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Elimination kinetics of perfluorohexanoic acid in humans and comparison with mouse, rat and monkey

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HIGHLIGHTS

- Elimination half-life of PFHxA determined from blood of ski wax technicians.
- Geomean human elimination half-life of PFHxA is 32 d (range 14–49 d).
- Elimination half-life of PFHxA in mammalian species is proportional to body weight.
- Rate of PFHxA elimination from mammals is useful for subsequent risk assessment.

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ABSTRACT

Major fluorinated chemical manufacturers have developed new short-chain per- and polyfluorinated substances with more favorable environmental, health and safety profiles. This study provides the first evaluation of the elimination half-life of perfluorohexanoic acid (PFHxA) from the blood of humans. PFHxA biomonitoring data were obtained from a recently published study of professional ski wax technicians. These data were analyzed to provide estimates of the apparent half-life of PFHxA from humans, and comparisons were made with kinetic studies of PFHxA elimination from mice, rats and monkeys. The apparent elimination half-life of PFHxA in highly exposed humans ranged between 14 and 49 d with a geomean of 32 d. The half-lives of PFHxA in mice, rats, monkeys and humans were proportional to body weight with no differences observed between genders, indicating similar volumes of distribution and similar elimination mechanisms among mammalian species. Compared to long-chain perfluoroalkyl acid analogs, PFHxA is rapidly cleared from biota. The consistent weight-normalized elimination half-lives for PFHxA in mammalian species indicates that results obtained from animal models are suitable for establishment of PFHxA benchmark dose and reference dose hazard endpoints for use in human risk assessments.

1. Introduction

Long-chain perfluoroalkyl acids (PFAAs) such as perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorooctanoic acid (PFOA) have been widely found in the environment and in humans from both their direct use and from precursor substances that degrade to form them (OECD, 2010; Buck et al., 2011). Leading global fluorinated chemical manufacturers have committed to work toward the elimination of long-chain PFAAs (i.e., perfluoroalkyl sulfonic acids with $\geqslant$6 perfluorinated carbons or perfluoroalkyl carboxylic acids with $\geqslant$7 perfluorinated carbons) and their potential precursors (USEPA, 2010). New products have been developed based on shorter-chain per- and poly-fluoroalkyl substances that have a more favorable environmental, health and safety profile (Chengelis et al., 2009a; Loveless et al., 2009; Olsen et al., 2009; Iwai, 2011) and have been approved by regulators (Ritter, 2010; Cronkhite, 2012). A key attribute of these new short-chain substances is their rapid rate of elimination from biota including humans which results in very low or non-detectable concentrations in blood and renders these substances non-bioaccumulative.

PFAAs such as perfluorocarboxylic acids (PFCAs, e.g., $C_nF_{2n+1}COOH$) and perfluoroalkane sulfonates (PFSAs, e.g., $C_nF_{2n+1}SO_3^-$) are generally recognized to be stable under normal environmental and biological conditions (Liou et al., 2010). The widespread detection of persistent long-chain PFCAs and PFSAs such as PFOA, PFOS and PFHxS in human blood reflects the net result of the competitive rate of uptake via various routes of exposure and the

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subsequent rate of bioelimination. PFOA, PFOS and PFHxS are reported to have geomean elimination half-lives of 3.5 years, 4.8 years and 7.3 years, respectively in humans (Olsen et al., 2007). In contrast to the long systemic elimination half-lives determined for PFOA, PFOS and PFHxS, short-chain PFAAs, such as perfluorobutanoic acid (PFBA), perfluorobutane sulfonate (PFBS) and perfluorohexanoic acid (PFHxA) rapidly eliminate from blood, plasma and serum of mammals (e.g., monkey, rat and mouse) with no appreciable gender differences (Chang et al., 2008; Olsen et al., 2009; Gannon et al., 2011). Significant kinetic differences between long and short chain PFAAs in uptake and elimination have also been observed in aquatic studies with the conclusion that short-chain PFAAs neither bioconcentrate nor bioaccumulate in fish (Martin et al., 2003b,a; Conder et al., 2008).

In biomonitoring studies of the general human population, short-chain PFAAs such as PFBA, PFBS and PFHxA have been included as analytes but are rarely detected (Kato et al., 2011; Olsen et al., 2012). In more highly exposed populations (e.g., due to local contamination or workplace exposure), rapid elimination half-lives of PFBA and PFBS have been calculated (Olsen et al., 2009). Recently, a biomonitoring study was conducted on a group of ski wax technicians who were highly exposed to PFAAs and potential PFAA precursors during multiple World Cup racing seasons (Nilsson et al., 2010a,b, 2013). The analytes in this study included PFHxA, making this the first biomonitoring study useful for evaluation of the elimination half-life of this PFCA from human blood.

The objective of this paper is threefold: to provide an overview of the current human biomonitoring data for perfluorohexanoic acid (PFHxA, CAS 307-24-4) in blood, plasma and serum; to calculate the elimination half-life of PFHxA from humans; and to compare the human elimination half-life of PFHxA with the values observed in three other mammalian species: mice, rats, and monkey. This is the first study to calculate the elimination half-life of PFHxA from humans and to compare the results with other mammalian species.

2. Current observations of PFHxA in human blood

2.1. Biomonitoring of PFHxA

Over the past decade, human blood biomonitoring for perfluoroalkyl acids (PFAAs) has broadened from a predominant focus on PFOS and PFOA to evaluation of a wide range of corresponding homologs and potential precursors. Many recent studies have included analysis of short-chain PFCAs including PFHxA in human blood. Published biomonitoring results for PFHxA in human blood are summarized in Table 1. These results include concentrations observed in the general population in Europe, Asia and North America as well as concentrations reported in more highly exposed individuals who were occupationally exposed or lived in communities adjacent to manufacturing sites.

With few exceptions, PFHxA concentrations in large-scale biomonitoring surveys of the general population are low with median plasma or serum values at or below typical method limit of quantification (LOQ) values of 0.05–0.10 ng mL^{-1}. PFHxA concentrations in this range are 40–400 times lower than the biomonitoring concentrations for PFOA and PFOS which are currently reported to have median values of 4 ng mL^{-1} and 21 ng mL^{-1}, respectively, in the general population of North America (Kato et al., 2011). Biomonitoring of PFHxA has not been routinely included in the CDC National Health and Nutrition Examination Survey (NHANES) due to the low potential for detecting significant PFHxA concentrations in human blood (Calafat, A., personal communication).

In a biomonitoring study of over 60 000 members of a community adjacent to a manufacturing facility, the median PFHxA serum concentration was 0.5 ng mL^{-1} with 47% of the population having no detectable plasma concentration (i.e., less than the LOQ of 0.05 ng mL^{-1}) (Frisbee et al., 2009). In contrast, the median serum PFOA concentration in this same study was 28 ng mL^{-1} with detectable concentrations in 99.9% of the population (Frisbee et al., 2009).

2.2. Normalization of biomonitoring results

One important note should be made when comparing data from various PFCA biomonitoring studies. PFCAs primarily bind to proteins present in the plasma or serum fraction of blood with typical bound fractions of approximately 99% for PFHxA, PFOA and PFOS (Bischel et al., 2011). Since hematocrit values for adults are typically 42–45%, PFCA concentrations in plasma or serum are approximately twice as high as concentrations in blood. Therefore, comparisons of biomonitoring results for PFHxA should include appropriate consideration of the specific blood fraction included in the analysis. Fortunately, kinetic calculations within a single study are not affected by the specific blood fraction in which PFHxA is reported (i.e., in whole blood, in serum or in plasma) enabling direct comparison across studies.

3. Design and conduct of biomonitoring study of ski wax technicians

Due to the typically low PFHxA background concentrations in human blood (i.e., <LOQ or <LOD), it is difficult if not impossible to accurately calculate bioelimination half-life values from biomonitoring studies of the general population. However, a unique study of ski wax technicians who were occupationally exposed to PFAAs and potential precursors was recently published (Nilsson et al., 2010a,b, 2013). The temporal PFHxA biomonitoring data from ski wax technicians provide a valuable multi-year data set that may be used to calculate values for the apparent elimination half-life of PFHxA from humans.

3.1. Study design

Blood samples ($n = 94$) were collected from 11 male professional ski wax technicians at 11 World Cup events in Cross Country skiing during the period 2007–2011. The technicians applied fluorinated ski wax for approximately 30 h a week during each skiing season which lasts from December through March. Blood samples were taken periodically at the end of the working day during ski season and then monthly from April to August 2008 when the technicians were not working with ski wax. Before study initiation, a written informed consent was received from all participants and the study protocol was approved by the ethical vetting board of Uppsala, Sweden (Reference No. Dnr 2010/056).

3.2. Chemical analysis

Details of the analytical procedures used to detect a suite of per- and poly-fluoroalkyl chemicals including PFHxA in periodic blood samples from the ski wax technicans have previously been published (Nilsson et al., 2010b). A summary of this information, including chemical sources, extraction and analytical methodology and quality assurance/control steps are provided in Supplementary Material (SM).