

PFOS

Disposition

The material is found in rats in the liver. There is about thirty percent of the material in the liver at eighty nine days after a single dose. The disposition in rats is shown in Table 1 and is based on work done with radioactive PFOS.

Excretion is mainly via the feces. The cumulative excretion is shown in Figures 1 and 2 and is again based on radioactive PFOS.

The mechanism of retention is through a enterohepatic cycle. The material is placed into the gut lumen via bile and reabsorbed and passed to the liver by the portal blood. This enterohepatic cycle can be interrupted by cholestyramine. This was a published paper.(Johnson, Gibson, and Ober).

Human serum levels

We have found PFOS in human serum (Plant workers and blood bank).

✓ We do not know the source of the PFOS in human serum.

FC-807 components (FOSE has been shown to be metabolized to PFOS in rats) and it is easily conjectured that the monoester which is orally absorbed would also be biotransformed to PFOS.

Methyl FOSE would very likely be biotransformed to PFOS.

FX-12 has been shown to be metabolized to PFOS in rabbits.

FC-170, the sultone foamer, and L4640 are also likely to be metabolized to PFOS.

Any exposure through skin, ingestion, or by breathing the material in the form of dust or aerosol could and probably would lead to an increase in the serum level of PFOS.

The half-life of PFOS in humans is not known. It is very likely quite long. The most compelling argument is that PFOS is found in many

**Exhibit
1408**

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people. If the half-life were short, it would follow that all of these individuals would have had to have been recently exposed. It seems more likely that the material is appearing in human blood as a result of a small but continuous exposure either to the compound directly or to another material that is biotransformed to PFOS.

Toxicity Considerations

It is not known if the material has different toxicity in different species. Most of the work done on PFOS has been done in rats. There is some evidence that there was some toxicity in monkeys.

1) Although the basic disposition and distribution of PFOS in mammals would likely be the same, there is no particular reason to believe that there would not be a sensitivity in one species not present in another.

✓ 2) PFOS is known to be a peroxisomal proliferator. Peroxisomal proliferation is for other compounds frequently associated with carcinogens.

3) PFOS is very highly protein bound--presumably to albumin.

✓ 4) The extent of interaction of PFOS with other compounds (drugs) or disease states is not known and might not be properly assessed using rats. (For instance, what would happen with alcoholism and the concomitant problems with fatty liver and liver disease? What happens with age? What happens with kidney failure? For drugs, there is a relationship between the free unbound drug and the effect of the drug so if a drug is 98% bound and displaced by some other drug or compound to the extent that it would only be 96% bound, then the effective free "active" drug would be doubled.)

✓ 5) The exact binding of PFOS is not known. How many residues per molecule of albumin are bound is not known. The binding constants, the nature of the binding to albumin, the effect on the albumin with respect to its other function (carrier of fatty acids for example) is not known.

6) The effect of chain length and the extent of branching on toxicity of alkane sulfonates is not known. Both chain length and branching can vary between products.

7) There is evidence that there is a relationship between toxicity and extent of branching for FX-12
(Evidence from Griffin Chemical and FX-12.)

8) We do not know if there is a preferential elimination of PFOS with regard to the extent of branching and chain length. Since we do not know the effect of either, we have the possibility that the

effect of PFOS can change with time and repeated small exposures as the type of PFOS in the body burden could change with time.

9) The effect of PFOS and the effect of PFO are studied independently in toxicity tests. Yet, they are frequently present together in human plasma and have some of the same properties (long half-life and propensity to bind to protein for example). It could be a possibility that their effects are cumulative or that there is a toxicity effect not observed when the compounds are studied individually.

10) To my knowledge, we do not know if there is any effect of these compounds on fertility, sperm count, etc. There is a world wide drop in fertility and sperm count. A correlation of serum level of PFOS and a drop in fertility or sperm count would be a very difficult problem. There is some indication of hormonal mimicry from a large variety of chemicals and recent literature seems focused on finding an environmental culprit.

✓ 11) Nothing is known about the transport across the placenta of perfluorooctanesulfonates. Although the difficulty of fetal liver metabolism biotransforming the compounds to more polar substances in the fetal liver which subsequently are not able to pass the placenta does not exist (no biotransformation), in the mature animal, there is the puzzling aspect of the materials leaving the carrier protein and crossing the hepatocyte via some unknown mechanism and then reaching the gut via the bile. There is no knowledge available as to state of the carrier mechanism in fetal liver with respect to PFOS nor if the presence of PFOS could cause an untoward effect.

✓ 12) There is some preliminary evidence that in lactating goats PFOS is transferred to milk. It is likely that lactating human females would also transfer PFOS to milk.

Environmental Consideration

There is no doubt that the compounds that contain derivatives of perfluorooctanesulfonate as part of the molecule will eventually be degraded to perfluorooctanesulfonate when these molecules are exposed to living organisms (plant, animal, fungi, and microbes).

- 1) Does the perfluorooctanesulfonate bioaccumulate?
- 2) Is perfluorooctanesulfonate particularly toxic to any organism in the biosphere?
- 3) Is there uptake in plants if perfluorooctanesulfonate is present in sludge?

- 4) Is PFOS formed in compost?
- 5) Does PFOS transfer in eggs? Do birds handle PFOS differently than mammals? In aquatic birds, is PFOS excreted in the salt gland?
- 6) Is PFOS appearing in any of the common human foods (honey, fish, milk, liver & kidney, eggs, clams & oysters,)?

Kinds of Studies for Human PFOS Aspects

Toxicity tests in several species including primates should be carried out. These studies would necessarily include collaboration between metabolism/analytical and toxicity considerations. For instance the blood level and tissue level of the material at those dosing concentrations which lead to obvious effects or death should be determined. The idea is to find out just how much variation there is between species and where man falls in the picture of toxicity with respect to blood levels. Also at high levels, is the ratio of liver and serum concentration fairly constant across species. What animal is a good predictor for humans? Is the rat a proper model? We could use African Greens (or some other suitable primate), rabbits, dogs, hamsters, and/or guinea pigs.

We need to have a wider scope characterization of human blood levels on a global basis. This can be partially accomplished by using blood bank blood from all over the world. These samples will possibly be contaminated with HIV virus. A better feel for the total organic flourine in human blood and the extent of perfluorooctanate and perfluorooctanesulfonate in human blood will possibly establish a baseline for current contamination and will allow us to compare our plant workers with the general population. Cadaver liver would also be a very useful tool if we could also obtain blood from the same cadaver.

We need to drive the sensitivity level of our current analytical method to much lower levels. We also need to develop a way to look at the branching of PFOS in human serum.

A study of the factors involving albumin binding should be initiated. Vicki Wysocki at Richmond along with Fenn (probably one of the world's foremost experts in electrospray mass spec and who Vicki now has access to) would be the logical candidates to do the analytical but a "real" expert in albumin is still required. I think what is needed is to connect such an expert with the analytical

expertise (myself, and Vicki) and then really develop a research program on the binding, liver, and other tissue handling and disposition of PFOS, as well as other such aspects of PFOS. These items probably comprise the keystone in the whole structure. If these aspects were properly understood, the rest of the questions could be more easily answered. If all of these things are left unanswered, then counting dead animals and looking at tissue slides until we are all retired may not solve this problem.

We need to look at milk from lactating animals, foods, etc. to see the extent that PFOS and PFO might be contaminating food stuff besides that which comes in contact with coated paper. We also have to consider the possibility that a lactating human would pass the PFOS to a nursing infant.

We need to revisit some of the analytical for water and see that this material is not present at sub ppm in water. Even sub ppm exposure would eventually show up as substantial quantities in human serum. (If 1 ppm in water and at 1 liter/day, the exposure would be more than 350 mg/year. If t 1/2 greater than 1 year, there could be enough of a dose to show up analytically in human serum.)

We need to do metabolism studies on FOSE, FC-170, monoester, and other molecules to see the extent to which they are biotransformed to perfluorooctanesulfonate. These should be done in rats at a minimum but perhaps in some of the other animals that could be identified with the acute tox tests.

We need to look at the transfer of PFOS across the placenta and the possibility of accumulation of the PFOS in fetal liver.

The direct effect of fluorochemicals on fertility and on sperm viability should be studies (especially PFOS).

Environmental Considerations

We need to do some studies on biological uptake. We need to do some fish studies to see if PFOS bioaccumulates in fish. If PFOS accumulates in fish, is tissue affected such that there is increased exposure for human or animals consumers of the fish. We need to see if PFOS is taken up by plants. And as with fish, we will have to do studies to see if there is increased exposure upon consumption of the plants. This is a large undertaking, and some probe plants will need

to be used to see in which kind of plants and to what extent the uptake if it happens occurs.

We need to see if PFOS is handled differently by birds. Do birds retain the material longer than mammals? Are birds more susceptible to PFOS? Is the toxicity profile different in birds? Are there any obvious effects on fertility in birds or are there any strange effects on chicks? What about the salt gland, preening, etc.

What is the binding constants in activated sludge? Does PFOS affect sludge's capacity to process other materials?

Does AFFF biodegrade to perfluoroalkane sulfonate? Does the diester in FC-807 degrade substantially to PFOS in compost and/or sludge? These are studies that need to be done in small scale but in sufficient rigor to provide these facts.