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

TABLE A

Elcombe et al., 2013. Individual patient PFOA doses, C_{max} and T_{max}. 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 C_{max} (μM)</u>	<u>C_{max} /(Dose)</u>	<u>T_{max} (hours)</u>	<u>Concentration Day 8</u>	<u>~1/2 life phase 1(days)</u>	<u>Dose (mg/kg-day)</u>
1	50	0.67	25.72	39	1.5	8.54	5	na
2	50	0.67	29.79	45	1.5	17.15	9	na
3	50	0.67	24.64	37	1.5	8.6	6	na
4	50	0.67	19.95	30	2	12.76	10	0.10
5	100	1.33	23.66	18	4	18.96	13	0.19
6	100	1.33	32.32	24	2	26.16	13	0.19
7	100	1.33	30.91	23	2	12.23	6	0.19
8	200	2.67	114.25	43	2	64.56	9	0.38
9	200	2.67	93.43	35	2	60.06	10	0.38
10	200	2.67	58.6	22	24	51	14	0.38
11	300	4.00	111.65	28	4	57.87	8	0.57
12	300	4.00	122.9	31	4	64.83	8	0.57
13	300	4.00	85.32	21	4	na	na	0.57
14	300	4.00	131.24	33	2	79.64	10	0.57
15	450	6.00	231.36	39	3	137.59	10	0.86
16	450	6.00	164.05	27	24	181.57	18	0.86
17	450	6.00	163.18	27	4	146.02	14	0.86
18	600	8.00	338.52	42	2	180.97	9	1.14
20	600	8.00	413.39	52	24	125.29	5	1.14
21	600	8.00	203.29	25	24	217.79	17	1.14
22	600	8.00	198.74	25	4	143.49	12	1.14
23	600	8.00	236.13	30	4	204.11	14	1.14
24	600	8.00	282.55	35	4	211.59	12	1.14

25	600	8.00	230.00	29	na	180	13	1.14
26	750	10.00	200.07	20	24	185.64	15	1.43
27	750	10.00	240.51	24	3	167.86	11	1.43
28	750	10.00	206.86	21	2	160.74	12	1.43
29	950	12.67	352.58	28	24	288.92	13	1.81
30	950	12.67	332.61	26	4	na	na	1.81
31	950	12.67	347.52	27	24	237.01	11	1.81
32	950	12.67	291.69	23	2	192.28	11	1.81
33	1200	16.00	441.43	28	2	317.41	12	2.29
34	1200	16.00	559.64	35	4	350.51	10	2.29
35	1200	16.00	316.74	20	4	254.36	13	2.29
36	1200	16.00	708.42	44	24	285.95	6	2.29
37	1200	16.00	418.44	26	24	422.38	16	2.29
38	1200	16.00	314.43	20	3	268.04	14	2.29
40	1000	13.33	189.71	14	4	119.66	10	1.90
41	1000	13.33	232.54	17	3	171.34	12	1.90
42	1000	13.33	358.73	27	3	250.6	11	1.90

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

Avg Cmax	29	Average 1/2 life phase 1	11	1.23
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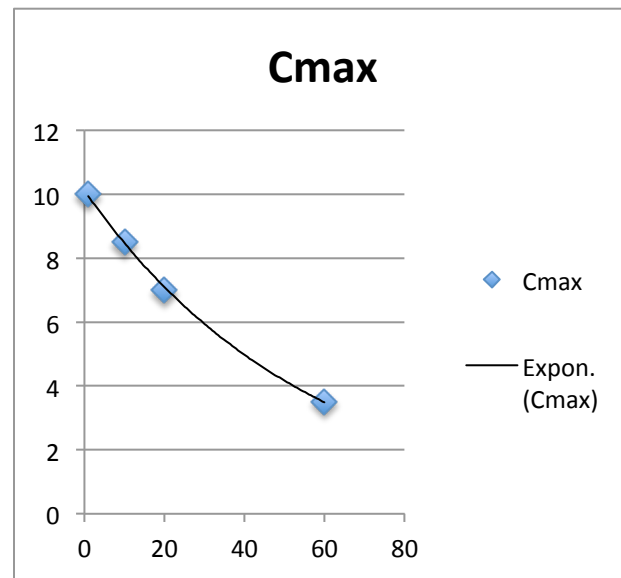
Average daily dose

Avg. Cmax	=	29	μM per mg/kg
Molecular		414	grams/mole (or 414
Avg. Cmax	=	11,995	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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From Lou et al., 2009, Figure 3, single dose

	Dose (mg/day)	Cmax
	1	10
	10	8.5
estimated from graph below	20	7
	60	3.5



'FOA)

TABLE B
Information not used in manuscript

<u>Cmax at Last dose</u>	<u>Cmax/Dose</u>	<u>Days</u>	<u>Comment</u>
		36	only one dose in 6 weeks
		36	only one dose in 6 weeks
		36	only one dose in 6 weeks
81.07	851	37	
109.10	573	37	
138.38	726	36	
63.42	333	23	
414.33	1088	36	
373.31	980	36	
232.44	610	36	
386.77	677	37	
334.20	585	30	
85.32	149	1	not enough time for 2nd phase
562.63	985	36	
800.55	934	36	
906.59	1058	29	
525.98	614	37	
590.95	517	15	
770.32	674	36	
995.39	871	37	
595.95	521	23	
635.73	556	15	
966.13	845	37	

980	858	35	from Elcombe Figure 84
823.68	577	36	
811.16	568	29	
853.05	597	36	
971.71	537	29	
332.61	184	1	not enough time for 2nd phase
1031.14	570	30	
516.70	286	8	
1317.84	577	37	
1448.79	634	29	
1172.95	513	23	
1293.03	566	36	
1530.33	670	30	
958.10	419	37	
826.44	434	37	
1209.31	635	37	
1251.90	657	37	

From Table E, average human Cmax at 6 weeks	732	μMoles per mg/kg
when multiplied by 414 grams/mole (or 414 μg/μmole)		
equals	303,048	μg/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)		
	<u>Dose (mg/kg-day)</u>	<u>~1 day Cmax (mg/L)</u>	<u>~17 day SS (mg/L)</u>
lowest human dose >>>	0.1	0.7	5
~ avg. human dose >>>	1	5	35
	5	20	60

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 based on low human Cmax	=	6.1
Human/mouse CSAF based on avg. human Cmax	=	8.7

11	Avg. 1/2 life of phase 1 in days
~5 weeks	1/2 life of phase 2 based on Figure 78 (based on 5 half-lives to steady state, or ~25 weeks)