



Appendix: Data Derived Extrapolation Factors for Developmental Toxicity: Preliminary Research Case Study with Perfluorooctanoate

TABLE A

Elcombe et al., 2013. Individual patient PFOA doses, Cmax. Human weights given as 75 kg (Convertino et al., 2018).

<u>Patient #</u>	<u>Dose (mg)</u>	<u>Single Dose (mg/kg)</u>	<u>Single Dose Cmax (µM)</u>	<u>Cmax /(Dose)</u>	<u>Dose (mg/kg-day)</u>
1	50	0.67	25.72	39	na
2	50	0.67	29.79	45	na
3	50	0.67	24.64	37	na
4	50	0.67	19.95	30	0.10
5	100	1.3	23.66	18	0.19
6	100	1.3	32.32	24	0.19
7	100	1.3	30.91	23	0.19
8	200	2.7	114.25	43	0.38
9	200	2.7	93.43	35	0.38
10	200	2.7	58.6	22	0.38
11	300	4.0	111.65	28	0.57
12	300	4.0	122.9	31	0.57
13	300	4.0	85.32	21	0.57
14	300	4.0	131.24	33	0.57
15	450	6.0	231.36	39	0.86
16	450	6.0	164.05	27	0.86
17	450	6.0	163.18	27	0.86
18	600	8.0	338.52	42	1.1
20	600	8.0	413.39	52	1.1
21	600	8.0	203.29	25	1.1
22	600	8.0	198.74	25	1.1
23	600	8.0	236.13	30	1.1
24	600	8.0	282.55	35	1.1

25	600	8.0	230.00	29	1.1
26	750	10	200.07	20	1.4
27	750	10	240.51	24	1.4
28	750	10	206.86	21	1.4
29	950	13	352.58	28	1.8
30	950	13	332.61	26	1.8
31	950	13	347.52	27	1.8
32	950	13	291.69	23	1.8
33	1200	16	441.43	28	2.3
34	1200	16	559.64	35	2.3
35	1200	16	316.74	20	2.3
36	1200	16	708.42	44	2.3
37	1200	16	418.44	26	2.3
38	1200	16	314.43	20	2.3
40	1000	13	189.71	14	1.9
41	1000	13	232.54	17	1.9
42	1000	13	358.73	27	1.9

19 information not found
39 information not found
43 information not found

Avg Cmax	29	1.2	Avg daily dose
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Avg. Cmax = 29 μM per mg/kg
Molecular = 414 grams/mole (or 414
Avg. Cmax = 11,998 μg/L per mg/kg
= 12 mg/L per mg/kg

Average Cmax in female mice
Figure 3 of Lou et al., (2009) = 9 mg/L per mg/kg

CSAF based on 1 day Cmax	=	1.3
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Table 4 of manuscript. Cmax values after each dose from Elcombe et al. (2013)

Patient	Daily Dose mg/kg-day*	Cmax after each weekly dose in μM					
	week>	1	2	3	4	5	6
1	0.67	25.72	na	na	na	na	na
2	0.67	29.79	na	na	na	na	na
3	0.67	24.64	na	na	na	na	na
4	0.10	19.95	40.37	40.6	52.28	77.49	81.07
	Avg	25	40	41	52	77	81
5	0.19	23.66	50.82	80.2	87.35	100.84	109.1
6	0.19	32.32	47.47	70.55	97	89.54	179.07
7	0.19	30.91	-	55.78	73.03	-	-
	Avg	29	49	69	86	95	144
8	0.38	114.25	171.02	276.84	368.27	426.16	414.33
9	0.38	93.43	170.29	253.19	362.32	471.59	373.31
10	0.38	58.6	119.44	181.86	276.15	256.06	232.44
	Avg	89	154	237	336	385	340
11	0.57	111.65	178.42	237.26	288.21	326.13	386.77
12	0.57	122.9	182.32	240.93	303.06	372.99	-
13	0.57	85.32	-	-	-	-	-
14	0.57	131.24	179.97	297.35	420.49	478.38	562.63
	Avg	113	180	259	337	393	475
15	0.86	231.36	324.96	463.43	578.86	707.8	800.55
16	0.86	164.05	348.41	545.74	721.48	906.59	-
17	0.86	163.18	276.16	341.96	427.08	497.22	525.98
	Avg	186	317	450	576	704	663
18	1.1	338.52	406.73	590.95	-	-	-

20	1.1	413.39	327.38	474.01	562.88	651.85	770.32
21	1.1	203.29	504.5	652.79	734.36	847.13	995.39
22	1.1	198.74	309.8	433.41	595.95	-	-
23	1.1	236.13	400.07	635.73	-	-	-
24	1.1	282.55	488.31	691.46	858.92	813.92	966.13
25	1.1	230	360	480	640	750	780
	Avg	272	400	565	678	766	878
26	1.4	200.07	397.76	624.63	625.39	732.46	823.68
27	1.4	240.51	410.69	569.22	719.7	811.16	-
28	1.4	206.86	321.26	472.99	654.6	757.67	853.05
	Avg	216	377	556	667	767	838
29	1.8	352.58	606.03	896.3	896.9	971.71	1043.2
30	1.8	332.61	-	-	-	-	-
31	1.8	347.52	554.28	799.77	998.35	1031.14	-
32	1.8	291.69	516.7	-	-	-	-
40	1.9	189.71	367.81	487.42	554.18	697.26	826.44
41	1.9	232.54	412.52	558.23	748.03	802.5	1209.31
42	1.9	358.73	585.96	764.91	1231.51	1281.13	1251.9
	Avg	301	507	701	886	957	1083
33	2.3	441.43	734.84	925.6	1172.58	1231.36	1317.84
34	2.3	559.64	893.14	1115.82	1440.82	1448.79	-
35	2.3	316.74	592.29	704.4	1172.95	-	-
36	2.3	708.42	679.68	968.95	1143.19	-	1293.03
37	2.3	418.44	841.24	1135.41	1393.91	1530.33	-
38	2.3	314.43	538.47	808.36	787.75	931.5	958.1
	Avg	460	713	943	1185	1285	1190

* Doses given in mg/week. Mg/kg-day doses are determined from average body weight of 75 kg as stated by Convertino et al. (2018) and further dividing by seven days/week.

Table 5 of manuscript. Average Cmax values after each dose in μM per mg/kg-day.

Daily Dose mg/kg-day*	Average Cmax after each weekly dose in μM per mg/kg-day					
	week>	1	2	3	4	5
0.1	250	404	406	504	775	801
0.19	152	259	353	452	501	758
0.38	234	404	530	883	1012	895
0.57	198	316	454	577	689	833
0.86	217	368	495	670	818	771
1.1	253	362	520	625	700	828
1.4	154	269	397	476	548	599
1.85	163	263	364	474	517	585
2.3	200	310	407	515	559	517
Average	202	328	436	575	680	732

From Table 5, avg human Cmax at 6 weeks =	732	$\mu\text{Moles per mg/kg}$
when multiplied by 414 grams/mole (or 414 $\mu\text{g}/\mu\text{mole}$)		
equals	303,048	$\mu\text{g/L per mg/kg}$
or	303	mg/L per mg/kg
Elcombe et al doses	From Manuscript Figure 2 (Lou et al., 2009, Figure 7b)	
	Dose mg/kg-d	~ 17 day SS
lowest human dose >>>	0.1	0.7
\sim avg. human dose >>>	1	5
	5	20
Cmax-SS in mg/L per mg/kg-day in	50	at 0.1 mg/kg-day
female mice from Figure 7b of Lou et al. (2009)	35	at 1.0 mg/kg-day

Human/mouse CSAF with low human dose	=	6.1
Human/mouse CSAF with avg. human dose	=	8.7

Figure 78 of Elcombe et al. (2013)

TABLE B

Patient	Dose	6 week level	SS level	ratio SS/6
5	100	109	280	2.6
9	200	373	520	1.4
10	200	232	600	2.6
11	300	387	530	1.4
14	300	563	950	1.7
15	450	801	1050	1.3
20	600	770	1000	1.3
25	600	780	950	1.2
26	750	824	750	0.9
Value used to adjust 6 week DDEF in TERA report				1.6

TABLE C. Information from Elcombe et al. (2013) on patients beyond 6 weeks of exposure

Patient	Dose	6 week level	Measurements Past 6 weeks				Average of Past 6 wk	Ratio past/6
			1st	2nd	3rd	4th		
5	100	109	276				276	2.5
9	200	399	471	617	501	540	532	1.3
10	200	232	570	650	660	570	613	2.6
11	300	387	574				574	1.5
14	300	562	890	980	940		937	1.7
15	450	801	1175	1000			1088	1.4
20	600	770	950				950	1.2
25	600	780	1050				1050	1.3
26	750	823	670				670	0.8

Values in yellow were read from Figure 78; other values were read from patient tables

Average 1.6