Evaluation of the Short-term Clearance of Perfluorooctanoic Acid (PFOA) in a Clinical Trial Using a PBPK Model and Markov Chain Monte Carlo Analysis


1) Ramboll Environ, RTP, NC; 2) Independent Consultant, Chapel Hill, NC; 3) Medical Department/Epidemiology, 3M, St. Paul, MN; 4) CXR Biosciences, Dundee, United Kingdom; 5) The Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; 6) ScitoVation, LLC, RTP, NC

Abstract
Several studies have estimated a terminal half-life for the urinary clearance of perfluorooctanoic acid (PFOA) in the range of 2-4 years; however, the short-term half-life of PFOA has not been previously reported. In this study, single- and repeated-dose pharmacokinetic data from a human clinical trial with 50 patients being treated for cancer (cXR clinical) was analyzed using a physiologically based pharmacokinetic (PBPK) model in a Markov chain Monte Carlo (MCMC) analysis. The MCMC approach allowed for incorporation of prior knowledge about PFOA kinetics and a hierarchical structure accounting for inter-individual variability. The median age of the patients in the trial was 63 with a minimum of 36 and maximum of 74. The half-life in these patients had a mean of 0.13 yrs with a range of 0.013 to 0.8 yrs, significantly shorter than estimates of the terminal half-life derived from chronic exposures. The relationship of PFOA levels to age was suggestive of a significant departure from linearity for doses ranging from 50 to 1200 mg/day for up to 6 weeks. Only a small portion of the variance in the data was accounted for by GFR, suggesting that filtration is not as influential as renal excretion in the short-term clearance of PFOA. Based on this finding, the calibration was designed to refine the most sensitive parameters in the model, including the maximum velocity and affinity constant for renal reabsorption and the free fraction in plasma.

Introduction
A significant uncertainty identified during the development of the human PFOA model (Loccisano et al., 2012) was the existence of divergent estimates of the half-life of PFOA. While kinetic data are available to support estimation of the half-life in experimental species, the data for humans are much less certain. The principal half-life studies in humans was an assessment based on the decrease in serum concentration in retired workers (Olsen et al., 2008). However, the study was particularly valuable for estimating both the fraction of kidney blood flow and the effective filtration rate is approximately equal to GFR.

Methods
• Loccisano et al. (2011) adult human model modified to fit the time-course shape of the 50 mg dose in CXR
• 2 compartment pseudo intestinal model used for oral uptake
• TMC, KT, KURINEC were visually to fit the plasma and urine from CXR clinical trial - mean value used for calibration
• Fractional blood flows were constrained to unity by dividing the fractional blood flow for each tissue by the sum of all fractional blood flows
• Tissue volumes were constrained to sum to 86% BW representing perfused tissue

PBFOA PBPK Model
- Primary objective to determine the safety, toxicity, dose limiting toxicity (DLT), and maximum tolerated dose (MTD) of TMC 1000
- Male and female patients with advanced solid tumors that are refractory to standard therapy or no standard therapy exists
- Six weekly oral doses of 50, 150, 200, 300, 450, 650, 750, 950, or 1000 mg with 3 patients administered a single 50 mg or dose
- Plasma conc. measured at 2, 3, 4, 24, and pre-dose each week
- 24 hour urine collected weekly on day of dosing for 650 mg (1 patient) to 1000 mg (12 patients) dose groups

Results

Table 1. Prior distributions for MCMC analysis of the CXR Database

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Label</th>
<th>Mean</th>
<th>CV</th>
<th>Shape</th>
<th>Scale</th>
<th>Lower</th>
<th>Upper</th>
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<tbody>
<tr>
<td>Maximum rate of resorption (µg/h/BW0.75)</td>
<td>TMC</td>
<td>2900.0</td>
<td>1253; 6925</td>
<td></td>
<td></td>
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<tr>
<td>Affinity for resorption (µg/L)</td>
<td>KT</td>
<td>85.4; 145.8</td>
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<tr>
<td>Fraction Unbound in plasma</td>
<td>Free</td>
<td>0.02; 0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraction of Kidney Blood Flow</td>
<td>FracFil</td>
<td>0.237; 0.26</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Figure 1. PFOA PBPK model schematic.

Figure 2. Simulation of measured PFOA plasma concentrations in 4 subjects using 500 iterations of the MCMC chains for each subject (Blue line = mean, Green lines = 95% CI, Red line = Loccisano model).

Figure 3. Simulation of measured mass of PFOA excreted in urine of 2 subjects using 500 iterations of the MCMC chains for each subject (Red line = Loccisano model).

Figure 4. Histogram of the half-life distribution from the MCMC analysis of the cXR clinical study (0.1 mg dose bolus dose with half-life estimate in 3000 days; 3 iterations of a posterior distribution for each of the 43 subjects used to generate the frequency plot).

Conclusions
• Results from the calibration of the human PFOA model clearance parameters greatly improved the overall model fit to the cXR clinical database.
• The CXR study data was highly informative for the human TMC and KT for resorption because plasma data were collected in both linear and non-linear regions of the dose-response.
• The maximum half-life from the 0.1 mg bolus dose was 1.5 weeks (95% CI: 1.0-2.4 weeks). This half-life for short-term clearance appears to be lower than the terminal half-lives derived from epidemiological studies, although based on confidence intervals the difference is not statistically significant.

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