Study No. T-7098.1; DT35

Title:

Pharmacokinetic Study of Perfluorooctanesulfonyl Fluoride (POSF) Following a Single Oral Gavage Dose In Rats

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Summary

Rats received a single oral dose of 5 mg/Kg perfluorooctanesulfonyl fluoride. Necropsies were performed on days 1, 4, and 29 post dose. POSF was metabolized to PFOS which was maximum in the liver on day 4 post-dose at approximately 11 ppm, or ~ 10% of the dose. PFOS was present in sera at approximately one tenth of the level found in the liver. Thus, perfluorooctanesulfonyl fluoride (POSF) was absorbed and metabolized to perfluorooctanesulfonate (PFOS) by rats following and oral dose.

Study Objective

The objective of this study was to assess the potential for oral absorption, urinary and fecal clearance, and biological persistence of perfluorooctanesulfonyl fluoride (POSF) in male Sprague Dawley rats after a single oral dose. POSF is the starting material for the synthesis of a variety of perfluorooctane sulfonate (PFOS) based materials. Data gathered in this study help define the rate of metabolism of POSF to PFOS by the liver and provide data for proper risk characterization of POSF.

Method Summary

This study was performed in the 3M Strategic Toxicology Laboratory under a defined protocol (1) and classified as a "Class B Study" as explained in TOX SOP 0950, Strategic Toxicology Lab GLP Program Procedure (2).

Briefly, the procedure was as follows. Thirty male Sprague Dawley rats (obtained from Harlan Laboratories), 6-8 weeks in age and approximately 150-250g, were divided into the following dose groups:

Group	Dose POSF	N	Euthanasia
1	0 mg/kg	5	day 1 post dose
2	0 mg/kg	5	day 4 post dose
3	0 mg/kg	5	day 29 post dose
4	5 mg/kg	5	day 1 post dose
5	5 mg/kg	5	day 4 post dose
6	5 mg/kg	5	day 29 post dose

Rats received either a 5 ml/Kg dose of vehicle control (2% Tween 80), or a 5 mL/Kg dose of a 1 mg/mL POSF suspension in 2% Tween 80 (final dose = 5 mg/Kg) via oral gavage on day zero of the study. Three specified rats from groups 3 and 6 were housed individually in metabolism cages for portions of the study. Urine and feces were collected on days 1, 2, 4, 14, and 29-post dose. Necropsies were performed on days 1, 4, and 29 post dose. At necropsy, liver and sera were collected from each animal. For metabolite analysis, these specimens were packed in dry ice and shipped to Kris Hansen, 3M Environmental Technology and Safety Services for FC

analysis. Liver and sera were analyzed and the raw data was reported (3) . Urine and feces analysis was not performed and was canceled.

Results

Treatment with PFOS at 5 mg/Kg had no effect on body weight or liver weight (Table 1A, B).

Extraction and analysis of the tissues showed that PFOS was detected in the livers of all POSF dosed animals at all time points and was maximum in the liver on day 4 post-dose at approximately 11 ppm (Table 2). Trace amounts of perfluorooctanesulfonamidoacetate (PFOSAA, M556) were also reported for liver samples from POSF treated animals on days one and 4 post-dose (Table 2). The origin of the M556 in the liver samples is unknown, and all samples were near the practical quantitation limit for PFOSAA of 0.06 μg/g. Approximately 10 % of the dose was present in the liver as PFOS on day 4 post dose as calculated from the sum of the liver PFOS and liver PFOS equivalents from PFOSAA (Table 3).

The PFOS levels in the sera of the rats were approximately one tenth of the level found in the liver sample extracts and were maximal on day one post dose (Table 4). No other metabolites were detected in the sera. Approximately 0.1 % of the dose was present in the sera as PFOS on day 1 post-dose (Table 4).

Conclusions

These data support the conclusion that perfluorooctanesulfonyl fluoride (POSF) can be absorbed by rats following a single oral gavage dose, and metabolized to perfluorooctanesulfonate (PFOS).

List of Tables

Table 1A: Biological Parameters. Control Group						
Time Point	Dose	animal # 9R00-xxx	Initial BW (g)	Terminal BW (g)	Kidney Weight (g)	Liver wt (g)
Day 1	0 mg/kg	001	202	207	1.7	8.7
Day 1	0 mg/kg	002	204	213	1.7	9.3
Day 1	0 mg/kg	003	188	196	1.6	8.4
Day 1	0 mg/kg	004	203	207	1.7	9.5
Day 1	0 mg/kg	005	200	207	1.6	9
	Avg		**199**	**206**	**1.7**	**9.0**
	SD		**6**	**6**	**0.1**	**0.4**
	Range Min		188	196	1.6	8
	Max		204	213	1.7	10
	N	5	5	5	5	5
Day 4	0 mg/kg	006	193	206	1.6	8.2
Day 4	0 mg/kg	007	198	215	1.7	8.6
Day 4	0 mg/kg	008	204	228	1.8	9.5
Day 4	0 mg/kg	009	204	220	1.7	9.1
Day 4	0 mg/kg	010	191	209	1.7	9.1
	Avg		**198**	**215**	**1.7**	**9**
	SD		**6**	**9**	**0.1**	**1**
	Range Min		191	206	1.6	8
	Max		204	228	1.8	10
	N	5	5	5	5	5
Day 29	0 mg/kg	011	196	275	2.1	11.9
Day 29	0 mg/kg	012	203	302	2.2	11.8
Day 29	0 mg/kg	013	202	297	2.3	11.8
Day 29	0 mg/kg	014	201	277	1.9	10.3
Day 29	0 mg/kg	015	199	275	1.9	11.1
	Avg		**200**	**285**	**2.1**	**11**
	SD		**3**	**13**	**0.2**	**1**
	Range Min		196	275	1.9	10
	Max		203	302	2.3	12
	N	5	5	5	5	5

Table 1:

Table 1B: Biological Parameters. POSF Dose Group						
Time Point	Dose	animal # 9R00-xxx	Initial BW (g)	Terminal BW (g)	Kidney Weight (g)	Liver wt (g)
Day 1	5 mg/kg	031	211	215	1.6	10.0
Day 1	5 mg/kg	032	199	203	1.6	8.7
Day 1	5 mg/kg	033	204	213	1.9	9.8
Day 1	5 mg/kg	034	197	205	1.5	8.7
Day 1	5 mg/kg	035	212	216	1.7	8.6
	Avg		**205**	**210**	**1.7**	**9**
	SD		**7**	**6**	**0.2**	**1**
	Range Min		197	203	1.5	9
	Max		212	216	1.9	10
	N	5	5	5	5	5
Day 4	5 mg/kg	036	215	240	1.9	10.2
Day 4	5 mg/kg	037	195	216	1.7	9.0
Day 4	5 mg/kg	038	200	221	1.7	9.3
Day 4	5 mg/kg	039	203	229	1.9	9.8
Day 4	5 mg/kg	040	199	224	1.7	9.3
	Avg		**202**	**226**	**1.8**	**10**
	SD		**7**	**9**	**0.1**	**0**
	Range Min		195	216	1.7	9
	Max		215	240	1.9	10
	N	5	5	5	5	5
Day 29	5 mg/kg	041	202	310	2.3	13.0
Day 29	5 mg/kg	042	205	301	2.2	11.4
Day 29	5 mg/kg	043	196	306	2.2	11.7
Day 29	5 mg/kg	044	202	295	2.1	11.0
Day 29	5 mg/kg	045	203	288	2.0	10.6
	Avg		**202**	**300**	**2.2**	**12**
	SD		**3**	**9**	**0.1**	**1**
	Range Min		196	288	2.0	11
	Max		205	310	2.3	13
	N	5	5	5	5	5

Table 2:

Table 2: Liver PFOS and M556 in the POSF dose Group					
Time Point	**Dose POSF**	**animal # 9R00-xxx**	**Liver [PFOS] ppm**	**Liver [M556]ppm**	**Liver M556 PFOS eq (ppm) [1]**
Day 1	5 mg/kg	031	2.35	0.125	0.11
Day 1	5 mg/kg	032	3.41	0.0957	0.09
Day 1	5 mg/kg	033	13.80	0.0815	0.07
Day 1	5 mg/kg	034	3.73	0.114	0.10
Day 1	5 mg/kg	035	11.20	SE	
	Avg		**6.90**	**0.10**	**0.09**
	SD		**5.22**	**0.02**	**0.02**
Day 4	5 mg/kg	036	6.76	0.0166	0.01
Day 4	5 mg/kg	037	6.79	0.0331	0.03
Day 4	5 mg/kg	038	8.22	SE	
Day 4	5 mg/kg	039	12.50	0.0125	0.01
Day 4	5 mg/kg	040	19.70	SE	
	Avg		**10.79**	**0.02**	**0.02**
	SD		**5.50**	**0.01**	**0.01**
Day 29	5 mg/kg	041	2.55	<PQL	
Day 29	5 mg/kg	042	3.30	<PQL	
Day 29	5 mg/kg	043	7.54	<PQL	
Day 29	5 mg/kg	044	5.47	<PQL	
Day 29	5 mg/kg	045	2.57	<PQL	
	Avg		**4.29**		
	SD		**2.17**		
1. Liver M556 PFOS equivalents = Liver M556 concentration * (MW PFOS/MW M556) = Liver M556 * (499/556)					
PQL = practical quantitation limit in liver for M556 = 0.060 ug/g					
SE = sample evaporated, no sample remaining					

Table 3:

Table 3: Liver PFOS equivalents and Percent Dose in Liver						
Time Point	Dose POSF mg/Kg	Animal# 9R00xxx	PFOS eq in liver (ppm) [1]	Total PFOS eq in liver (ug)[2]	PFOS eq. In dose (ug) [3]	% PFOS eq dosed in liver (%) [4]
Day 1	5	031	2.5	24.6	1047.2	2.4
Day 1	5	032	3.5	30.4	988.1	3.1
Day 1	5	033	13.9	136.0	1014.9	13.4
Day 1	5	034	3.8	33.3	978.1	3.4
Day 1	5	035	11.2	96.3	1055.7	9.1
	Avg		**6.97**	**64.1**	**1016.8**	**6.3**
	SD		**5.19**	**49.6**	**34.5**	**4.8**
Day 4	5	036	6.8	69.1	1066.1	6.5
Day 4	5	037	6.8	61.4	968.2	6.3
Day 4	5	038	8.2	76.4	992.5	7.7
Day 4	5	039	12.5	122.6	1009.4	12.1
Day 4	5	040	19.7	183.2	989.6	18.5
	Avg		**10.81**	**102.5**	**1005.2**	**10.2**
	SD		**5.50**	**51.0**	**37.1**	**5.2**
Day 29	5	041	2.6	33.2	1004.0	3.3
Day 29	5	042	3.3	37.6	1020.4	3.7
Day 29	5	043	7.5	88.2	975.6	9.0
Day 29	5	044	5.5	60.2	1002.5	6.0
Day 29	5	045	2.6	27.2	1009.4	2.7
	Avg		**4.29**	**49.3**	**1002.4**	**4.9**
	SD		**2.17**	**25.1**	**16.5**	**2.6**
1. PFOS equivalents in liver (ppm) = Liver PFOS (ppm) + Liver M556 PFOS equivalents (ppm)						
2. Total PFOS equivalents in whole liver (ug) = PFOS equivalent concentration in liver (ppm) * liver weight (g)						
3. PFOS equivalents in dose (ug) = Initial BW (g) * dose (mg/kg)*MW PFOS/MW M556 = BW*5*(499/556)						
4. % PFOS eq dosed as M556 in liver = PFOS equivalents in whole liver (ug)/ PFOS equivalents in dose						

Table 4:

Table 4: Percent Dose: Serum PFOS equivalents in POSF Group							
Time Point	Dose POSF	animal # 9R00-xxx	Sera [PFOS] ppm	Serum volume (ml) [1]	Total PFOS Eq in Serum (ug) [2]	POSF PFOS equivalents in dose (ug)[3]	% PFOS eq dosed in serum (%)[4]
Day 1	5 mg/kg	031	0.0291	7.0	0.2	1047.2	0.02
Day 1	5 mg/kg	032	0.0297	6.6	0.2	988.1	0.02
Day 1	5 mg/kg	033	0.564	6.9	3.9	1014.9	0.38
Day 1	5 mg/kg	034	0.0484	6.6	0.3	978.1	0.03
Day 1	5 mg/kg	035	0.177	7.0	1.2	1055.7	0.12
	Avg		**0.17**	**6.8**	**1.2**	**1016.8**	**0.11**
	SD		**0.23**	**0.2**	**1.6**	**34.5**	**0.16**
Day 4	5 mg/kg	036	0.1008	7.7	0.8	1066.1	0.07
Day 4	5 mg/kg	037	0.094	7.0	0.7	968.2	0.07
Day 4	5 mg/kg	038	0.0712	7.1	0.5	992.5	0.05
Day 4	5 mg/kg	039	0.121	7.4	0.9	1009.4	0.09
Day 4	5 mg/kg	040	0.119	7.2	0.9	989.6	0.09
	Avg		**0.10**	**7.3**	**0.7**	**1005.2**	**0.07**
	SD		**0.02**	**0.3**	**0.2**	**37.1**	**0.02**
Day 29	5 mg/kg	041	0.0523	10.0	0.5	1004.0	0.05
Day 29	5 mg/kg	042	0.0928	9.7	0.9	1020.4	0.09
Day 29	5 mg/kg	043	0.21	9.9	2.1	975.6	0.21
Day 29	5 mg/kg	044	0.152	9.5	1.4	1002.5	0.14
Day 29	5 mg/kg	045	0.0671	9.3	0.6	1009.4	0.06
	Avg		**0.11**	**9.7**	**1.1**	**1002.4**	**0.11**
	SD		**0.07**	**0.3**	**0.6**	**16.5**	**0.07**
1. There are 32.3 mL Plasma per Kg of rat.							
2. Total PFOS equivalents in sera (ug) = PFOS equivalent concentration in sera (ppm) * serum volume (ml)							
3. PFOS equivalents in dose (ug) = Initial BW (g) * dose (mg/kg) * MW PFOS/ MW M556 = BW*5*(499/556)							
4. % PFOS equivalents dosed in serum = (PFOS equivalents in sera (ug)/ PFOS equivalents in dose (ug)) *100							

Signatures:

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