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3M

Deterimination of Serum Elimination Half-Lives of Ammonium Perfluorooctanoate, Perfluorooctane Sulfonic Acid, Perfluoroheaxane sulfonic acid and Total Organic Fluorine in Decatur Chemical Plant Retirees

The objective of this study is quantitate the human serum elimination half life of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA) , perfluoroohexanesulfonate (PFOS) and total organic fluorine (TOF). Blood will be collected biannually from approximately 25 retireed 3M Decatur employees for a period of 5 years. Upon collection and analysis of the third sample (baseline, 6 months and then 12 months) and thereafter, an interim draft half-life analysis report will be prepared.

PROTOCOL

Epidemiology,220-3W-05
Medical Department
3M Company
St. Paul, MN 55144

Date: October 14, 1998

Title: DETERMINATION OF SERUM ELIMINATION HALF-LIVES OF AMMONIUM PERFLUOROOCTANOATE, PERFLUOROOCTANE SULFONIC ACID, PERFLUOROHEXANE SULFONIC ACID AND TOTAL ORGANIC FLUORINE IN 3M DECATUR CHEMICAL PLANT RETIREES.

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ABSTRACT

3M manufactures products which contain chemical compounds, either as intentional components or residual impurities, that have as a parent molecule, perfluorooctane sulfonyl fluoride (POSF). These compounds may be expected to transform metabolically, to an undetermined degree, to PFOS as an end-stage metabolite. Other compounds manufactured by 3M include ammonium perfluorooctanoate (PFOA) and perfluorohexane sulfonic acid (PFHS). These molecules enter a number of product applications (e.g., surfactants, food packaging additives, polymers).

The biological elimination rates of fluorochemicals have been studied in rats, pregnant rats, female rabbits and hamsters. Biological half-lives have been calculated from the studies in rats and dogs. In addition, the half-life of serum total organic fluorine in a fluorochemical worker was estimated using serial collections of serum total organic fluorine. These studies reveal that PFOS and PFOA may persist in the body for prolonged periods, and with continuing exposure, accumulate over time in biological systems. To date, the actual elimination half-life of perfluorooctane sulfonate (PFOS), ammonium perfluorooctanoate (PFOA), perfluorohexane sulfonic acid (PFHS), and total organic fluorine (TOF) in human serum is not completely understood. The objectives of this study are to quantitate the elimination half life in human serum of PFOA, PFOS, PFHS, and TOF. These half -lives will be calculated from declines in serum fluorochemical levels in 3M Decatur Chemical Plant Retirees.

INTRODUCTION

3M manufactures products which contain chemical compounds, either as intentional components or residual impurities, that have as a parent molecule, perfluorooctane sulfonyl fluoride (POSF). These chemicals include: perfluorooctane sulfonate (PFOS), N-ethyl perfluorooctanesulfonamide, N-ethyl perfluorooctanesulfonamido ethanol, N-methyl perfluorooctanesulfonamido ethanol and chemicals derived from it, and the mixture of mono-, di- and tri [N-ethyl perfluorooctane sulfonamidoethyl] phosphates. There may be other precursors in the workplace, including perfluorohexanesulfonyl fluoride (PHSF). These molecules enter a number of product applications (e.g., surfactants, food packaging additives, polymers). These compounds may be expected to transform metabolically, to an undetermined degree, to PFOS (and PFHS) as an end-stage metabolite. Potassium perfluorooctane sulfonate ($C_8F_{17}OSO_2K^+$) is itself, a surfactant used as a wetting and foaming agent in industrial and commercial processes. (Olsen, et al., 1998)

Subchronic studies in rats and primates suggest there may be a potential for cumulative toxicity with PFOS over time with the primary effect related to metabolic wasting. These molecules have long elimination half lives in biological systems. Although the mechanism of toxicity is not fully understood, toxicity may be due to an effect on peroxisome proliferation, fatty acid metabolism, membrane function, protein synthesis and/or mitochondrial bioenergetics. (Olsen, et al., 1998)

The biological elimination rates of fluorochemicals have been studied in rats, pregnant rats, female rabbits and hamsters. Biological half-lives have been calculated from the studies in rats and dogs. In addition, the half-life of serum total organic fluorine in a fluorochemical worker

was estimated using serial collections of serum total organic fluorine. These studies reveal that PFOS and PFOA may persist in the body for prolonged periods, and with continuing exposure, accumulate over time in biological systems. To date, the actual elimination half-life of perfluorooctane sulfonate (PFOS), ammonium perfluorooctanoate (PFOA), perfluorohexane sulfonic acid (PFHS), and total organic fluorine (TOF) in human serum is not completely understood.

The objectives of this study are to quantitate the elimination half life in human serum of PFOA, PFOS, PFHS, and TOF; these half lives will be calculated from declines in serum fluorochemical levels in 3M Decatur Chemical Plant Retirees. This information is necessary in order to: 1) plan the most appropriate periodicity of medical surveillance and 2) guide medical decision making of workers from fluorochemical production facilities when those workers' serum fluorochemical levels are determined to be unsafely elevated. A benefit of this research will be to understand the natural history of fluorochemical excretion.

LITERATURE REVIEW

AMMONIUM PERFLUOROOCTANOATE (PFOA or FC-143)

Excretion rates of PFOA have been observed in rats, and found to be different by gender and route of excretion. Following single i.v. doses of ^{14}C-FC-143 (carbonyl carbon labeled) in rats, Johnson et al, found that females excreted virtually all the administered ^{14}C within 1 day. Urinary excretion for males was about 50% of the dose by day 6 and 83% by day 36. Fecal ^{14}C excretion for females was 1.5% by 3 days and for males was 5.4% by 36 days. (Johnson, et al.,

1980) Rapid urinary excretion of ^{14}C following oral doses of ^{14}C-FC-143 was also shown to occur in pregnant rats. (Johnson, et al., 1983)

Excretion rates vary by species studied. Excretion of radiolabeled PFOA was studied in four species by Dupont in 1988. Excretion as a percentage of administered dose 120 hours after dosing was in the following order; female rat, male and female rabbit and male hamster (> 99%); female hamster (60%); male rat (39%); male and female mice (21%). (Dupont, 1988) Of note, the administered dose and routes of exposure and excretion were not specified in this study report.

Rats and dogs respond to pharmacologic interventions that change PFOA excretion rate. In male rats administered single i.v. doses of ^{14}C-FC-143 (carbonyl carbon labeled) cholestyramine (4% w/w in feed) increased cumulative 15 day fecal ^{14}C excretion 9.8-fold versus controls. Total ^{14}C excretion (feces plus urine) was also enhanced, although less dramatically (84.3% of dose vs. 71.8% for controls). (Johnson, et al., 1980a; Johnson JD, et al., 1984) There is no difference between the renal clearances of ^{14}C in male and female dogs either before or after probenecid. Probenecid significantly reduces PFOA clearance in dogs. Glomerular filtration rates of PFOA were similar in rats and dogs. (Hanhijarvi, et al., 1988)

Elimination half-life has been calculated under numerous conditions in rats and dogs. The results show the same differential elimination rate in rats by gender (i.e., female > male), as well as half-life differences by route of exposure and species. Following a single oral dose of ^{14}C-FC-143 (carbonyl carbon labeled) in male rats, the plasma half-life was 4.8 days. (Johnson, et al., 1979)

In female rats administered oral or i.v. doses of ^{14}C-FC-143 (carbonyl carbon labeled), over 90% of the administered dose was recovered in the urine within the first 12 hours. The whole body elimination half-life of PFOA in male and female rats was 15 days and less than one day, respectively, following a single 4-mg/kg intraperineal dose. (Vanden Heuval, et al., 1991) (Johnson, et al., 1983; Johnson, et al., 1980) The half-life of PFOA in the liver was 60 hours for females and 210 hours for male rats. (Ylinen, et al., 1990) The decreased excretion rate (i.e., increased elimination half-life) in males is seen across at least two species: rats (as above) and dogs. The plasma half-life of PFOA was longer in male dogs (473 to 541 hours) than in females (202 to 305 hours). (Hanhijarvi, et al., 1988)

The elimination half-life appears to be similar in male rats exposed to either inhalational or dermal exposure. Following repeated inhalation exposures to FC-143 over a two-week period, blood organic fluoride levels in male rats showed a half-life of five to seven days. (Kennedy, et al., 1986) A blood half-life of five to seven days was seen following repeated dermal exposures in male rats. (Kennedy, 1985)

A calculation of the elimination half-life of an organic fluorine species has been reported in the human. The half-life of total serum organic fluorine in a fluorochemical worker who was removed from further exposure was greater than 18 months. This worker had a blood organic fluorine level of 40 parts per million over the period of one year. The worker's organic fluorine level rose to 70 parts per million for no apparent reason. The worker was then removed from the fluorochemical production area and his blood and urine samples were periodically checked for organic fluorine and PFOA over an 18-month period. A total of 18 months transpired before the

worker's blood organic fluorine level had returned to its base line of 40 parts per million. (Ubel, et al. 1980) Other estimates of serum fluorochemical half-lives have been calculated in the one thousand day range. Ψ This anecdotal account does not actually track the serum PFOA level, but rather the serum total organic fluorine (TOF) level. It was found through empirical means that 90% of the blood organic fluorine existed as PFOA. (Ubel, et al. 1980)

PERFLUOROOCTANE SULFONIC ACID (PFOS or FC-95)

Perfluorooctane sulfonic acid appears to persist in biological systems, being excreted more slowly than PFOA. Single i.v. doses (mean 4.2 mg/kg) of ^{14}C-FC-95 and 0.9% NACL were administered to male rats. By 89 days after dosing, 30.2% of the administered ^{14}C had been excreted in the urine and 12.6% had been excreted in the feces. (Johnson, et al., 1979)

Pharmacologic interventions do appear to increase the excretory rate of PFOS. Fecal and total excretion of ^{14}C were markedly increased in male rats administered Cholestyramine (about 2.7 gm/kg per day) and their diet following single i.v. doses of ^{14}C-FC-95. The results suggest that there was significant enterohepatic circulation of FC-95. (Johnson, et al., 1980a; Johnson, et al., 1984)

Much less is known concerning elimination half-life of PFOS than PFOA; only one calculation of the elimination half-life of PFOS has been attempted. The plasma elimination half-life of ^{14}C following single oral administration of ^{14}C-FC-95 (mean dose 4.2 mg/kg) to male rats was 7.5 days. (Johnson, et al. 1979a)

Ψ Mandel, J. Personal communication.

RESEARCH METHODS

The overall research design is prospective in nature, obtaining multiple serial blood samples from retirees throughout the course of a five-year period. We will track the decline in several serum fluorochemical levels in humans. The health outcomes that will be documented in this study are the half-life determinations of serum ammonium perfluorooctanoate (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHS), and serum total organic fluorine (TOF).

High-performance liquid chromatography mass spectrometry/mass spectrometry will be utilized to analyze all serum samples. The accuracy and reliability of this device will be the state of the art at the time of analysis. Periodically, split samples from one or two subjects will be utilized to assess reliability of the analysis.

Only individuals who have retired from 3M Decatur chemical plant from the 1st of January 1995 through the 1st of January 1998, will be included in the study. Using information received from the Human Resources Department of 3M Decatur, 34 individuals were identified to have retired during this time period. Of the 34 individuals identified, 7 have previously been enrolled in the fluorochemical medical surveillance program. Four of these individuals participated in the medical surveillance program in 1994 but not 1997; 3 individuals participated in 1997 only. We will attempt to enroll all 34 retirees into the study. Future retirees will not be enrolled. Serum fluorochemical levels will be drawn every six months. All serum fluorochemical levels will be drawn within a one-month time frame (i.e., within one month of March and September).

Retirees will be recruited to the study through first, an introductory letter and second, a phone conversation from the principle investigator or his designee. Subsequent to the follow-up telephone conversation and if the retiree is willing to enter the study, a written informed consent form (Appendix A) and a medical questionnaire (Appendix B) will be sent to the retiree for his review. Once the retiree signs the consent form, completes the questionnaire, and returns the documents to the principle investigator, he will be entered into the study and scheduled for blood collection. Participation in the study is voluntary and retirees may drop out at any time.

Blood collection will be scheduled biannually, in April and October (to not conflict with Holiday and summer vacation travel). Letters announcing blood collection dates and times will be sent out to each study subject one month prior to each blood collection month. Retirees will update their medical questionnaire at each blood collection. All blood collections will be performed under the supervision of the 3M Decatur plant nurse, Cathy Simpson, RN. Two red-topped tubes will be obtained from each retiree; the 3M Occupational Medicine Service methodology for handling and shipping of fluorochemical blood samples will be applied to all blood samples. Samples will be analyzed by the 3M Environmental Laboratory or its designated contract laboratory. Retirees will receive written reports of their serum fluorochemical levels following each blood collection cycle.

Two methods of calculating the serum fluorochemical half life will be utilized. In the first method, a one compartment model will be assumed and the formula

$$q_t = q_0 (0.5)^{t/t_{1/2}}$$

will be utilized to estimate the half life of elimination for PFOS, PFOA, PFHS, and TOF. The terms q_t *and* q_0 refer to the serum concentrations at time t and time 0, t is the elapsed time; $t_{½}$ is what we seek to solve.

The second method will be used to verify the first. It also assumes a one compartment model. Each retiree's fluorochemical levels will be graphed on a log-linear scale as serum fluorochemical vs. elapsed time from t_0 (in months) and entered into a database. Statistical analysis will be performed to determine the best-fit model that describes the slope of the log-linear line. (Appendix C)

The slope of the log-linear line is related to the elimination constant ($-k_{el}$) through the equation

$$Slope = -k_{el}(2.303)$$

Once the elimination constant is calculated, the half life can be calculated using the relationship

$$t_{½} = 0.693/k_{el}$$

Elimination half lives for TOF, PFOS, PFHS, and PFOA will be determined. (Benez, et al. 1985, Medinsky, et al. 1996.)

DISCUSSION

There are a number of limitations associated with the study, including:

1. The lack of pre-study serum fluorochemical levels in the majority of retirees, making it impossible to develop baseline levels for the majority of the study group. The *t0* values will therefore need to be their first fluorochemical level *post-retirement.*

2. Previous studies have performed serum total organic fluorine levels and not serum testing specific for serum PFOS or PFOA; comparability with previous work is thereby compromised.
3. Retirees on medications such as colestipol or cholestyramine, which can artificially increase the rate of elimination of fluorochemicals from the blood will artificially increase the elimination in unpredictable ways, thereby causing an underestimation of the elimination half life in the entire study population.
4. Retirees may unknowingly have medical conditions that will decrease their toxicant elimination rate unpredictably (e.g., renal failure, congestive heart failure, cholelithiasis, etc.), thereby causing an inaccurate estimation of the elimination half life in the entire study population.

For these reasons, the study will occur over the protracted period of five years instead of a shorter time period (i.e., three years). As the only human data plotting total organic fluorine suggest plasma elimination half-life of 18 months, a three year study would allow for verification of that estimate since three years would be equal to two half-lives. A five-year study, therefore, should include over three half-lives of elimination, and make it possible to use several years' data to calculate the elimination half life.

The overall results collected in this study may be used in publications or in public presentations. Retiree names or other individual data will not be revealed in any publication or other documentations intended for public examination. Individual results will be communicated only to the retiree. Individual results will be considered confidential information and will not be disclosed to anyone outside of the 3M Medical Department without the retiree's written consent.

Quality assurance will be performed per the guidelines set forth in the standard operating procedure for the creation, review, and approval of 3M epidemiology study protocols.

Archiving of study materials, upon completion of the study, will be performed per the standard operating procedure for the creation, auditing, review and approval of 3M epidemiology final reports.

The study will be communicated to the retirees, management, and the technical community. Communications to the retirees will be in the form of a letter, which states the retiree's various blood fluorochemical levels. These letters will be sent out following each blood draw. Communication to management will be in the form of a written document which will undergo the review process as set forth in the standard operating procedure for the creation, auditing, review and approval of 3M epidemiology final reports. The communication to the technical community will be in the form of a scientific paper, which will be submitted to a relevant peer reviewed scientific publication.

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Appendix A

CONSENT FORM FOR COLLECTION OF BLOOD FOR SERUM FLUOROCHEMICAL LEVEL HALF-LIFE DETERMINATION

INTRODUCTION

You and your colleagues were involved in fluorochemical production at 3M Decatur prior to your retirement. You are invited to participate in a research study being conducted by 3M Occupational Medicine Services regarding fluorochemicals. Your participation would involve donating one red-topped test tube of blood approximately every six months for the next five years. Your blood will only be tested for the amount and kind of fluorochemicals it contains; it will not be used to test for any other substances or disease. Please review this consent form carefully and be sure your questions are answered before you make a decision to participate. The plant nurse will be available to provide you with additional information at the time of your medical surveillance blood donation.

PURPOSE OF STUDY

The purpose of the study is to determine how much and what types of fluorochemicals are eliminated from the human body over time.

STUDY PROCEDURES

Your blood will be drawn with one needle stick and require two test tubes. This will occur about every six months for the next five years. A letter will be sent to you in advance informing you of the proper date, time, and place to report to for blood collection.

POTENTIAL RISKS/BENEFITS

The only discomfort you may feel is from the needle stick. You may also have some temporary redness/bruising/swelling in this area after blood collection.

BENEFITS

There will be no direct benefit from your participation in this study. However, the information gained from this study will further help us understand human exposures to fluorochemicals. Your individual results as well as the overall results will be communicated to you only. Your individual results will be considered confidential information and will not be disclosed to anyone outside the 3M Medical Department without your written consent.

COMPENSATION

If you suffer injury or a medical condition that appears to be the result of participating in this study, you will be referred to another health care professional at no cost to you. In the event of a research related injury, compensation will be determined on a case by case basis by 3M.

CONFIDENTIALITY

The overall results collected in this study may be used in publications or public presentation. Your name will not be revealed in any publication or other documents intended for publication examination. Your individual results will be communicated to you only. Your individual results will be considered confidential information and will not be disclosed to anyone outside the 3M Medical Department without your written consent.

SUBJECT RIGHTS/AVAILABILITY OF INFORMATION

If you have any questions about the study now, or later, or in the event of a research related injury or emergency, contact Dr. Jeffrey Mandel (651-733-8670) or Jean Burris, R.N. (651-737-7867). For answers to questions about your rights in regard to this research, you may contact Dr. Larry Zobel, Chair, 3M Institutional Review Board at 651-733-5181.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is voluntary. Refusal to participate will involve no penalty of loss of benefits to which you are otherwise entitled. You are free to withdraw from the study at any time for any reason. The investigator may stop your participation in this study should it be determined that continued participation may be detrimental to your health. Following each semi-annual blood collection, you will receive a check for $50.00 as compensation for your time and effort.

SUBJECT CONSENT

By signing the consent form, I certify that I am at least 18 years old. I confirm that I have read this consent form, and that I have been given adequate opportunity to ask any questions I may have about this consent form or the study. I also confirm that I understand the scope of my participation in this study, and that all of my questions have been answered to my satisfaction. I am signing this consent form voluntarily, and I desire to participate in the study. I understand that I will receive a copy of this signed consent form. I understand that I will receive a check for $50.00 immediately following each semi-annual collection of my blood.

_____ _____

Signature Date

_____

Printed Name

_____

Witness

Appendix B

MEDICAL HISTORY QUESTIONNAIRE

Please list the names of the **ALL** the medications you take at least once a day.

Please circle the conditions you now suffer from or have suffered from in the last three years.

Kidney Failure

Gall Bladder Disease

Hepatitis/Jaundice

Congestive Heart Failure

Liver Disease

Inflammatory Bowel Disease

Crohn's Disease

Pernicious Anemia

Appendix C

Example of a log-linear plot that will be used to estimate the serum fluorochemical elimination half life in Decatur retirees.