Regulatory Toxicology and Pharmacology 59 (2011) 157–175

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model

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ARTICLE INFO

Article history:
Received 18 August 2010
Available online 17 December 2010

Keywords:
Physiologically-based pharmacokinetic modeling
PBPK
Toxicokinetic modeling
Perfluoroalkyls
Pharmacokinetics
PFOA
PFOS

ABSTRACT

Perfluoroalkyl acid carboxylates and sulfonates (PFAAs) have many consumer and industrial applications. The persistence and widespread distribution of these compounds in humans have brought them under intense scrutiny. Limited pharmacokinetic data is available in humans; however, human data exists for two communities with drinking water contaminated by PFAAs. Also, there is toxicological and pharmacokinetic data for monkeys, which can be quite useful for cross-species extrapolation to humans. The goal of this research was to develop a physiologically-based pharmacokinetic (PBPK) model for PFOA and PFOS for monkeys and then scale this model to humans in order to describe available human drinking water data. The monkey model simulations were consistent with available PK data for monkeys. The monkey model was then extrapolated to the human and then used to successfully simulate the data collected from residents of two communities exposed to PFOA in drinking water. Human PFOS data is minimal; however, using the half-life estimated from occupational exposure, our model exhibits reasonable agreement with the available human serum PFOS data. It is envisioned that our PBPK model will be useful in supporting human health risk assessments for PFOA and PFOS by aiding in understanding of human pharmacokinetics.

1. Introduction

Perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) are fully fluorinated man-made chemicals that have a wide spectrum of industrial and consumer uses. These compounds are used as surfactants in situations requiring stability towards heat and chemical degradation or other unique properties imparted by the perfluorinated chain (Lau et al., 2007). They can also be formed from the degradation (environmental or metabolic) of certain fluorinated materials (Olsen et al., 2007, 2003a). Due to the high electronegativity of the fluorine atom, the C–F bond has a significant dipole moment, imparting ionic character to the bond through partial charges; the partial charges are attractive, making the C–F bond one of the strongest in organic chemistry (Lau et al., 2007). The stability imparted to these compounds by the C–F bond is very desirable industrially; they are stable in air at high temperature, nonflammable, and not readily degraded by strong acids, bases, or oxidizers (Lau et al., 2007). The C–F bond also provides these compounds with low surface tension making them ideal surfactants (Lau et al., 2004). However, the same properties that make these compounds so useful make them resistant to breakdown by metabolism, hydrolysis, photolysis, or biodegradation and thus they can be persistent in the environment indefinitely. Industrial use of PFOA began in the late 1940s, and since then it has been estimated that cumulative global emissions are between 2400 and 5200 metric tons (Prevedouros et al., 2006). Production and use of PFOS and materials which can form PFOS were initially greater than that of PFOA, but since the phaseout of PFOS by its major manufacturer between 2000 and 2002, global production has dropped (175 metric tons in 2003) (3M, 2003).

Although exposure sources and routes for humans are not well understood, perfluoroalkyl carboxylates and sulfonates (collectively perfluoroalkyl acids or PFAAs) escape to the environment through production, manufacture, disposal, and degradation of other fluoropolymers (Andersen et al., 2008). These compounds are now widespread throughout the global ecosystem. They have been found in wildlife samples from remote ocean sites and the Arctic, although concentrations are usually greater in animals living in more populated and industrial areas (Lau et al., 2007). These compounds have also been identified in parts-per-billion levels in human serum from the general population and in parts-per-million levels for occupationally exposed workers and other populations with high exposure to these compounds (Calafat et al., 2007b; Emmett et al., 2006; Olsen et al., 2007). The long plasma

Abbreviations: PFAAs, collectively refers to perfluoroalkyl acid carboxylates and sulfonates; PBPK model, physiologically based pharmacokinetic model; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.

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doi:10.1016/j.yrtph.2010.12.004

half-lives of PFOA and PFOS (3–5 years) observed in humans is of particular concern because this indicates that they can accumulate, which may result in higher body burdens and potential adverse health effects. Possible exposure sources for humans include drinking water, dust in homes, food and food packaging, fabrics, carpeting, and cookware (Fromme et al., 2009; Ostertag et al., 2009; Sinclair et al., 2007; Skutlarek et al., 2006; Strynar and Lindstrom, 2008; Vestergren and Cousins, 2009; Washburn et al., 2005; Wilhelm et al., 2008).

The pharmacokinetic properties of PFOA and PFOS have been studied. In summary, animal studies have shown that these compounds are well absorbed orally, poorly eliminated, and not metabolized (Johnson et al., 1984; Kuslikis et al., 1992; Ophaug and Singer, 1980; Vanden Heuvel et al., 1991). They are distributed mainly to the serum, liver, and kidney, usually with liver concentrations being 3–5 times higher than serum concentrations in the rat, while liver concentrations in humans and non-human primates are only ~1.3–2 times higher than in serum (DePierre, 2009; Hundley et al., 2006; Johnson et al., 1979; Kemper, 2003; Kudo et al., 2007; Olsen et al., 2003b; Seacat et al., 2002). Distribution at steady state is mainly extracellular (Butenhoff et al., 2004a; Noker and Gorman, 2003). Both compounds have a high affinity for binding to albumin and are thus highly bound in plasma, and to a lesser extent, β-lipoproteins and liver fatty acid binding protein (Han et al., 2003; Kerstner-Wood et al., 2003; Luebker et al., 2002). Both compounds have been found in rodent fetuses as well in as umbilical cord blood of humans and in breast milk indicating that they can cross the placenta and partition into milk, exposing the fetus and neonate (Apelberg et al., 2007; Hinderliter et al., 2005; Karrman et al., 2007; Kuklenyik et al., 2004; Thibodeaux et al., 2003). The most notable aspect of PFOA and PFOS PK is that they exhibit major differences in plasma half-lives across species, and for PFOA, a sex difference in elimination is observed in rats. The elimination half-life for PFOA in female rats is 2–4 h; it is 4–6 days in male rats (Hanhijarvi et al., 1987; Kemper, 2003; Kudo et al., 2002). The gender difference in elimination is age-dependent and the slower elimination in males is observed starting around 3–5 weeks in age (Hinderliter et al., 2006). This gender difference in elimination is not observed for PFOS in rats (half-life is ~30–50 days, depending on the isomer) or mice (half-life is ~40 days) (Benskin et al., 2009; Butenhoff, 2010). Monkeys have half-lives of 21–30 days for PFOA and 4–6 months for PFOS while human half-lives are even longer for both compounds (3–5 years) (Bartell et al., 2010; Butenhoff et al., 2004a; Noker and Gorman, 2003; Olsen et al., 2007; Seacat et al., 2002). Neither the monkey nor human appears to have any major sex differences in elimination of either compound, and this appears to be true for the mouse also (Butenhoff et al., 2004a; Noker and Gorman, 2003; Olsen et al., 2007; Rodriguez et al., 2009; USEPA, 2005). The cause of the differential elimination across sexes and species has not been conclusively demonstrated, but there is evidence from studies performed both in rats and in vitro with rat and human transporters that transporters in the proximal tubule of the kidney may be responsible (Andersen et al., 2006; Kudo et al., 2002; Tan et al., 2008; Weaver et al., 2009; Yang et al., 2010, 2009).

Potential toxicities in animals have been characterized. Subchronic exposure to PFOS led to significant weight loss, reductions in serum cholesterol and thyroid hormones, and hepatotoxicity. Developmental toxicity studies with PFOS in rats, mice, and rabbits reveal reduction of fetal weight, cleft palate, and reduced neonatal survival (Lau et al., 2004). Repeated-dose studies with PFOA in rodents showed induction of liver tumors, Leydig cell tumors, and pancreatic acinar cell tumors (Andersen et al., 2008; Biegel et al., 2001; USEPA, 2005). Reproductive toxicity studies with PFOA in rodents showed increased post weaning mortality, decreased body weight, and delayed sexual maturation (Butenhoff et al., 2004b). Both compounds are agonists for peroxisome proliferator activated receptor alpha (PPAR-α) and the tumor induction has been attributed to this activation (Elcombe et al., 2010). However, PPAR-α activation may not be of human relevance because humans express much lower levels of these receptors than do rodents and human liver cells have been shown to be much less responsive to the effects of ammonium PFOA than rat liver cells (Bjork and Wallace, 2009; Lake, 2009).

Due to their prevalence and stability in the environment, toxic effects observed in animal studies, and long half-life in humans, PFAAs have drawn considerable attention from public and regulatory agencies with regard to health risks that they may present. Risk assessments and interpretation of available human data are slowed due to lack of framework to understand and estimate human pharmacokinetics. Previously, a biologically based compartmental model was developed by our group that was able to describe the complex PK of PFOA and PFOS in rats and monkeys (Andersen et al., 2006; Tan et al., 2008). The key process required to describe kinetics was resorption by renal transporters in the filtrate compartment. The goal of the present work was to develop a complete PBPK model for the monkey for PFOA and PFOS and then scale up to the human. The consistency of renal resorption to describe the kinetics in both the rat and monkey suggests the existence of a saturable, high-affinity resorption process that governs the kinetics of these compounds in other species, including humans (Tan et al., 2008). If confirmed, once the transporter protein that is responsible for renal resorption of PFOA and PFOS is identified, information on the activity of that transporter can then be used to identify susceptible sub-populations due to polymorphic variation. The human model was used to successfully simulate available data and also to predict and thus examine variability in human half-lives of PFOA. The result of these efforts is a human PBPK model with reasonable predictive ability that can be used to aid in risk assessment for perfluorinated compounds.

2. Methods

2.1. Monkey model development

The structure for the monkey model was developed from a biologically based compartmental model for PFOA and PFOS in rats and monkeys (Fig. 1) (Andersen et al., 2006; Tan et al., 2008). The compartmental model contained compartments for plasma, liver, tissues, and filtrate, and it was developed to examine the role of renal resorption through a saturable transport process that is thought to be responsible for the long half-life of PFOA and PFOS in rats and monkeys. Free chemical in the central (plasma) compartment can move to the liver compartment, tissue compartment, or be filtered by the filtrate (i.e., kidney) compartment. Once in the filtrate compartment, the chemical can be resorbed back to the plasma compartment by a saturable process with transporter maximum Tm and affinity constant Kt. This model was able to successfully describe PFOA and PFOS kinetics from oral and IV dosing in rats and monkeys, but in order to extrapolate the model to the human to aid in risk assessment, a physiologically based model with realistic tissue volumes and blood flows and physicochemical and biochemical properties of the chemical under study were needed. Thus, a physiologically-based pharmacokinetic (PBPK) model was developed for PFOA and PFOS in the monkey for use in extrapolation to the human.

2.1.1. Study designs and data – PFOA in monkeys

Pharmacokinetic data for PFOA in the monkey have been reported by Butenhoff et al. (2004a) for oral and IV dose routes. Both data sets were used to develop the current model. In the IV dosing