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A comparison of the pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans

Geary W. Olsen[a,*], Shu-Ching Chang[a], Patricia E. Noker[b], Gregory S. Gorman[b], David J. Ehresman[a], Paul H. Lieder[a], John L. Butenhoff[a]

[a] Medical Department, 3M Company, St. Paul, MN 55144-1000, United States
[b] Southern Research Institute, Birmingham, AL 35255-5305, United States

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ABSTRACT

Materials derived from perfluorobutanesulfonyl fluoride (PBSF, $C_4F_9SO_2F$) have been introduced as replacements for eight-carbon homolog products that were manufactured from perfluorooctanesulfonyl fluoride (POSF, $C_8F_{17}SO_2F$). Perfluorobutanesulfonate (PFBS, $C_4F_9SO_3^-$) is a surfactant and potential degradation product of PBSF-derived materials. The purpose of this series of studies was to evaluate the pharmacokinetics of PFBS in rats, monkeys, and humans, thereby providing critical information for human health risk assessment. Studies included: (1) intravenous (i.v.) elimination studies in rats and monkeys; (2) oral uptake and elimination studies in rats; and (3) human serum PFBS elimination in a group of workers with occupational exposure to potassium PFBS (K^+PFBS). PFBS concentrations were determined in serum (all species), liver (rats), urine (all species), and feces (rats). In rats, the mean terminal serum PFBS elimination half-lives, after i.v. administration of 30 mg/kg PFBS, were: males 4.51 ± 2.22 h (standard error) and females 3.96 ± 0.21 h. In monkeys, the mean terminal serum PFBS elimination half-lives, after i.v. administration of 10 mg/kg PFBS, were: males 95.2 ± 27.1 h and females 83.2 ± 41.9 h. Although terminal serum half-lives in male and female rats were similar, without statistical significance, clearance (CL) was significantly greater in female rats (469 ± 40 mL/h) than male rats (119 ± 34 mL/h) with the area under the curve (AUC) significantly larger in male rats (294 ± 77 μg·h/mL) than female rats (65 ± 5 μg·h/mL). These differences were not observed in male and female monkeys. Volume of distribution estimates suggested distribution was primarily extracellular in both rats and monkeys, regardless of sex, and urine appeared to be a major route of elimination. Among 6 human subjects (5 male, 1 female) followed up to 180 days, the geometric mean serum elimination half-life for PFBS was 25.8 days (95% confidence interval 16.6–40.2). Urine was observed to be a pathway of elimination in the human. Although species-specific differences exist, these findings demonstrate that PFBS is eliminated at a greater rate from human serum than the higher chain homologs of perfluorooctanesulfonate (PFOS) and perfluorohexanesulfonate (PFHxS). Thus, compared to PFOS and PFHxS, PFBS has a much lower potential for accumulation in human serum after repeated occupational, non-occupational (e.g., consumer), or environmental exposures.

1. Introduction

Materials derived from perfluorobutanesulfonyl fluoride (PBSF, $C_4F_9SO_2F$) have been introduced by the 3M Company as replacements for its eight-carbon homolog products that were manufactured from perfluorooctanesulfonyl fluoride (POSF, $C_8F_{17}SO_2F$). 3M phased out of manufacturing POSF-based materials after a metabolite and environmental degradation product, perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$), was found to be widespread in human populations and wildlife (Butenhoff et al., 2006; Houde et al., 2006). Hydrolysis of POSF and metabolic and environmental degradation of N-alkyl derivatives of perfluorooctanesulfonamide, precursors used in various commercial and consumer application technologies, can lead to the formation of PFOS (Xu et al., 2004, 2006; Schultz et al., 2006; Schröder, 2003). Similarly, the N-alkyl derivatives of perfluorobutanesulfonamides are used in various applications including fabric, carpet, and upholstery protectants,

* Corresponding author at: Medical Department, 3M Company, 3M Center 220-06-W-08, St. Paul, MN 55144, United States. Tel.: +1 651 737 8569; fax: +1 651 733 9066.
E-mail addresses: gwolsen@mmm.com (G.W. Olsen), s.chang@mmm.com (S.-C. Chang), noker@southernresearch.org (P.E. Noker), gorman@southernresearch.org (G.S. Gorman), djehresman@mmm.com (D.J. Ehresman), phlieder@mmm.com (P.H. Lieder), jlbutenhoff@mmm.com (J.L. Butenhoff).

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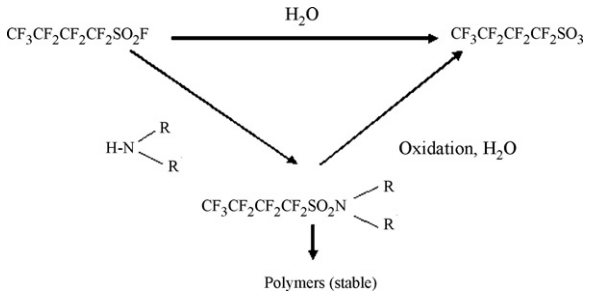

Fig. 1. Outline of the production of PBSF-based materials.

and surfactants. Perfluorobutanesulfonate (PFBS, $C_4F_9SO_3^-$) would be expected to be formed from comparable pathways from PBSF and N-alkyl derivatives of perfluorobutanesulfonamides (Fig. 1). Atmospheric degradation of N-methyl perfluorobutanesulfonamidoethanol has been shown to produce among other degradation products, PFBS (D'eon et al., 2006).

PFOS has a serum elimination half-life of approximately 7 days in rats (Johnson et al., 1979a), a mean of 132 ± 13 days (SD) days in male monkeys and 110 ± 26 days in female monkeys (Noker and Gorman, 2003a), and a geometric mean of 1751 days [95% confidence interval (CI) 1461–2099] days in humans (Olsen et al., 2007). These species-specific differences in serum elimination half-lives have been hypothesized to be governed by a saturable renal resorption process (Andersen et al., 2006). On the other hand, PFBS is likely to have a much faster serum elimination rate in these species due to its shorter perfluorinated chain and/or higher percentage of free PFBS concentration in serum than compared to PFOS (Kerstner-Wood et al., 2003).

To date, only mild effects have been observed in repeat-dose studies with PFBS in rats at relatively high dose levels compared to PFOS. In a 90-day study of potassium PFBS (K^+PFBS) in rats by oral gavage, observed effects included decreased red blood cell count, hemoglobin, and hematocrit at 200 and 600 mg/kg and, in kidneys, minimal to mild papillary/medullary epithelial tubular and ductal hyperplasia in addition to limited interstitial edema and focal necrosis (Lieder et al., 2009). As may be expected due to its structure and chemical properties, PFBS did not cause mutations, chromosomal aberrations, or contact sensitization in standard test systems (Paul Lieder, personal communication).

The differences in toxicological data between PFOS and PFBS suggest that PFBS might have more rapid elimination kinetics. We undertook a series of studies to: (1) determine the extent of urine and fecal elimination of PFBS in rats after administration of single intravenous (i.v.) and oral doses; (2) estimate the pharmacokinetic parameters of PFBS in rats after single intravenous (i.v.) and oral doses; (3) estimate pharmacokinetic parameters of PFBS in cynomolgus monkeys after a single i.v. dose; and (4) estimate the serum elimination half-life of PFBS among workers who manufactured its potassium salt.

2. Materials and methods

2.1. Overview

Studies were completed over a 6-year time frame in the following chronological order: monkeys, humans (pilot and main study), and rats. Analytical methods changed by time period of the study. Analyses were completed in two different bioanalytical laboratories, depending on the study segment. Both laboratories were experienced in the analysis of perfluorinated chemistries; however, no interlaboratory validation studies were conducted between the laboratories. Study samples were analyzed by high performance liquid chromatography mass spectrometry (LC–MS) methods.

The cynomolgus monkey study was completed at Southern Research Institute laboratories using an Applied Biosystems-Sciex model API 3000 mass spectrometer (Applied Biosystems/MDS-Sciex Instrument Corporation, Foster City, CA). This system was operated in the negative ion mode with parent ion (Q1) detection only. The extraction was based on an ion-pairing extraction method using a non-labeled internal standard, perfluoropentanoate (PFPnA). For PFBS, the negative ion monitored was at 299 atomic mass units (amu). For the internal standard PFPnA, the negative ion monitored was 219 amu.

The human pilot- and main-study samples were analyzed at the 3M Medical Department Bioanalytical Laboratory using a Finnigan TSQ 7000 mass spectrometer (ThermoFinnigan, San Jose, CA). This system was operated in the negative ion mode using parent ion (Q1) detection only. The extraction was based on an ion-pairing extraction method and used a non-labeled internal standard, perfluorohexanesulfonate (PFHxS). The negative ions monitored were 299 amu for the PFBS and 399 amu for the internal standard. For both phases of the human studies, the sample extraction method was based on an acidic pH primary extraction followed by a basic pH, reverse extraction method.

The rat pharmacokinetic study samples were analyzed at the 3M Medical Department Bioanalytical Laboratory using an Applied Biosystems-Sciex model API 4000 mass spectrometer. The API 4000 was operated in the negative ion mode using LC–MS/MS tandem mass spectrometry. A new solid-phase extraction (SPE) method was developed using stable-isotope-labeled PFBS [$^{18}O_2$-PFBS, $(CF_3(CF_2)_3S(^{18}O_2)O^-)$, Research Triangle Institute, Research Triangle Park, NC] as an internal standard. The transitions monitored were 299 → 80 amu with PFBS, and 303 → 84 amu with stable-labeled $^{18}O_2$-PFBS internal standard.

For the three species studied, the analytical methods had the following features in common. First, internal standards were added to all extraction tubes (samples, blanks, and controls) prior to extraction. Second, matrix-matched standard curves were prepared by spiking PFBS into the appropriate matrix. The ranges of the standard curves were from 0.5 to 500 ng/mL of PFBS. Third, overall recoveries were greater than 80% and less than 120% of theoretical for all methods employed. Fourth, when a given sample exceeded the high standard, the sample was diluted with matrix-matched material, re-extracted, and then re-analyzed such that the quantitation was accomplished within the range of the standard curve. More specific details of methods employed for analysis of the various samples follow in the appropriate sections for each species studied.

2.2. Pharmacokinetic studies in rats

2.2.1. Materials

All chemicals used in the pharmacokinetic studies in rats were reagent-grade and were purchased from Sigma–Aldrich (St. Louis, MO) or VWR (West Chester, PA). K^+PFBS (98.2% pure) was supplied by the 3M Company (St. Paul, MN).

2.2.2. Laboratory animals and animal care

Male and female Sprague–Dawley (SD) rats (8–10 weeks old, 200 g–250 g) were purchased from Charles River Laboratory (Portage, MI). All rats were housed in standard cages. Teklad Mouse/Rat Chow and tap water were provided to all rats *ad libitum* throughout the study except when fasting was required. Environmental controls for the animal room were set to maintain a temperature of 22.2 ± 1.7 °C, humidity of 30–70%, a minimum of 10 exchanges of room air per hour and a 12 h light/dark cycle. Studies were performed in 3M facilities accredited by the Association for Assessment and for the Accreditation of Laboratory Animal Care International. All procedures involving rats were reviewed and approved by the Institutional Animal Care and Use Committee. Animal care and procedures followed the U.S. Department of Health and Human Services Guide for the Care and the Use of Laboratory Animals (Institute of Laboratory Animal Resources, 1996).

2.2.3. Experimental designs

In the three rat studies described below, serum samples were obtained after blood clotting and centrifugation (2000 × *g*, 15 min). All samples taken, including serum, urine, feces, and liver, were frozen with liquid nitrogen and stored at −80 °C pending analysis for PFBS by LC–MS/MS. Dosing solution concentration and homogenicity analyses were not performed.

2.2.3.1. Urinary and fecal elimination study in rats. Male and female Sprague–Dawley rats (n = 3/sex) were given a single dose of 30 mg K^+PFBS/kg body weight by either intravenous injection (via tail vein) or oral gavage. The K^+PFBS solution was prepared in vehicle (saline or deionized water for i.v. and oral routes, respectively). Immediately after dosing, rats were placed in metabolism cages, and urine and fecal samples were collected every 24 hours (h) for 96 h post-dose. At the end of 96 h, rats were euthanized via CO_2 asphyxiation, blood (collected via abdominal aorta) and liver samples were harvested.

2.2.3.2. Intravenous dose pharmacokinetic study in rats. Male and female Sprague–Dawley jugular-cannulated rats (n = 3/sex) were given a single i.v. injection (via tail vein) of 30 mg K^+PFBS/kg body weight. The PFBS solution was prepared in saline. Interim blood samples (approximately ~0.5 mL) were collected from cannula at 0.25, 0.5, 1, 2, 4, 8, 18, and 24 h post-dose.