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Physiologically based pharmacokinetic modeling of human exposure to perfluorooctanoic acid suggests historical non drinking-water exposures are important for predicting current serum concentrations

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ABSTRACT

Manufacturing of perfluorooctanoic acid (PFOA), a synthetic chemical with a long half-life in humans, peaked between 1970 and 2002, and has since diminished. In the United States, PFOA is detected in the blood of >99% of people tested, but serum concentrations have decreased since 1999. Much is known about exposure to PFOA in drinking water; however, the impact of non-drinking water PFOA exposure on serum PFOA concentrations is not well characterized.

The objective of this research is to apply physiologically based pharmacokinetic (PBPK) modeling and Monte Carlo analysis to evaluate the impact of historic non-drinking water PFOA exposure on serum PFOA concentrations.

In vitro to in vivo extrapolation was utilized to inform descriptions of PFOA transport in the kidney. Monte Carlo simulations were incorporated to evaluate factors that account for the large inter-individual variability of serum PFOA concentrations measured in individuals from North Alabama in 2010 and 2016, and the Mid-Ohio River Valley between 2005 and 2008.

Predicted serum PFOA concentrations were within two-fold of experimental data. With incorporation of Monte Carlo simulations, the model successfully tracked the large variability of serum PFOA concentrations measured in populations from the Mid-Ohio River Valley. Simulation of exposure in a population of 45 adults from North Alabama successfully predicted 98% of individual serum PFOA concentrations measured in 2010 and 2016, respectively, when non-drinking water ingestion of PFOA exposure was included.

Variation in serum PFOA concentrations may be due to inter-individual variability in the disposition of PFOA and potentially elevated historical non-drinking water exposures.

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1. Introduction

Perfluorooctanoic acid (PFOA) is a synthetic chemical comprised of a fully fluorinated eight carbon chain with a carboxylic acid functional group. Interest in PFOA has increased since the turn of the century, in part due to evidence that PFOA is highly environmentally and biologically persistent and that it has a much longer biological half-life in humans than in laboratory animals. The discovery that people living near a PFOA manufacturing facility in the Mid-Ohio River Valley had serum PFOA concentrations higher than the general United States Population (Frisbee et al., 2009) has also increased interest. Some, but not all studies in humans have shown that exposure to PFOA may affect the developing fetus and child, including possible changes in growth (Darrow et al., 2013; Johnson et al., 2014), learning, and behavior (Stein and Savitz, 2011; Stein et al., 2014). In addition, PFOA exposure may be associated with various reproductive effects (Stein et al., 2009; Savitz et al., 2012; Darrow et al., 2013), increased cholesterol (Steenland et al., 2009b; Frisbee et al., 2010), altered immune function (Grandjean et al., 2012; Steenland et al., 2013), and increased cancer risk (Steenland et al., 2010; Steenland and Woskie, 2012; Barry et al., 2013; Nicole, 2013).

The manufacture and use of PFOA began in the 1950s, reached a peak between 1970 and 2002, and has diminished since then (DeWitt, 2015). PFOA is both hydrophobic and lipophobic (DeWitt, 2015) and has been used in the manufacture of many consumer products including fast food wrappers, pizza boxes, nonstick cookware, and stain resistant coatings used on carpets and other fabrics (ATSDR, 2016b). As a result, human PFOA exposure has historically occurred through contact with

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these products, consumption of foods and beverage packaged in these materials, and ingestion of contaminated drinking water. Additionally, precursor compounds including 1H,1H,2H,2H-perfluorodecanol (8:2 FTOH) have been shown to degrade to form PFOA (Dinglasan et al., 2004). Therefore, past exposure to 8:2 FTOH could also result in the accumulation of PFOA in the serum (Henderson et al., 2007). As production of PFOA and its precursors has decreased in the United States, PFOA serum concentrations measured in the general United States population have decreased (Kato et al., 2011), indicating that these exposures have also decreased over time.

PFOA is highly stable, not readily degraded by strong acids or oxidizing agents, and does not undergo photolysis (DeWitt, 2015). As a result, PFOA does not biodegrade in the environment (Prevedouros et al., 2006). Although PFOA and its precursors are no longer manufactured or used in the United States, many communities are still exposed as a consequence of persisting environmental contamination that occurred when the chemical was made, used, or disposed of (Frisbee et al., 2009). While exposures to PFOA via contact with consumer products appear to be decreasing, PFOA and other per- and polyfluoroalkyl substances (PFAS) are regularly detected in municipal drinking water supplies, private drinking water wells, and recreational waters located in areas where PFAS were manufactured or used (Holzer et al., 2008; ATSDR, 2013; Winquist et al., 2013; USEPA, 2016).

PFOA is readily absorbed in the gastrointestinal tract (Butenhoff et al., 2004b; Andersen et al., 2006), highly bound to human serum albumin (Wu et al., 2009; Salvalaglio et al., 2010), not metabolized (Ophaug and Singer, 1980; Butenhoff et al., 2004a; Kennedy et al., 2004; Fasano et al., 2006), and excreted unchanged primarily via the kidneys (Han et al., 2012). The biological half-life of PFOA is much longer in humans (2–4 years) than in rats (2 h–6 days) (Butenhoff et al., 2004b; Andersen et al., 2006; Fasano et al., 2006; Olsen et al., 2007; Lou et al., 2009; Bartell et al., 2010; Tatum-Gibbs et al., 2011). This is thought to be the consequence of species-dependent differences in hormonal regulation of organic anion transporters (OATs) in the proximal tubule cells of the kidney. In vitro studies have demonstrated that OAT1 (*Slc22a6*) and OAT3 (*Slc22a8*) mediate transport of PFOA through the basolateral membrane of the proximal tubule cells and facilitate renal excretion (Nakagawa et al., 2007). OAT4 (*Slc22a11*) and urate transporter 1 (URAT1, *Slc22a12*) have been shown to mediate transport of PFOA through the apical membrane of the proximal tubule cells and to facilitate the reabsorption of PFOA back into the blood (Nakagawa et al., 2009; Yang et al., 2010).

Because PFOA clearance from the serum is very slow in humans, past exposures may be an important determinant of current serum concentrations. Exposure to PFOA via contaminated drinking water is well characterized in many communities (Holzer et al., 2008; Frisbee et al., 2009; Bartell et al., 2010; USEPA, 2016). However, data on PFOA exposure via air, dust, and food are sparse, in part due to the analytical challenges of measuring trace amounts of PFOA in environmental media (Lorber and Egeghy, 2011). Thus characterization of past non-drinking water exposure to PFOA is challenging. Previous efforts include "forward-based" approaches in which concentrations are measured in environmental media and combined with contact rates to estimate intake (Fromme et al., 2009), and market basket surveys (Tittlemier et al., 2007; Ericson et al., 2008).

Pharmacokinetic modeling is a useful tool for a "backward-based" assessment of exposure to PFOA (Lorber and Egeghy, 2011) by which measured serum PFOA concentrations can be analyzed to predict past exposure levels. Previous efforts to model PFOA exposure in humans include PBPK models that describe resorption kinetics by non-specific renal transporters in a filtrate compartment (Loccisano et al., 2011; Fabrega et al., 2014). The work presented here improves upon these models through the incorporation of in vitro to in vivo informed extrapolation of experimentally measured kinetic descriptors of specific OATs that play a role in the renal excretion and reabsorption of PFOA.

Because of increased monitoring for PFAS in municipal drinking water systems and private wells, many communities have recently discovered that their drinking water supplies are contaminated with PFOA. Serum biomonitoring for PFOA and other PFAS has increased dramatically in response to demands from concerned communities. Interpretation of what these biomonitoring data suggest about mitigation needs is challenging. Through the application of Monte Carlo analysis, the PBPK model for human exposure to PFOA sheds light on the impact of historical non-drinking water PFOA exposures on current serum PFOA concentrations in two exposed populations in the United States. This work informs the interpretation of human biomonitoring data.

2. Methods

2.1. Key studies

Measured serum PFOA concentrations, collected from communities located near PFAS manufacturing facilities in North Alabama and the Mid-Ohio River Valley, were used for calibration and evaluation of the PBPK model for adult PFOA exposure.

2.2. North Alabama

ATSDR measured serum PFOA concentrations in community members living in Lawrence, Morgan, and Limestone Counties in North Alabama (ATSDR, 2013; ATSDR, 2016a). Blood samples were collected in 2010 and again in 2016. Forty-five people provided blood samples at both sampling times. Thirty-nine of these participants reported that their primary drinking water source is the West Morgan East Lawrence Municipal Water Authority. The remaining six were excluded from PBPK analysis because they reported drinking primarily bottled water, or water from a municipal system without detectable level of PFOA. The West Morgan East Lawrence Municipal Water Authority is downstream of several PFAS manufacturing facilities and PFOA has been regularly detected in finished water samples. The average PFOA concentration in finished water samples collected between 2010 and 2016 as a part of the EPA's Third Unregulated Contaminant Monitoring Rule (UCMR3) and through regular monitoring by the Alabama Department of Environmental Management was 0.04 μg/L (USEPA, 2016).

2.3. Mid-Ohio River Valley

The population living around the DuPont Washington Works facility in the Mid-Ohio River Valley is one of the most well studied PFOA-exposed human populations (Frisbee et al., 2009). Evidence suggests that the water supplies in this area were contaminated with PFOA and other PFAS as a result of industrial releases from the Washington Works facility into the Ohio River, a primary source of public drinking water (Frisbee et al., 2009). This also resulted in contamination of the water table and aquifer systems that feed private drinking water wells (Frisbee et al., 2009). Measured serum PFOA concentrations from three large studies (Emmett et al., 2006; Steenland et al., 2009a; Bartell et al., 2010) in this area were used to develop the human PBPK model for PFOA exposure described here. Given that PFOA was manufactured in the Mid-Ohio River Valley beginning in 1951 and exposure has likely occurred in this community for several decades, measured serum PFOA concentrations were assumed to be at steady state prior to the introduction of granular activated carbon (GAC) filtration in 2007. When engineered and maintained properly, GAC filtration is an effective method for removal of PFOA. Concentrations of PFOA in drinking water were below detection limits in this community following GAC filtration implementation (Bartell et al., 2010).

Bartell et al. (2010) collected blood samples from people in the Mid-Ohio River Valley between May 2007 and August 2008. Forty participants reported that the Little Hocking Water Association was their primary source of drinking water and 132 participants reported that the