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Gender differences in pharmacokinetics and tissue distribution of 3 perfluoroalkyl and polyfluoroalkyl substances in rats

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ABSTRACT

The aim of this study was to confirm and investigate the gender differences in pharmacokinetic (PK) characteristics and tissue distribution of 3 perfluoroalkyl and polyfluoroalkyl substances (PFASs) consisted of perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS) in both male and female rats. For this study, a simultaneous determination method of the 3 PFASs in rat plasma and tissues was developed and validated using a UPLC-MS/MS system. The PK parameters after a single oral or intravenous administration of the 3 PFASs in both rats were calculated using WinNonlin® software. The mean half-life of the 3 PFASs in female and male rats was in the range of 0.15–0.19 and 1.6–1.8 days for PFOA, 23.5–24.8 and 26.4–28.7 days for PFOS, and 0.9–1.7 and 20.7–26.9 days for PFHxS, respectively. The 3 PFASs were highly distributed in the liver and kidney. These results suggest that there are gender differences in the PKs for PFOA and PFHxS in rats, whereas the PFOS represented no significant gender differences except the Kp value of liver. The validated simultaneous determination method of the 3 PFASs was also within the accepted criteria of the international guidance.

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) were introduced in 1950s and have been extensively used in various industrial and commercial applications including polishes, food packaging, surfactants, fabrics, coatings for paper, fire-fighting foams, and textile surface treatments (3M, 1999). PFASs are long-chain fatty acid analogs in which the carbon–hydrogen (C–H) bonds are replaced by carbon–fluorine (C–F) bonds. Because of the strong C–F bonds, they have a strong stability to metabolic and environmental degradation (Butenhoff et al., 2004). For this reason, they are persistent and widely distributed in the environment and have been found worldwide in wildlife and the general populations (Kannan et al., 2004; Olsen et al., 2004a, 2004b; Taniyasu et al., 2003). The two most widely known PFASs are perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), and the third most frequently detected perfluorohexane sulfonic acid (PFHxS) was found in blood and milk in the general populations (Calafat et al., 2007; von Ehrenstein et al., 2009). The 3 PFASs comprised PFOA, PFOS, and PFHxS with a similar chemical structure (Fig. 1). The common chemical property is their solubility in the environmental media, and they persist in the environment because of their high stability and non-biodegradability. Numerous reports have been presented on their widespread environmental distribution, presence in human blood and wildlife samples, and toxic effects in animals (Calafat et al., 2007; Key et al., 1997; Numata et al., 2014; Taniyasu et al., 2003; von Ehrenstein et al., 2009).

The previous toxicological studies of 3 PFASs are summarized in Table 1. In rodents, the PFOA and PFOS were reported to cause neurotoxicity, hepatotoxicity, and reproductive and developmental toxicities in common (Austin et al., 2003; Lau et al., 2006). The high exposure of 3 PFASs may lead to early menopause, but the underlying mechanism is not known yet (Taylor et al., 2014).

As reported in the toxicity study, PFOA was recently replaced, and as a result, PFOA is no longer used in industry. In addition, the worldwide production of PFOS was phased out in 2002 (3M, 2012; DuPont., 2013). The bioaccumulation and toxicity of PFOS have led

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Abbreviations

$AUC_{0-\infty}$	the area under the concentration-time curve from zero to infinity
C–F	carbon-fluorine
CL	clearance
CL_R	renal clearance
C_{max}	the maximum plasma concentration
IS	internal standard
IV	intravenous
Kp	the tissue-to-plasma partition coefficient
LC-MS/MS	liquid chromatography coupled tandem mass spectrometry
LLE	liquid–liquid extraction
LLOQ	the lower limit of quantification
MPFHxS	sodium perfluoro–1–hexane[$^{18}O_2$]sulfonate
MPFOA	Perfluoro–n–[1,2,3,4–$^{13}C_4$]octanoic acid
MPFOS	sodium perfluoro–1– [1,2,3,4–$^{13}C_4$]octanesulfonate
PBPK	physiologically-based pharmacokinetic model
PFASs	perfluoroalkyl and polyfluoroalkyl substances
PFHxS	perfluorohexane sulfonic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
PK	pharmacokinetic
PPT	protein precipitation
SPE	solid–phase extraction
$t_{1/2}$	the elimination half-life
T_{max}	the time to reach C_{max}
UPLC-MS/MS	ultra-liquid chromatography coupled tandem mass spectrometry
V_d	the volume of distribution
$X_{u(t)}$	the amounts of unchanged drug excreted into the urine from time zero to t
$X_{f(t)}$	the amounts of unchanged drug excreted into the feces from time zero to t

to regulatory restrictions on its use in the European Union (EU, 2006), the United States (USEPA, 2002), and the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2009). Although the production of several PFASs has reduced in the last decade, it has been still detected in wildlife and human populations around the globe (Houde et al., 2006). The main sources of exposure in the general population were found in food and water in contaminated areas (Hoffman et al., 2011; Tittlemier et al., 2007). Previous biomonitoring results showed the presence of PFASs in the serum of children and adults (Calafat et al., 2006; Kubwabo et al., 2004; Taniyasu et al., 2003) and cord blood (Arbuckle et al., 2013) and breast milk (Fromme et al., 2010). PFASs are being detected in humans worldwide.

A few pharmacokinetic studies of the 3 PFASs have been previously published. The elimination half-lives of 3 PFASs are listed in Table 1. The plasma elimination half-lives of the 3 PFASs were different among species, and those in humans were longer than in the experimental animals. The PFOA and PFHxS showed a significant gender difference in rats (Kudo and Kawashima, 2003; Sundstrom et al., 2012). Kerstner-Wood et al. (2003) reported that PFOA, PFOS, and PFHxS showed affinity for β-lipoproteins and were highly bound to rat plasma.

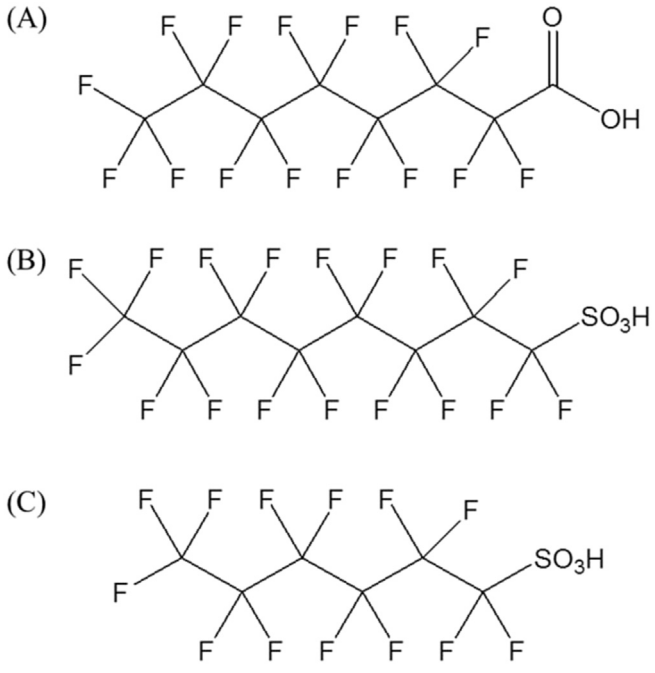

Fig. 1. Chemical structures of 3 perfluoroalkyl and polyfluoroalkyl substances (A) PFOA, (B) PFOS, and (C) PFHxS.

The tissue distribution studies of the 3 PFASs in rodents were mainly tested in the liver and kidney. Only the tissue concentration of PFOS was investigated in the liver, kidney, lung, spleen, testes, bone marrow, skin, muscle, and brain, following a single oral or intravenous (IV) administration in rats (Chang et al., 2012). PFOA was tested in the liver and kidney after a single and repeated oral dose in mice and IV dose in rats (Kudo et al., 2007; Lou et al., 2009). The tissue distribution of PFHxS except liver in rodents has not been reported up to now. Numata et al. (2014) and Lupton et al. (2014) published the tissue distributions of the 3 PFASs in pig and beef cattle. Some researchers reported that the 3 PFASs excreted through urine and feces in rat, and the urinary elimination was the main excretion route (Andersen et al., 2006; Kudo and Kawashima, 2003; Olsen et al., 2007; Sundstrom et al., 2012).

For the aforementioned reasons, in spite of their decreased use, they have been still detected in the environment, animals, and humans around the world. Even though the concentration of these 3 PFASs was low in biological samples such as plasma and tissues from rodents or humans, their long half-lives could indicate the tendency of bioaccumulation, leading to higher body burdens and associated long-term health risks (Rodriguez et al., 2009). Moreover, the gender difference of the PKs and tissue distributions of PFOA has been reported (Hundley et al., 2006; Ohmori et al., 2003; Vanden Heuvel et al., 1991). The PFHxS also showed a significant gender different PKs and liver concentrations in rats (Sundstrom et al., 2012). However, the PFOS didn't show any gender differences in the PKs in rats, mice, and monkeys (Chang et al., 2012). Therefore, the necessities for additional investigation for the tissue distributions of PFOS and PFHxS in female rats have been raised, and a direct confirmatory comparison study for the gender differences in PKs and tissue distribution of 3 PFASs in rats will be interesting.

For the disposition study of the 3 PFASs, more improved analytical method should be developed for their determination in biological samples. The recently published reports mainly used