studies

PFAS elimination half-lives in pigs are longer than in most animals reported in the literature. Numata et al. (2014) investigated the transfer of a mixture of PFAS from contaminated feed in Germany (hay and barley grown in contaminated soil; range 10–137 µg/kg of feed; fed for 21 d) into the edible tissues of 24 fattening pigs. As percentages of unexcreted PFAS, the substances accumulated in plasma (up to 51%), fat, and muscle tissues (collectively, meat 40–49%), liver (under 7%), and kidney (under 2%) for most substances; an exception was PFOS, with lower affinity for plasma (23%) and higher for liver (35%) (Numata et al., 2014). The authors developed a toxicokinetic model to quantify the absorption, distribution, and excretion of PFAS and to calculate elimination half-lives. PFHxA had the shortest half-life at 4.1 days, whereas the half-life for PFOS was 634 days (Numata et al., 2014). The elimination half-life was influenced by the end functional group, with sulfonic versus carboxylic acid end groups leading to much longer half-lives (irrespective of carbon chain length) (Numata et al., 2014).

Guruge et al. (2016) found the blood half-life after a single oral dose of a mixture of ten PFAS (3 mg/kg bw of each of 10 PFAS) in minipigs

ranged from 1.6 to 86.6 days. The liver was the greatest site of accumulation of PFOS and longer chain PFAS such as perfluorodecanoic acid (PFD(*e*)A), perfluoroundecanoic acid (PFU(*nD*)A) and perfluorododecanoic acid (PFDoDA). The study authors observed an increasing accumulation trend of PFAS associated with the fluorinated carbon chain length and perfluorononanoic acid (PFNA), a 9-carbon PFAS, showed the highest body burden of the administered PFAS (Guruge et al., 2016).

A recent study investigated the tissue distribution of 8:2 fluorotelomer alcohol (8:2 FTOH) of which a primary metabolite is PFOA, after dosing 30 pigs (70 days old) at 5 mg/kg bw for one week (Xie et al., 2020). The parent compound was not detected in tissues 3 d after exposure cessation but the absolute half-life of PFOA in the kidney was 61.4 days, which was marginally longer than liver half-life, following a peak concentration in kidney and liver of 42 ± 7.0 µg/kg and 50 ± 4.8 µg/kg respectively (ww, SD) (Xie et al., 2020). PFOA concentrations in fat, lung and heart were similar after 21 days, and an order of magnitude higher than muscle concentrations (Xie et al., 2020).

5.6. Game bird studies

The dietary and migratory habits of game birds are important considerations for PFAS exposure, for example ducks that feed in the sediment layer are likely to have higher exposure, and determination of the origin of exposure is complex due to movement (Larson et al., 2018).

Work in free-ranging waterfowl is limited, with some studies in wild birds showing relatively low PFAS concentrations, such as mallard and pintail (*Anas acuta*) ducks in Japan (**Table S3**) (Taniyasu et al., 2003). High concentrations of PFAS have been found in liver and muscle samples of ducks hunted in contaminated Australian wetlands (Sharp et al., 2020). Pacific Black (*Anas superciliosa*) and Grey Teal (*Anas gracilis*) ducks from a wetland near a military base had PFOS and PFHxS detected in all liver and muscle samples, with PFOS concentrations approximately 100 times higher than PFHxS (**Table S3**; Senversa, 2018). These concentrations are similar to those seen in liver and serum from great tits (*Parus major*) roosting near a fluorochemical plant in Belgium (Dauwe et al., 2007). Almost all concentrations of PFAS other than PFOS and PFHxS (including PFOA) were below the LOR (0.0002 mg/kg) (Senversa, 2018).

A subsequent state-wide survey of 4 species of duck (Pacific Black duck, Grey Teal, Chestnut Teal (*Anas castanea*) and Pink-eared duck (*Malacorhynchus membraneaceus*)) was conducted across 19 wetlands in Victoria, Australia in 2018 and showed relatively lower tissue concentrations (**Table S3**), but resulted in an advisory notice to avoid or minimise consumption of ducks hunted at three wetlands (EPA, 2019; Sharp et al., 2020). PFOS + PFHxS were detected in 95% of liver samples, whereas PFOA was detected in 29% (Sharp et al., 2020). Relatively higher PFAS concentrations were observed in water and sediments at wetlands near sources of contamination, and even though PFAS concentrations in duck tissues did not necessarily correlate with the environmental samples at all sites, only ducks inhabiting wetlands near local sources of PFAS were deemed likely to pose a risk to consumers (Sharp et al., 2020). This study demonstrates the limitations of using abiotic PFAS criteria to assess risk to biota, due to the complexities of bioaccumulation, movement of animals and spatiotemporal variation (Sharp et al., 2020), which supports the need to sample animal tissues to assess exposure and effects.

5.7. Mammalian game species

Relatively high PFAS concentrations have been reported in European wild boar, with liver as the main site of accumulation. Wild boar feeding behaviour, which includes rooting in soil and access to dumpsites that often contain municipal waste, is likely to influence exposure (EFSA, 2018). Wild pigs ($n = 13$) sampled near an open waste dumping site in India showed an average PFOS concentration of 71 ± 70 (SD) µg/kg

ww in adult female liver ($n = 7$) compared to concentrations at a reference site of 19 ± 8.6 (SD) µg/kg ww ($n = 4$) (Watanabe et al., 2010).

In 2014, PFOA and PFOS in the liver of German wild boars showed an average ratio of PFOS:PFOA concentration in liver of 21:1 (**Table S3**) (Kowalczyk et al., 2018). Stahl et al. (2012) also reported maximum liver PFOA and PFOS concentrations in German wild boar that were at least an order of magnitude higher than muscle concentrations (**Table S3**). In 2019, PFOS was detected in 25% of muscle samples from wild boar collected in North West Italy at concentrations lower than those reported from Germany (**Table S3**) (Arioli et al., 2019).

Müller et al. (2011) found that tissue distribution of PFAS in caribou/reindeer (*Rangifer tarandus*) from the Canadian Arctic was similar to that observed in dairy cows. Total PFAS concentrations in muscle and kidney were both approximately one order of magnitude lower than liver (Müller et al., 2011).

A retrospective German study demonstrated a reduction in the mean PFOS concentration in roe deer (*Capreolus capreolus*) liver from 9.2 µg/kg in 2000 to 1.8 µg/kg ww in 2010 (Falk et al., 2012). The reduction of PFOA was less conspicuous than that of PFOS, but was still significant (Falk et al., 2012). Livers from chamois (*Rupicapra rupicapra*) in Austria in 2016 showed similar mean PFOS concentrations to the 2010 German roe deer samples, with a detection rate of 91% (Riebe et al., 2016). In contrast in 2019, PFOS in muscle samples from 12 roe deer, 24 chamois and 23 red-deer (*Cervus elaphus*) hunted in North West Italy were below the LOQ of 150 pg/g ww (Arioli et al., 2019).

5.8. Synthesis of findings from studies in livestock

In livestock, detrimental health effects were not reported, and are therefore assumed not to have been observed, even at high maximum observed blood plasma PFOS concentrations, including up to 0.24 mg/L in sheep (Kowalczyk et al., 2012), 0.25 mg/L in pigs (Kowalczyk, 2014) and between 2.46 mg/L (Kowalczyk et al., 2013) and 76.3 mg/L (Lupton et al., 2015) in cattle.

While the studies outlined above showed similarities in overall PFAS tissue distribution between species, there are also notable differences that vary by species, to some extent by dose and, to a lesser extent, by sex. For example, in cattle, the shorter-chain PFAS like PFHxS and PFBS have lower accumulation potential compared to the long-chain compounds like PFOS (Lupton et al., 2011, 2014), whereas in chicken eggs PFHxS showed greater accumulation potential than PFOS (Wilson et al., 2020) and ongoing exposure is likely to offer partial explanation for some observed differences. Livestock studies consistently demonstrated that following experimental exposure in cattle (Kowalczyk et al., 2013; Lupton et al., 2014; Lupton et al., 2015), pigs (Numata et al., 2014; Guruge et al., 2016) and chickens (Guruge et al., 2008; Yeung et al., 2009; Yoo et al., 2009), PFAS concentrations in muscle, likely the most commonly consumed animal product, were consistently lower than those measured in offal (primarily liver and blood, but also kidney).

The variation in elimination half-lives within and between livestock and game species is also large and studies showed that elimination generally occurs more rapidly for PFOA compared to PFOS (Table 1). PFAS elimination half-lives in pigs are longer (236 days to 1.7 years, see Table 1) than in most animals reported in the literature (Numata et al., 2014, Guruge et al., 2016). Studies in cattle showed large variation (19.2 h to 3 months, see Table 1) depending on the PFAS chemical and dose, and the age and sex of the study subjects (Vestergren et al., 2013; Lupton et al., 2015; Lupton et al., 2011). Avian elimination of PFAS is more rapid (3.5–160 days, see Table 1) than mammals and in laying hens, PFAS transfer to eggs is almost exclusively as PFOS in the yolk (Wilson et al., 2020).

Experiments in sheep, chickens and steers showed an initial increase of PFOS concentrations in plasma after dosing stopped (Kowalczyk et al., 2012; Lupton et al., 2011; Yeung et al., 2009), indicating slow excretion, enterohepatic circulation, and continued release of accumulated

chemical from other organs prior to steady state being achieved and the commencement of depuration. However, PFAS concentrations in these species began (i.e. within days (Yeung et al., 2009) to weeks (Kowalczyk et al., 2012)) relatively predictable declines soon after exposure ceased, providing a management opportunity for depuration with uncontaminated feed and water.

Excretion of some PFAS into eggs was demonstrated to be a major excretory pathway for laying hens, explaining the differences between elimination half-lives in female (Wilson et al., 2020) and male chickens (Tarazona et al., 2015). However, after PFAS exposure ceased in laying hens, concentrations in eggs declined to undetectable concentrations within several weeks (Wilson et al., 2020). While PFAS excretion in cattle and sheep milk has been demonstrated, PFAS is not preferentially excreted or concentrated in milk (van Asselt et al., 2013; Kowalczyk et al., 2012; Kowalczyk et al., 2013). For example, during the 21-day feeding period in two sheep, a total PFOS transfer into milk of ≤2% of the estimated intake dose was calculated (Kowalczyk et al., 2012).

6. PFAS in animal products - the food chain

Product sampling studies have concurred with the livestock experimental data in showing that muscle concentrations are lower than those measured in offal (see **Table S3**). While offal and blood are not very popular diet components, the propensity for PFAS to accumulate in these protein rich tissues warrants particular attention (Sznajder-Katarzyńska et al., 2019). A study by Hlouskova et al. (2013) of PFAS in a small sample of various food animals from four European countries showed that the PFAS concentrations in the analyzed food commodities from terrestrial species decreased in the following order: pig/bovine liver > egg > meat > dairy products (butter). Unfortunately, most animal product testing has occurred without any knowledge of antemortem PFAS exposure concentrations.

6.1. Liver

One of the reasons for the preferential accumulation of PFAS in liver is that it is the main site of plasma albumin synthesis, and PFAS bind very effectively to plasma albumin (Lau, 2015). In a recent Chinese study, beef liver showed mean total PFAS concentrations that were over 60-fold higher than beef muscle (**Table S3**) (Wang et al., 2017). In chickens, PFOS first accumulates in the liver, after which it is redistributed into the blood and kidney for elimination (Yoo et al., 2009; Yeung et al., 2009) and elimination via eggs is also very important (Wilson et al., 2020). A comparative study of Japanese farm animals exposed to ambient concentrations of PFAS showed that chicken liver contained the highest PFOS concentrations compared to cattle, pig and goat liver (Guruge et al., 2008). In pigs, PFAS that were not measurable in other tissues were still measurable in liver, so Numata et al. (2014) suggest sampling liver in porcine monitoring programs. A Chinese study from 2010 showed the total PFAS concentrations were 30 times higher in liver from pigs compared to chickens (**Table S3**) (Wang et al., 2010b). The relative proportions of PFOA and PFOS in pig liver samples have been different across studies, with Chen et al. (2018) finding much higher concentrations of PFOA than PFOS in Taiwanese liver samples, and Wang et al. (2010b) finding the opposite in Chinese retail samples.

Recently, EFSA (2018) reported that PFOS and PFOA concentrations were particularly high for liver samples of game mammals, especially wild boar, with the maximum PFOS concentrations being two orders of magnitude higher than PFOA concentrations (**Table S3**), and PFOA concentrations in the edible offal of European farmed animals were much lower than wild boar liver (EFSA, 2018). Zafeiraki et al. (2016a) sampled livers from farmed (i.e. ambient exposure only) sheep, horses, cows, pigs and chickens collected from the Dutch market. PFOS was the only measurable PFAS and its concentration was higher in free ranging animals like cows and sheep, nevertheless measured concentrations of

PFOS in the liver samples were very low (**Table S3**) (Zafeiraki et al., 2016a).

6.2. Blood

The two tissues with the higest PFAS concentrations are the liver and the blood (Kudo, 2015), and studies outlined above in livestock have shown this proportion varies bewteen species. Experimental studies in cattle have shown PFOS to have the highest relative plasma concentrations of studied PFAS compounds (Lupton et al., 2015). In a Japanese study, mean sera concentrations of PFOS were seen in descending order in chickens > cattle > and pigs (**Table S3**) (Guruge et al., 2008). Numata et al. (2014) showed that in pigs, compared to cows and sheep, PFAS had an even higher affinity for blood over other tissues. Male chickens, when compared to dairy cows, showed a greater tendency to accumulate PFOA and PFOS in the blood, and a more rapid elimination of PFOA from blood (Kowalczyk, 2014). The affinity of PFAS compounds for blood indicates that dietary practices where blood contributes a significant portion should be evaluated as part of determining human exposure risk.

6.3. Kidney

Across experimental animal species, concentrations of PFAS are generally lower in the kidney compared to the blood and liver (Roberts, 2016), but PFHxS concentrations in kidney were relatively higher than other tissues in one dairy cattle study (Kowalczyk et al., 2013). When comparing concentrations of PFAS in different livestock tissues, primarily in pigs (Wang et al., 2010b; Xie et al., 2020) and poultry (Yoo et al., 2009), there is a pattern of preferential binding of PFOA in renal tissues, compared to blood or liver. In 20 Chinese retail samples of pork kidney in 2010, the maximum PFOA concentration was an order of magnitude higher than the maximum PFOS concentration (**Table S3**) (Wang et al., 2010b).

6.4. Eggs

Newsted et al. (2007) noted from their studies in mallard ducks (*Anas platyrhynchos*) and northern bobwhite quail (*Colinus virginianus*) that due to transfer to eggs in female birds, concentrations of PFOS measured in the liver and blood at study termination were greater in male birds compared to female birds. Zafeiraki et al. (2016b) found that PFAS concentrations in yolk were higher in home produced eggs from the Netherlands and Greece compared to supermarket eggs, which they hypothesized was due to access to soil and kitchen waste. To assess the risk of PFAS exposure to consumers from eggs laid by backyard chickens, Wilson et al. (2020) studied 119, 30-week old layers dosed with up to 300 μg/L of PFAS in water. The study showed that the vast majority of the PFAS (PFOS, PFOA, PFHxS and PFHxA) excretion in eggs is via the yolk and that once chicken PFAS exposure ceases, PFAS concentrations in the eggs laid by those chickens progressively reduce to below the Laboratory Limit of Reporting (LOR) within two to three weeks (Wilson et al., 2020). Wang et al. (2010b) also reported that close to 100% of the PFOS in the egg was distributed in egg yolk.

6.5. Milk

PFAS transfer from feed to milk has been confirmed in cattle (van Asselt et al., 2013; Kowalczyk et al., 2013) and sheep (Kowalczyk et al., 2012) and these studies showed species-specific differences in the transfer of PFAS from serum to milk. For PFOA, Kowalczyk et al. (2012, 2013) state the milk/serum concentration ratio was higher in dairy cows compared with sheep. For PFOS, the ratio in sheep was approximately 0.06, compared to 0.013 in cattle (Kowalczyk et al., 2012, 2013). Different PFAS also showed quite different milk elimination patterns in both cattle and sheep; PFOS and PFHxS were excreted in milk at

higher concentrations than PFBS and PFOA (Kowalczyk et al., 2012, 2013).

6.6. Muscle/meat

Measured concentrations of PFAS in muscle/meat are generally lower than concentrations in blood and offal. Kowalczyk et al. (2013) showed that in dairy cattle, PFOA concentrations in muscle were one hundredth of the concentrations in the liver, and PFOS concentrations in muscle were one tenth of the concentrations in the liver. In pigs, PFOS concentrations were an order of magnitude lower in pork muscle compared to liver, but PFOA concentrations were similar between these two tissues (**Table S3**) (Chen et al., 2018). In one study conducted in Australia, PFOS + PFHxS concentrations in duck breast muscle samples were approximately nine times lower than the corresponding liver concentrations (Senversa, 2018).

7. Conclusion

This review has compiled known information about PFAS in livestock and game species, as a source of dietary exposure in humans, and briefly summarised adverse health effects in experimental animal studies. Broader collection and publication of baseline data in livestock and game species is required to enable development of predictive models on the uptake and elimination of PFAS, and transfer to edible tissues. This would enable more accurate risk-based management of PFAS exposure in humans via livestock and game animals. One key gap in the literature has been that very few studies assessed if any detrimental effects on welfare or production occurred due to PFAS exposure. Thus it is suggested that future research measure both PFAS dynamics and potential detrimental health effects in livestock and game animals.

While the only conclusive evidence of health effects of PFAS in animals are from high dose studies and exposure scenarios, there remains concern globally about potential human and animal health effects of these widely distributed, persistent chemicals. Multiple studies have asserted that PFAS consumption by humans in food and water is the most significant route of exposure, and this is likely the same in livestock and game species. Applying the precautionary principle, food regulators wish to understand the potential risks to the human population from consumption of PFAS in livestock and game products.

As there are only two to five studies per livestock species published in the international scientific literature, with low sample sizes and dosing regimes that do not necessarily reflect environmental relevance, there is uncertainty with respect to the tissue distribution and clearance information. It is therefore difficult to assess human health risks associated with the consumption of livestock products with a high degree of certainty. More research into the concentrations of PFAS in livestock and game populations is required globally, to better understand the potential transfer of these chemicals into the human food chain. There are many PFAS, and PFAA precursors, which are known to be widely distributed in the environment that still require investigation in livestock and game species, and the use of total fluorine measurements could be explored. Further detailed studies into the pharmacokinetics of PFAS in livestock, and more comprehensive approaches to health assessment of exposed stock, are also necessary. In addition, assessment of new (or replacement) PFAS should continue, preferably prior to their large-scale use to ensure new PFAS chemicals are less harmful than the original longer perfluorocarbon chain compounds (e.g. PFOS and PFOA) (Briels et al., 2018).

Additional clearance and tissue distribution data in livestock are required to enable confident assessment of potential tissue concentrations via non-invasive serum sampling. Determination of serum/tissue partition coefficients enables prediction of body burdens of various PFAS from blood serum samples in various classes of stock. Such data enable appropriate management of PFAS exposed livestock. Generally, livestock will eliminate PFAS over time if the contaminated source (e.g. stock water) is removed (EPA Vic, 2020). It is important to

understand how long it takes different PFAS in different species to reduce to a level that minimises the exposure to humans consuming the animal products (EPA Vic, 2020).

Understanding concentrations of PFAS in the edible tissues of game species is also important for public health, and data currently being collected at contaminated locations will enable informed management of hunting. From an animal health perspective, further work will be needed to demonstrate whether PFAS cause toxic effects on free-living vertebrates (Costantini et al., 2019). Collection of additional data in livestock and game species (and their relevant exposure media) could also enable development of pharmacokinetic/pharmacodynamic models on the oral uptake and elimination of PFAS in different tissues, which could then be used to potentially estimate uptake and concentrations in edible tissues (van Asselt et al., 2011).

Once the transfer of PFAS through the food chain can be quantified, it will enable the effect of future pollution events on the consumer to be characterised using parameterised food chain models, which would allow the responsible authorities to take appropriate measures to ensure consumer confidence and health.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.144795.

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