

SRPT T-6295.8, T-6316.4, T-6868.2, T-7071.1, T-7132.1
DT15-B

3M MEDICAL DEPARTMENT, CORPORATE TOXICOLOGY

Title: Comparative Molecular Biology of Perfluorooctanesulfonate (PFOS, T-6295), N-ethyl perfluorooctanesulfonamido ethanol (N-EtFOSE, T-6316), N-Ethyl perfluorooctanesulfonamide (N-EtFOSA, T-6868), Perfluorooctanesulfonamido acetate (FOSAA, T-7071), and/or Perfluorooctanesulfonamide (FOSA, T-7132) of in Rats and Guinea Pigs following Oral dosing.

AMENDED Final Report

Date: July, 16 2004

Study Numbers. T-6295.8, T-6316.4, T-6868.2, T-7071.1, T-7132.1
Strategic Toxicology Study Number: DT-15-B

Sponsor: 3M Specialty Chemicals Division
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In-Life Start Date	Protocol:	11/16/1998
In-Life End Date	Protocol:	11/20/1998
In-Life Start Date	Amendment #1:	03/01/1999
In-Life End Date	Amendment #1:	03/05/1999
In-Life Start Date	Amendment #2:	02/19/2001
In-Life End Date	Amendment #2:	02/23/2001

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The purpose for this amendment was to change the conclusion drawn in the summary that Lin Xu and Drag Anders wrote in Appendix 6E (page 59) which read:

The original statement:

"These data showed that FOSA was consistently identified as a metabolite of PFOS, whether PFOS was administered directly or formed as a metabolite, but the source of the amino group is not readily apparent."

Was changed to read:

"These data showed that FOSA was consistently identified as a metabolite of PFOS, but that the source of the amino group is not readily apparent."

The rationale for these changes were that the original conclusion was not directly supported by the data presented in this study. That conclusion was not entirely correct because all of the administered compounds, besides PFOS, have a sulfonamido group within the parent compound. Therefore, the likely source of the amino group for sulfonamide moiety containing compounds would be the parent compound itself. There is quantitative evidence in these studies suggesting that the perfluorooctanesulfonamides were metabolized first to PFOS followed by metabolism of that PFOS back to a sulfonamide. The only evidence for a possible metabolism of PFOS to FOSA came from the PFOS dose groups, not the perfluorooctanesulfonamido derivative parent compound dose groups. Furthermore, in two out of three independent studies analyzed at Rochester, the control group liver samples had a high background of FOSA, suggesting possible contamination of the liver samples. Therefore, as stated, the conversion of PFOS to PFOSA would have to be verified by further studies.

Dr Anders is in agreement with the amended conclusion stated above.

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Signatures:

Final Report Amendment #1 prepared by,

Andrew M. Seacat

Andrew M. Seacat, PhD, DABT
Study Director

1/16/04

Date

E. Technical Report: Liver Fluorocarbon Metabolites – University of Rochester.

Title:

Summary of Quantitative Analysis of Fluorocarbon Metabolites in Rat Liver Samples

Lin Xu and M. W. Anders

This is a brief summary of the analysis of liver samples from rats given a range of fluorocarbons. The parent and metabolites of the fluorocarbons were determined in liver samples by LC-MS/MS. The results are presented below.

Three groups of liver samples were analyzed: The first group (Group 1) consisted of livers from control rats, from rats given 40 mg/kg/day FOSA orally, and from rats given 160 mg/kg/day FOSAA (M556) orally. The concentrations of parent compounds and their metabolites in livers were measured (Table 1). The data show that PFOS was the major metabolite found in the livers of rats given FOSA; FOSA *N*-glucuronide was identified as a minor metabolite. Two metabolites were identified in the livers of rats given FOSAA (M556): PFOS and FOSA. It is noteworthy that the control animals (1R00742, 1R00743, and 1R00743) contained significant concentrations of FOSA. A parallel analysis of livers from Fischer 344 rats maintained in the University of Rochester Vivarium did not show detectable concentrations of FOSA.

The second group (Group 2) of rats was treated in November, 1998. Group 2 contained livers from control rats, from rats given 40 mg/kg/day PFOS orally, from rats given 40 mg/kg/day *N*-EtFOSE alcohol orally, and from rats given 40 mg/kg/day *N*-EtFOSA orally. The concentrations of parent compounds and identified metabolites are shown in Table 2. The data show that livers from rats given PFOS contained parent compound PFOS; FOSA was also found in these samples. The livers from rats given *N*-EtFOSE alcohol contained several metabolites. The major metabolites were *N*-EtFOSAA, PFOS, and FOSAA (M556). The minor metabolites were FOSA, FOSE alcohol, *N*-EtFOSE alcohol glucuronide, and FOSA *N*-glucuronide. PFOS was the major metabolite in livers from rats given *N*-EtFOSA; FOSA and FOSA *N*-glucuronide were identified as minor metabolites. In contrast to Group 1, the livers from control rats did not contain detectable concentrations of parent compounds or metabolites.

The third group (Group 3) was treated in March, 1999. Group 3 contained livers from control rats, from rats given 40 mg/kg/day PFOS orally, and from rats given 160 mg/kg/day *N*-EtFOSE alcohol orally. The concentrations of the chemicals and metabolites are shown in Table 3. As with Group 2, PFOS and low concentrations of FOSA were identified in livers from rats given PFOS. In the livers of rats given *N*-EtFOSE alcohol, *N*-EtFOSAA, PFOS, and FOSAA (M556) were identified as major metabolites, and the minor metabolites identified were FOSA, FOSE alcohol, *N*-EtFOSE alcohol glucuronide, and FOSA *N*-glucuronide. Similar to Group 1, control animals showed detectable hepatic concentrations of FOSA.

Discussion: These data allow conclusions about the overall metabolic fate of the fluorocarbons studied (see Scheme), but do not allow inferences about the exact routes of metabolite formation. FOSA was consistently identified as a metabolite of PFOS, but the source of the amino group is not readily apparent. Whatever its route of formation, FOSA was metabolized to FOSA *N*-glucuronide.

N-EtFOSE alcohol gives rise to a range of major and minor metabolites. FOSE alcohol could arise from the *N*-deethylation of *N*-EtFOSE alcohol, and *N*-EtFOSAA could arise by the oxidation of the alcohol to the carboxylic acid. Glucuronidation of the parent *N*-EtFOSE alcohol would give the observed *N*-EtFOSE alcohol glucuronides. FOSAA could be formed by the *N*-deethylation of *N*-EtFOSAA or by the oxidation of FOSE alcohol, or both. FOSA could be formed by the *N*-deethylation of *N*-EtFOSA or by the removal of the carboxymethyl group of FOSAA as glyoxylate. FOSA *N*-glucuronide may be formed by the glucuronidation of FOSA.