

Appendix "Practical Guidance on the Development of a Data Derive Extrapolation Factors for Developmental Toxicity:

A Preliminary Research Case Study with PFOA" Dated 1-30-19

Elcombe et al., 2013. Individual Patient PFOA doses and related Cmax and Tmax.

Human weights were given as a 75 kg average based on the published paper by 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>Tmax (hours)</u>
1	50	0.67	25.72	39	1.5
2	50	0.67	29.79	45	1.5
3	50	0.67	24.64	37	1.5
4	50	0.67	19.95	30	2
5	100	1.33	23.66	18	4
6	100	1.33	32.32	24	2
7	100	1.33	30.91	23	2
8	200	2.67	114.25	43	2
9	200	2.67	93.43	35	2
10	200	2.67	58.6	22	24
11	300	4.00	111.65	28	4
12	300	4.00	122.9	31	4
13	300	4.00	85.32	21	4
14	300	4.00	131.24	33	2
15	450	6.00	231.36	39	3
16	450	6.00	164.05	27	24
17	450	6.00	163.18	27	4
18	600	8.00	338.52	42	2
20	600	8.00	413.39	52	24
21	600	8.00	203.29	25	24
22	600	8.00	198.74	25	4
23	600	8.00	236.13	30	4
24	600	8.00	282.55	35	4
25	600	8.00	230.00	29	na
26	750	10.00	200.07	20	24

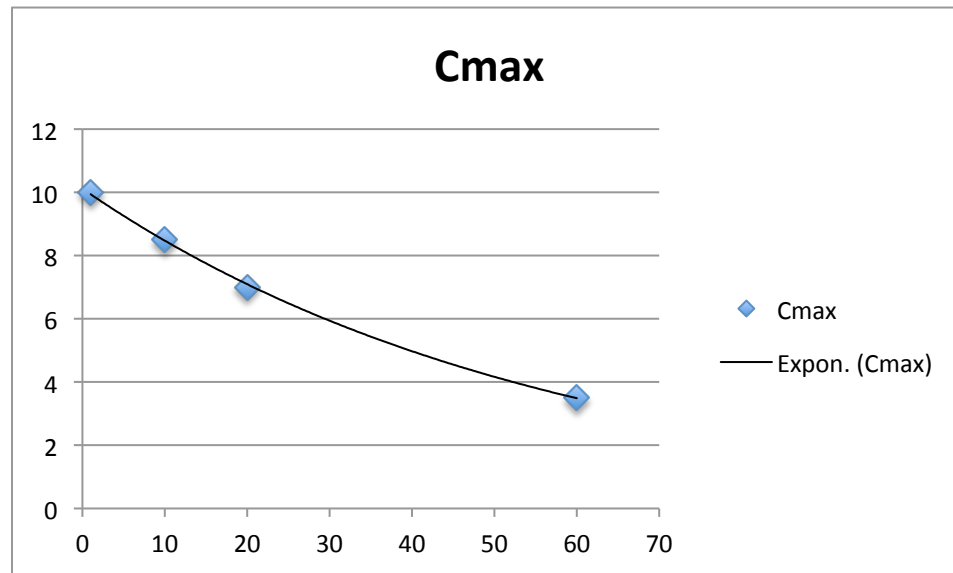
27	750	10.00	240.51	24	3
28	750	10.00	206.86	21	2
29	950	12.67	352.58	28	24
30	950	12.67	332.61	26	4
31	950	12.67	347.52	27	24
32	950	12.67	291.69	23	2
33	1200	16.00	441.43	28	2
34	1200	16.00	559.64	35	4
35	1200	16.00	316.74	20	4
36	1200	16.00	708.42	44	24
37	1200	16.00	418.44	26	24
38	1200	16.00	314.43	20	3
40	1000	13.33	189.71	14	4
41	1000	13.33	232.54	17	3
42	1000	13.33	358.73	27	3
19	information not found				
39	information not found				
43	information not found				

Avg. Cmax	=	29	μM per mg/kg
Molecular		414	grams/mole (or
Weight of			414 μg/μmole)
PFOA			
Avg. Cmax	=	11,998	μg/L per mg/kg
	=	12	mg/L per mg/kg
Average Cmax in female mice			
from 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



<u>Concentration day 8</u>	<u>~1/2 life phase 1(days)</u>	<u>Daily Dose (mg/kg-day)</u>
8.54	5	na
17.15	9	na
8.6	6	na
12.76	10	0.10
18.96	13	0.19
26.16	13	0.19
12.23	6	0.19
64.56	9	0.38
60.06	10	0.38
51	14	0.38
57.87	8	0.57
64.83	8	0.57
na	na	0.57
79.64	10	0.57
137.59	10	0.86
181.57	18	0.86
146.02	14	0.86
180.97	9	1.14
125.29	5	1.14
217.79	17	1.14
143.49	12	1.14
204.11	14	1.14
211.59	12	1.14
180	13	1.14
185.64	15	1.43

167.86	11	1.43
160.74	12	1.43
288.92	13	1.81
na	na	1.81
237.01	11	1.81
192.28	11	1.81
317.41	12	2.29
350.51	10	2.29
254.36	13	2.29
285.95	6	2.29
422.38	16	2.29
268.04	14	2.29
119.66	10	1.90
171.34	12	1.90
250.6	11	1.90

Average 1/2 life phase 1	11	1.23	Average daily dose
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from Table 7 of "Cmax" sheet = 732 μ Moles per mg/kg
414 grams/mole (or 414 μ g/ μ mole)

303,048 μ g/L per mg/kg
303 mg/L per mg/kg

Cmax-SS in female mice
from Figure 7b of Lou et al. (2009) 35

CSAF based on multiple day Cmax	8.7
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From Lou et al., 2009, Figure 7b, multiple doses

	Dose (mg/day)	1 day Cmax	17 day SS	ratio
	0.1	0.7	5	7.1
~ avg. human dose	1	5	35	7.0
	5	20	60	3.0

11
~5 weeks

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

Information not used

<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
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

not enough time for 2nd phase

Table 6 of TERA report. 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
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 x. Average Cmax values after each dose (not used in TERA Report)

Daily Dose mg/kg-day*	Average Cmax after each weekly dose in μM					
	1	2	3	4	5	6
0.1	25	40	41	50	77	80
0.19	29	49	67	86	95	144
0.38	89	154	201	336	385	340
0.57	113	180	259	329	393	475
0.86	186	317	425	576	704	663
1.1	279	398	572	688	770	911
1.4	216	377	556	667	767	838
1.8 & 1.9	301	487	673	877	957	1083
2.3	460	713	937	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.

Figure of Table x (not used in TERA Report)

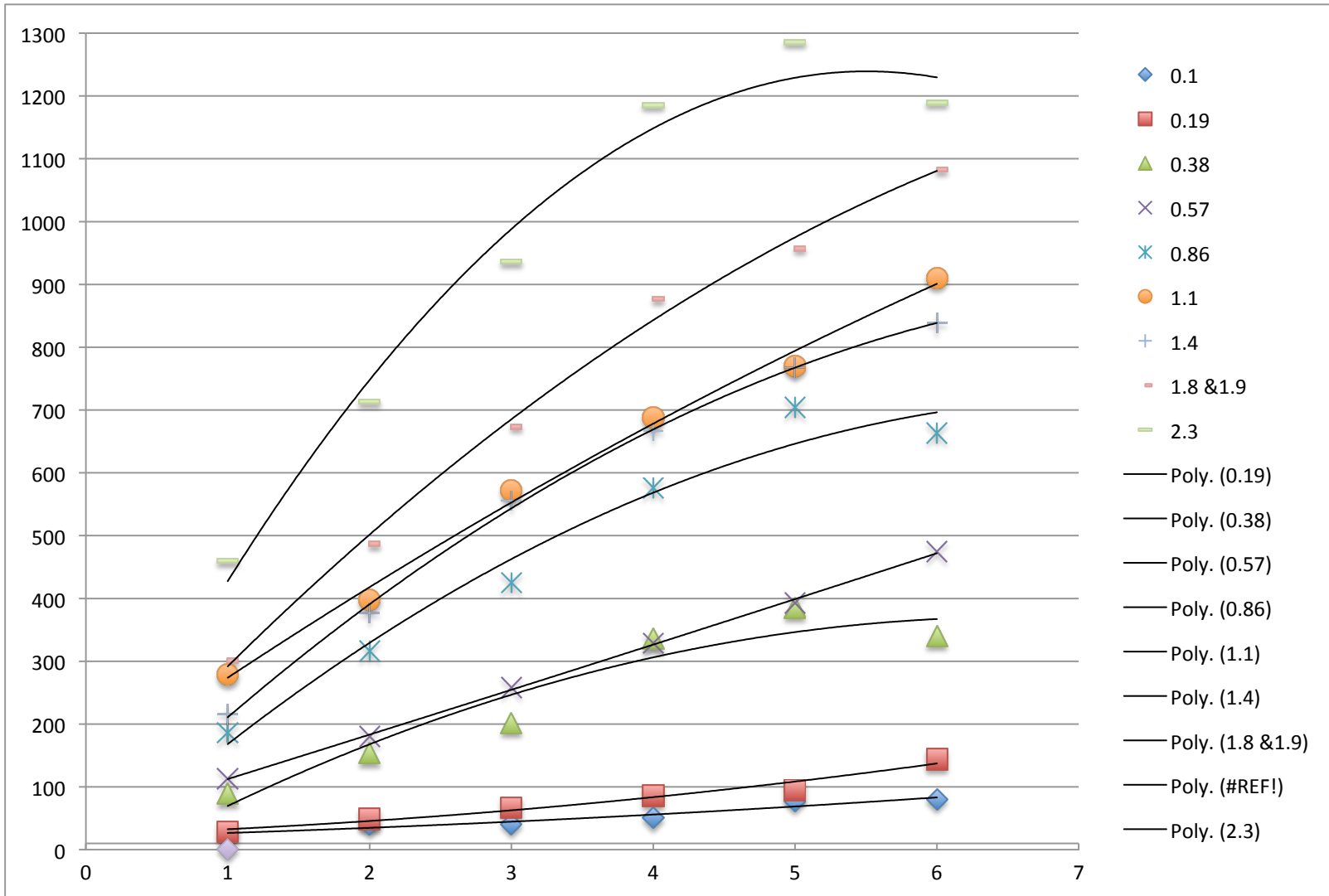
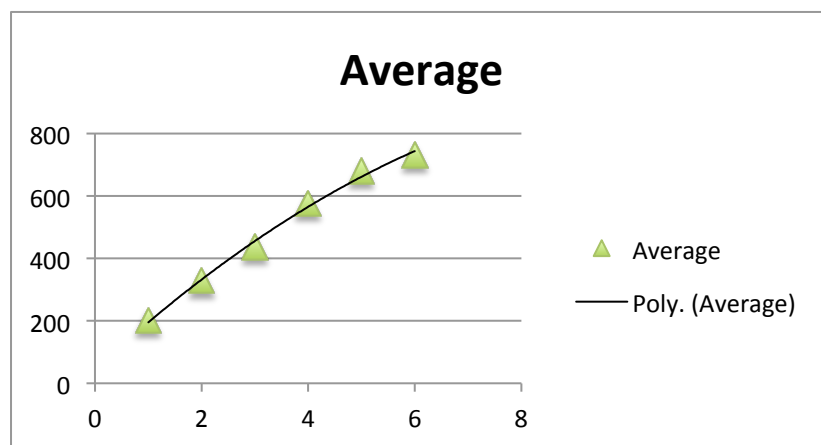


Table 7 of TERA Report. Average Cmax values after each dose in μM per mg/kg-day.

Daily Dose mg/kg-day*	Average Cmax after each weekly dose in μM per mg/kg-day						Data not used		
	week>	1	2	3	4	5	6	Weighted Analysis	
0.1	250	404	406	504	775	801	# of patients	Week 1	week 6
0.19	152	259	353	452	501	758	1	250	801
0.38	234	404	530	883	1012	895	2	305	1517
0.57	198	316	454	577	689	833	3	701	2684
0.86	217	368	495	670	818	771	2	396	1666
1.1	253	362	520	625	700	828	2	433	1542
1.4	154	269	397	476	548	599	4	1014	3311
1.85	163	263	364	474	517	585	2	308	1198
2.3	200	310	407	515	559	517	4	651	2341
Average	202	328	436	575	680	732	3	600	1552
							23	4657	16612
							average Cmax	202	722



Values were approximated from
Figure 78 of Elcombe et al. (2013)

Table y

<u>Patient</u>	<u>Dose</u>	<u>6 week level</u>	<u>SS level</u>	<u>ratio SS/6</u>
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

Average 1.6

Value used to adjust 6 week DDEF in TERA report