Reproductive Toxicology 33 (2012) 441–451

Contents lists available at ScienceDirect

Reproductive Toxicology

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

Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys

Maria Sundström[a], Shu-Ching Chang[b], Patricia E. Noker[c], Gregory S. Gorman[c,d,1], Jill A. Hart[b], David J. Ehresman[b], Åke Bergman[a], John L. Butenhoff[b,*]

[a] Environmental Chemistry Unit, Department of Materials and Environmental Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden
[b] Medical Department, 3M Company, St. Paul, MN 55144 United States
[c] Southern Research Institute, Birmingham, AL 35255 United States
[d] Samford University, Birmingham, AL 35229 United States

ARTICLE INFO

Article history:
Received 30 March 2011
Received in revised form 16 June 2011
Accepted 22 July 2011
Available online 11 August 2011

Keywords:
Perfluorohexanesulfonate
PFHxS
Pharmacokinetics
Rats
Monkeys
Mice

ABSTRACT

Perfluorohexanesulfonate (PFHxS) has been found in biological samples from wildlife and humans. The human geometric mean serum PFHxS elimination half-life has been estimated to be 2665 days. A series of studies was undertaken to establish pharmacokinetic parameters for PFHxS in rats, mice, and monkeys after single administration with pharmacokinetic parameters determined by WinNonlin® software. Rats and mice appeared to be more effective at eliminating PFHxS than monkeys. With the exception of female rats, which had serum PFHxS elimination half-life of approximately 2 days, the serum elimination half-lives in the rodent species and monkeys approximated 1 month and 4 months, respectively, when followed over extended time periods (10–24 weeks). Collectively, these studies provide valuable insight for human health risk assessment regarding the potential for accumulation of PFHxS in humans.

1. Introduction

Perfluorohexanesulfonate (PFHxS) is one of a number of functionalized, perfluorinated compounds that have been produced for over half a century for use in specialized applications [1] as well as becoming the subject of increasing investigation with regard to environmental and health-related properties [2]. The unique properties of this and other perfluorinated surfactants, such as high surface activity, exceptional stability to degradation, density, solubility characteristics, and low intermolecular interactions, have been exploited in numerous industrial and consumer applications [3]. However, these same properties also create challenges for managing these materials in the environment.

Due to its stability and use in product applications such as fire-fighting foam and carpet, fabric, and upholstery stain protectors, it may not be surprising that PFHxS initially was found in pooled serum from the United States general population [4]. The geometric mean serum PFHxS elimination half-life in 26 retired production workers was estimated to be approximately 7.3 years (95% CI = 5.8–9.2), suggesting poor elimination of PFHxS in humans [5]. Exceptional stability to environmental and metabolic degradation together with poor elimination from the body in the case of several perfluorinated surfactants [5], including PFHxS, create a potential for accumulation and biomagnification. Accordingly, 3M Company, the major manufacturer of PFHxS in the past, phased out the production of these compounds and associated products between 2000 and 2002.

Numerous biomonitoring studies have found PFHxS widely distributed at low ng/mL concentrations in individual samples from the general population [6–12]. The National Health and Nutrition Examination Survey (NHANES), a representative sample of the United States general population aged 12 and older, reported a geometric mean serum PFHxS concentration of 1.96 ng/mL (95% CI = 1.76–2.17) for the 2007/2008 survey period [11]. This geometric mean was similar to the 1999/2000 NHANES survey-period geometric mean of 2.13 ng/mL (95% CI = 1.91–2.38) [11], suggesting that serum PFHxS concentrations in the general population

* Corresponding author at: 3M Company, Medical Department, 3M Center 220-06-W-08, St. Paul, MN 55144, United States. Tel.: +1 651 733 1962; fax: +1 651 733 9066.
E-mail addresses: maria.sundstrom@mmk.su.se (M. Sundström), s.chang@mmm.com (S.-C. Chang), noker@southernresearch.org (P.E. Noker), ggorman@samford.edu (G.S. Gorman), jahart@mmm.com (J.A. Hart), djehresman@mmm.com (D.J. Ehresman), ake.bergman@mmk.su.se (Å. Bergman), jlbutenhoff@mmm.com (J.L. Butenhoff).
[1] Formerly with Southern Research Institute; currently with Samford University.

0890-6238/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.reprotox.2011.07.004

from 1999/2000 through 2007/2008 are not decreasing or are doing so at a much lower rate than was observed in the same study for serum concentrations of the eight-carbon congener, perfluorooctanesulfonate (PFOS), which showed a 57% decrease in serum geometric mean concentration, consistent with its estimated mean serum elimination half-life of 4.8 years (95% CI = 4.0–5.8 years) [5]. However, the NHANES data did show a decline from the 1999/2000 geometric mean of 2.14 to 1.67 ng/mL in the 2005/2006 sampling period, a reduction of 22%, but the geometric mean increased to 1.96 in the 2007/2008 survey. Olsen et al. [7] reported an approximately 30% (0.4 ng/mL) decline in geometric mean serum PFHxS among American Red Cross blood donors from six regional blood donation centers between 1999/2000 and 2006, consistent with the NHANES data through 2006. PFHxS has been measured in cord blood [13–15] and newborn blood spots [10]. Evaluations of dried blood spot samples obtained from the Newborn Screening Program in New York State by Spliethoff et al. [10] demonstrated that the mean whole-blood concentration of PFHxS among 10 sample pools was 2.4 ng/mL in 2000, declining to approximately 1.3 ng/mL in 2007, an approximate 46% reduction in the mean value. Trend analysis produced a statistically significant decreasing trend with a halving time of 8.2 years, consistent with the serum PFHxS elimination half-life reported by Olsen et al. [5]. In a longitudinal study of serum PFHxS in men, mothers, and children from three cities in Germany [16], geometric men serum PFHxS was found to decrease in all three cities and groups in the 2-year time period spanning 2006 and 2008 with percent reductions in the geometric mean ranging from 14.3% to 41.4%.

Although the distribution of PFHxS has typically been focused on blood-based media, human milk also has been studied [17,18]. In a temporal trend study with pooled human milk samples from Stockholm, Sweden, Sundström et al. [17] reported an apparent but non-statistically significant decreasing trend of 6.1% per year in the pooled sample concentrations from 2001 through 2008, associated with a halving time of 11 years.

These biomonitoring studies may provide evidence in support of a low elimination rate for PFHxS in humans, or, they may suggest continued low-level environmental exposure, or perhaps both of these plausible explanations. Active environmental exposures to PFHxS may still exist, because PFHxS has been frequently detected in house dusts in samples collected between 2000 and 2008 [19–22]. The dust containing PFHxS potentially could originate from carpet and upholstery that were previously treated with PFHxS-containing surface protectant products. Based on a study from The Netherlands, dietary sources may also contribute to PFHxS exposure [23].

A study of children serum concentrations of PFHxS and other fluorochemicals may provide some insight into the potential role of household exposures to PFHxS. Olsen et al. [12] surveyed PFHxS serum concentrations in 598 children aged 2–12 who participated in a national multi-center study of Streptococcal group A infection between January 1994 and March 1995. In that time period, the geometric mean of the childrens' serum PFHxS was 4.5 ng/mL (95% CI = 4.1–5.1), with boys having a somewhat higher geometric mean than girls (5.3 ng/mL versus 3.4 ng/mL, respectively). The distribution of serum PFHxS in the children appeared to be bimodal, with 11% having serum PFHxS greater than 30 ng/mL, 64% of those values being for boys. Because PFHxS residues may have been present in carpet and upholstery treated for stain resistance, the authors speculated that exposure patterns unique to children, such as playing on treated surfaces, may have accounted for the apparent bimodal distribution. Higher PFHxS concentrations were reported by Kato et al. in analysis of pooled children samples from NHANES [24]. Duplicate pooled samples from the 2001/2002 NHANES were used for each of two age categories (3–5 years and 6–11 years) divided by sex into three ethnic pools (non-hispanic whites, Mexican Americans, and non-hispanic blacks). Although the pooled nature of the samples limits the ability to make inferences, the mean pooled PFHxS serum concentrations in the children were generally higher than means for pooled 2001/2002 NHANES adolescents and adults. This observation of higher values in children than adolescents and adults was also made by both Olsen et al. [12] and Kato et al. [24] for a component of carpet and fabric protection chemistry formerly manufactured before the 3 M phaseout, *N*-methyl-*N*-(2-ethoxy)-perfluorooctanesulfonamide. These observations suggest a unique exposure pattern to PFHxS for children, and exposure to carpeted or upholstered surfaces treated with formulations containing PFHxS is a potential contributing factor.

Several cross-sectional epidemiological studies have evaluated associations of serum PFHxS with various health outcomes. No association of serum PFHxS concentrations have been found with: atopic dermatitis and serum IgE in Taiwanese based on cord blood concentrations of PFHxS taken in 2004 and evaluation of serum IgE and parent-reported atopic dermatitis at 2 years of age in 2006 [15]; thyroid hormones in New York anglers [25] with samples taken between 1995 and 1997 and in pregnant women from Edmonton, Alberta, Canada in a case–control study from 2005 to 2006 [26]; with maternal serum PFHxS and fetal weight and length of gestation in births from Alberta, Canada between 2005 and 2006 [27]. Stein and Savitz [28] reported a positive association of serum PFHxS concentrations in children aged 5–18 with parent- or self-reported ADHD with medication based on serum samples taken in the 2005/2006 time period (odds ratio 1.59, 95% CI = 1.21–2.08). Nelson et al. [29] found a negative association of total and non-HDL cholesterol and no associations with body size and insulin resistance with serum PFHxS based on cross-sectional analysis of NHANES data from the 2003/2004 survey period. This contrasted with positive associations with serum non-HDL cholesterol that were found for serum PFOS and perfluorooctanoate (PFOA). These studies are cross-sectional in nature and none have identified clear, causal associations of serum PFHxS with health outcomes in humans. Furthermore, none of these investigators has followed up with methodologically superior epidemiological study designs.

In contrast to its eight-carbon congener, PFOS, which has been extensively studied for potential health effects [2], there are only a few published studies related to the potential toxicological properties of PFHxS. In a study designed to investigate potential reproductive, developmental, systemic toxicological, and neurological responses, Butenhoff et al. [30] exposed male and female rats to potassium PFHxS by oral gavage at dose levels of 0, 0.3, 1, 3, and 10 mg/kg-d for 2 weeks prior to mating and during mating, gestation, and lactation (postnatal day 22) for parental females as well as during mating and through study day 42 for males (6 weeks). The F1 offspring were sacrificed on postnatal day 22 at the end of weaning. There were no treatment-related effects in maternal rats or their offspring. In males, notable effects included increased liver-to-body weight and liver-to-brain weight ratios, centrilobular hepatocellular hypertrophy, hyperplasia of thyroid follicular cells, and decreased hematocrit. The mean serum PFHxS concentrations in males across the PFHxS dose levels ranged from 44 μg/mL at 0.3 mg/kg to 201 μg/mL at 10 mg/kg. In pooled pup serum from post natal day 22, serum PFHxS concentrations ranged from 9 μg/mL at 0.3 mg/kg to 94 μg/mL at 10 mg/kg. At the end of gestation, maternal serum PFHxS ranged from 3 μg/mL at 0.3 mg/kg to 60 μg/mL at 10 mg/kg. These serum concentrations were at least three orders of magnitude higher than the geometric mean values reported for human general populations. PFHxS has been demonstrated as an agonist for both the human and the mouse forms of the xenosensor nuclear receptor NR1C1 (peroxisome proliferator activated receptor alpha, or PPARα) [31]. Therefore, the hepatic hypertrophic effects observed in the study by Butenhoff et al. likely resulted from activation of