

Supplemental Materials

Risk characterization and probabilistic concentration-response modeling of complex environmental mixtures using novel approach methodologies (NAMs) data from the organotypic *in-vitro* human stem cell assays

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1 Supplementary Data

The zip file contains the folder of R code (**codes**) and datasets (**datasets**) that can reproduce the modeling and analyze result (in **outputs** folder) and visualize plots (in **plots** folder) and final report (in **reports** folder). All data will publicly release on Github after the paper published. The details and data pipelines are included in:

- **codes:** The source code to reproduce the modeling and analyze result that include:
 - *hill_two.stan*: Stan code of Hill model for the concentration-response modeling.
 - *0_mcmc_ind_chems.R*: R code for conducting the Hamiltonian Monte chain Monte Carlo simulation for individual chemicals.
 - *1_mcmc_mixtures.R*: R code for conducting the Hamiltonian Monte chain Monte Carlo simulation for mixtures.
 - *2_ec_10_pred.R*: R code to estimate curve-fitting and predicted EC₁₀ in mixture for each phenotype.
 - *3_conc_resp_pred.R*: R code to reconstruct the concentration-response profiles.
 - *4_plot.R*: R codes to generate the figures in manuscript.
 - *5_plot_suppl.R*: R codes to generate the same figures in Supplemental Materials.
- **datasets:** The provided tidy data files include the individual chemical information (*chem_info.csv*) and cell assay results (*chem_data.csv*). The mixture information and cell assay results can be found in *mix_info.csv* and *mix_data.csv*. The data files contained the following columns:
 - *chemical*: Name of chemical.
 - *mixture*: Name of mixture.
 - *Replication*: Replication number. Two replications were conducted in individual chemicals. The mixtures had six replication.
 - *Concentration*: Experimental concentration (unit = micromole).
 - *Dilution*: Diluted factor according to the designed concentration in mixture.
 - *Response*: Response proportion that had been normalized (0 - 1) based on the control group.

- *celltype*: Name of human induced pluripotent stem cells-derived cells.
 - *phenotype*: Cytotoxicity and functional phenotypes for each cell.
- **outputs:** The files in the output folder are generated by the above R code and datasets. The Bayesain estimated model parameters for individual chemicals were named like *HUVECs_42_chem_params.rda*. Also, the mixtures were named like *HUVECs_mixtures_params.rda*. The outputs of curve-fitting and predicted EC₁₀ in the mixture for each phenotype were stored in *ec_10_pred.rda*. Also, the calculated outputs to reconstruct the mixture concentration-response profile are in *mix_CR.rda*.
 - **plots:** All plots showed in the manuscript were saved in this folder. The **suppl** folder includes the supplementary figures that showed below.

2 Supplementary Tables

Table S1. The list of chemical that were be used in this study.

No.	Chemical	CAS_trimmed	Class	Molecular.weight	class
1	Benz(a)anthracene	56-55-3	PAH	228.2900	PAH
2	Naphthalene	91-20-3	PAH	128.1700	PAH
3	Fluoranthene	206-44-0	PAH	202.2600	PAH
4	p,p'-DDT	50-29-3	Pesticide	354.4800	Pesticides
5	Dieldrin	60-57-1	Pesticide	380.9100	Pesticides
6	Aldrin	309-00-2	Pesticide	364.9000	Pesticides
7	Heptachlor	76-44-8	Pesticide	373.3200	Pesticides
8	Lindane	58-89-9	Pesticide	290.8300	Pesticides
9	Disulfoton	298-04-4	Pesticide	274.4040	Pesticides
10	Endrin	72-20-8	Pesticide	380.9070	Pesticides
11	Diazinon	333-41-5	Pesticide	304.3400	Pesticides
12	Heptachlor epoxide	1024-57-3	Pesticide	389.3200	Pesticides
13	Pentachlorophenol	87-86-5	HPV	266.3400	HPV
14	Dibutyl phthalate	84-74-2	Plasticizer	278.3500	Phthalates
15	Chlorpyrifos	2921-88-2	Pesticide	350.5700	Pesticides
16	Di(2-ethylhexyl) phthalate	117-81-7	Plasticizer	390.5600	Phthalates
17	2,4,6-Trichlorophenol	88-06-2	HPV	197.4500	HPV
18	Ethion	563-12-2	Pesticide	384.4800	Pesticides
19	Azinphos-methyl	86-50-0	Pesticide	317.3200	Pesticides
20	2,4,5-Trichlorophenol	95-95-4	HPV	197.4460	HPV
21	Parathion	56-38-2	Pesticide	291.2600	Pesticides
22	Benzo(b)fluoranthene	205-99-2	PAH	252.3200	PAH
23	Trifluralin	1582-09-8	Pesticide	335.2800	Pesticides

No.	Chemical	CAS_trimmed	Class	Molecular.weight	class
24	Acenaphthene	83-32-9	PAH	154.2100	PAH
25	p,p'-DDD	72-54-8	Pesticide	320.0400	Pesticides
26	Benzidine	92-87-5	HPV	184.2400	HPV
27	Endosulfan	115-29-7	Pesticide	406.9000	Pesticides
28	Methoxychlor	72-43-5	Pesticide	345.6500	Pesticides
29	2,4-Dinitrophenol	51-28-5	Pesticide	184.1100	Pesticides
30	2,4-Dinitrotoluene	121-14-2	HPV	182.1340	HPV
31	Dicofol	115-32-2	Pesticide	370.4800	Pesticides
32	p-Cresol	106-44-5	HPV	108.1300	HPV
33	o,p'-DDT	789-02-6	Pesticide	354.4900	Pesticides
34	2-Methyl-4,6-dinitrophenol	534-52-1	HPV	198.1300	HPV
35	1,2,3-Trichlorobenzene	87-61-6	HPV	181.4470	HPV
36	Lead nitrate	7439-92-1	Metal	331.2000	Heavy Metals
37	Cadmium chloride	7440-43-9	Metal	183.3100	Heavy Metals
38	Zinc chloride	7440-66-6	Metal	136.3150	Heavy Metals
39	Mercuric chloride	7487-94-7	Metal	271.5200	Heavy Metals
40	Potassium chromate (VI)	18540-29-9	Metal	194.1900	Heavy Metals
41	Cobalt chloride	7440-48-4	Metal	129.8390	Heavy Metals
42	Nickel chloride	7440-02-0	Metal	129.5994	Heavy Metals

Table S2. The summary of the AC50-based designed mixture.

Chemical	AC50-L (micromole)	AC50-H (micromole)	AC50-L (%)	AC50-H (%)
Benz(a)anthracene	0.018100	112.0	0.04	1.80
Naphthalene	0.002330	144.0	0.00	2.31
Fluoranthene	0.077900	164.0	0.16	2.63
p,p'-DDT	0.000479	253.0	0.00	4.06
Dieldrin	0.040600	169.0	0.08	2.71
Aldrin	0.912000	253.0	1.89	4.06
Heptachlor	5.050000	164.0	10.46	2.63
Lindane	5.680000	116.0	11.76	1.86
Disulfoton	5.870000	81.8	12.16	1.31
Endrin	0.219000	64.9	0.45	1.04
Diazinon	0.061600	118.0	0.13	1.89
Heptachlor epoxide	1.670000	107.0	3.46	1.72
Pentachlorophenol	0.993000	164.0	2.06	2.63
Dibutyl phthalate	0.010200	72.4	0.02	1.16
Chlorpyrifos	2.350000	164.0	4.87	2.63
Di(2-ethylhexyl) phthalate	0.370000	67.2	0.77	1.08
2,4,6-Trichlorophenol	0.808000	316.0	1.67	5.07
Ethion	0.163000	285.0	0.34	4.57
Azinphos-methyl	0.094200	253.0	0.20	4.06
2,4,5-Trichlorophenol	0.552000	133.0	1.14	2.13
Parathion	0.100000	81.8	0.21	1.31
Benzo(b)fluoranthene	0.004000	253.0	0.01	4.06
Trifluralin	0.094600	113.0	0.20	1.81
Acenaphthene	2.450000	78.1	5.07	1.25

Chemical	AC50-L (micromole)	AC50-H (micromole)	AC50-L (%)	AC50-H (%)
p,p'-DDD	0.981000	133.0	2.03	2.13
Benzidine	3.110000	632.0	6.44	10.13
Endosulfan	0.164000	253.0	0.34	4.06
Methoxychlor	0.476000	181.0	0.99	2.90
2,4-Dinitrophenol	0.094400	122.0	0.20	1.96
2,4-Dinitrotoluene	4.850000	28.3	10.04	0.45
Dicofol	0.634000	117.0	1.31	1.88
p-Cresol	0.156000	25.3	0.32	0.41
o,p'-DDT	0.105000	112.0	0.22	1.80
2-Methyl-4,6-dinitrophenol	0.002230	164.0	0.00	2.63
1,2,3-Trichlorobenzene	0.002150	15.5	0.00	0.25
Lead nitrate	1.000000	100.0	2.07	1.60
Cadmium chloride	5.000000	100.0	10.35	1.60
Zinc chloride	1.000000	100.0	2.07	1.60
Mercuric chloride	0.126000	126.0	0.26	2.02
Potassium chromate (VI)	1.000000	100.0	2.07	1.60
Cobalt chloride	1.000000	100.0	2.07	1.60
Nickel chloride	1.000000	100.0	2.07	1.60

Table S3. The summary of the exposure-based designed mixture.

Chemical	Expo-L (micromole)	Expo-H (micromole)	Expo-L (%)	Expo-H (%)
Benz(a)anthracene	0.0000004	0.0001142	0.00	0.00
Naphthalene	0.0005857	0.1578079	0.00	0.20
Fluoranthene	0.0000012	0.0003547	0.00	0.00
p,p'-DDT	0.0000000	0.0000047	0.00	0.00
Dieldrin	0.0000140	0.0047156	0.00	0.01
Aldrin	0.0000101	0.0036380	0.00	0.00
Heptachlor	0.0000000	0.0000021	0.00	0.00
Lindane	0.0000063	0.0051959	0.00	0.01
Disulfoton	0.0000001	0.0000846	0.00	0.00
Endrin	0.0000205	0.0110974	0.00	0.01
Diazinon	0.0000002	0.0001608	0.00	0.00
Heptachlor epoxide	0.0000000	0.0000021	0.00	0.00
Pentachlorophenol	0.0000017	0.0000052	0.00	0.00
Dibutyl phthalate	0.0000256	0.0044487	0.00	0.01
Chlorpyrifos	0.0000002	0.0000950	0.00	0.00
Di(2-ethylhexyl) phthalate	0.0000256	0.0044487	0.00	0.01
2,4,6-Trichlorophenol	0.0000000	0.0000173	0.00	0.00
Ethion	0.0000002	0.0001369	0.00	0.00
Azinphos-methyl	0.0000000	0.0000007	0.00	0.00
2,4,5-Trichlorophenol	0.0000001	0.0000954	0.00	0.00
Parathion	0.0000011	0.0006720	0.00	0.00
Benzo(b)fluoranthene	0.0000008	0.0004048	0.00	0.00
Trifluralin	0.0003642	0.1946423	0.00	0.24
Acenaphthene	0.0000002	0.0000342	0.00	0.00

Chemical	Expo-L (micromole)	Expo-H (micromole)	Expo-L (%)	Expo-H (%)
p,p'-DDD	0.0000043	0.0005338	0.00	0.00
Benzidine	0.0000014	0.0003953	0.00	0.00
Endosulfan	0.0000260	0.0167759	0.00	0.02
Methoxychlor	0.0000000	0.0000102	0.00	0.00
2,4-Dinitrophenol	0.0000048	0.0007032	0.00	0.00
2,4-Dinitrotoluene	0.0000008	0.0001844	0.00	0.00
Dicofol	0.0000004	0.0002233	0.00	0.00
p-Cresol	0.0000018	0.0002292	0.00	0.00
o,p'-DDT	0.0000000	0.0000050	0.00	0.00
2-Methyl-4,6-dinitrophenol	0.0000535	0.0446951	0.00	0.06
1,2,3-Trichlorobenzene	0.0000012	0.0004521	0.00	0.00
Lead nitrate	0.0723938	0.0723938	0.09	0.09
Cadmium chloride	0.0444800	0.0444800	0.06	0.06
Zinc chloride	76.9230769	76.9230769	96.84	96.29
Mercuric chloride	0.0099701	0.0099701	0.01	0.01
Potassium chromate (VI)	1.9232249	1.9232249	2.42	2.41
Cobalt chloride	0.0339386	0.0339386	0.04	0.04
Nickel chloride	0.4259452	0.4259452	0.54	0.53

Table S4. The summary of the POD-based designed mixture.

Chemical	POD-L (micromole)	POD-H (micromole)	POD-L (%)	POD-H (%)
Benz(a)anthracene	1.0000000	100.0000000	0.04	0.47
Naphthalene	564.2592537	2739.4526320	20.39	12.83
Fluoranthene	157.4135185	1015.6731090	5.69	4.76
p,p'-DDT	0.0072505	0.0321568	0.00	0.00
Dieldrin	0.5444496	5.2629070	0.02	0.02
Aldrin	9.6012594	299.5681404	0.35	1.40
Heptachlor	0.0218881	0.0492708	0.00	0.00
Lindane	1.0000000	100.0000000	0.04	0.47
Disulfoton	0.0590265	0.5495373	0.00	0.00
Endrin	9.6012594	299.5681404	0.35	1.40
Diazinon	0.0338929	0.5057353	0.00	0.00
Heptachlor epoxide	0.0218881	0.0492708	0.00	0.00
Pentachlorophenol	0.3042524	7.0331182	0.01	0.03
Dibutyl phthalate	34.8952467	351.8825255	1.26	1.65
Chlorpyrifos	0.2062983	2.0496652	0.01	0.01
Di(2-ethylhexyl) phthalate	34.8952467	351.8825255	1.26	1.65
2,4,6-Trichlorophenol	11.5355283	64.6773746	0.42	0.30
Ethion	0.0781195	0.8800805	0.00	0.00
Azinphos-methyl	0.0282547	0.0638165	0.00	0.00
2,4,5-Trichlorophenol	665.1268293	7335.1382110	24.04	34.36
Parathion	0.1244289	1.2897856	0.00	0.01
Benzo(b)fluoranthene	157.4135185	1015.6731090	5.69	4.76
Trifluralin	173.9842357	1486.5754780	6.29	6.96
Acenaphthene	534.1177738	2973.7880630	19.30	13.93

Chemical	POD-L (micromole)	POD-H (micromole)	POD-L (%)	POD-H (%)
p,p'-DDD	0.0072505	0.0321568	0.00	0.00
Benzidine	2.6654363	8.1475274	0.10	0.04
Endosulfan	83.3342176	1791.4633860	3.01	8.39
Methoxychlor	0.9835145	6.4378968	0.04	0.03
2,4-Dinitrophenol	155.1683360	439.4894992	5.61	2.06
2,4-Dinitrotoluene	13.9218878	96.1295837	0.50	0.45
Dicofol	0.4281083	5.1148034	0.02	0.02
p-Cresol	49.3945062	609.6607949	1.79	2.86
o,p'-DDT	0.0072505	0.0321568	0.00	0.00
2-Methyl-4,6-dinitrophenol	13.9218878	96.1295837	0.50	0.45
1,2,3-Trichlorobenzene	11.5355283	64.6773746	0.42	0.30
Lead nitrate	0.0723938	0.0723938	0.00	0.00
Cadmium chloride	0.0444800	0.0444800	0.00	0.00
Zinc chloride	76.9230769	76.9230769	2.78	0.36
Mercuric chloride	0.0099701	0.0099701	0.00	0.00
Potassium chromate (VI)	1.9232249	1.9232249	0.07	0.01
Cobalt chloride	0.0339386	0.0339386	0.00	0.00
Nickel chloride	0.4259452	0.4259452	0.02	0.00

Table S5. The summary of the RFD-based designed mixture.

Chemical	RFD-L (micromole)	RFD-H (micromole)	RFD-L (%)	RFD-H (%)
Benz(a)anthracene	0.0000029	0.0032744	0.00	0.00
Naphthalene	0.1589463	0.7716768	0.19	0.67
Fluoranthene	0.0508532	0.2475908	0.06	0.21
p,p'-DDT	0.0000725	0.0003216	0.00	0.00
Dieldrin	0.0054445	0.0526291	0.01	0.05
Aldrin	0.0023863	0.0169737	0.00	0.01
Heptachlor	0.0000730	0.0001642	0.00	0.00
Lindane	0.0000052	0.0089029	0.00	0.01
Disulfoton	0.0000590	0.0005495	0.00	0.00
Endrin	0.0054445	0.0526291	0.01	0.05
Diazinon	0.0003389	0.0050574	0.00	0.00
Heptachlor epoxide	0.0000730	0.0001642	0.00	0.00
Pentachlorophenol	0.0077979	0.0234437	0.01	0.02
Dibutyl phthalate	0.0319486	0.0833089	0.04	0.07
Chlorpyrifos	0.0020630	0.0204967	0.00	0.02
Di(2-ethylhexyl) phthalate	0.0319486	0.0833089	0.04	0.07
2,4,6-Trichlorophenol	0.0038452	0.0215591	0.00	0.02
Ethion	0.0007812	0.0088008	0.00	0.01
Azinphos-methyl	0.0002844	0.0006424	0.00	0.00
2,4,5-Trichlorophenol	0.6651268	7.3351382	0.79	6.34
Parathion	0.0004106	0.0042563	0.00	0.00
Benzo(b)fluoranthene	0.0000089	0.0129301	0.00	0.01
Trifluralin	1.7398424	14.8657548	2.08	12.84
Acenaphthene	0.2071549	0.6465155	0.25	0.56

Chemical	RFD-L (micromole)	RFD-H (micromole)	RFD-L (%)	RFD-H (%)
p,p'-DDD	0.0001958	0.0504065	0.00	0.04
Benzidine	0.0029616	0.0090528	0.00	0.01
Endosulfan	1.1467985	10.6739559	1.37	9.22
Methoxychlor	0.0009816	0.0064250	0.00	0.01
2,4-Dinitrophenol	0.1551683	0.4394895	0.19	0.38
2,4-Dinitrotoluene	0.0444733	0.1201537	0.05	0.10
Dicofol	0.0042811	0.0511480	0.01	0.04
p-Cresol	0.0000102	0.0067740	0.00	0.01
o,p'-DDT	0.0000725	0.0003216	0.00	0.00
2-Methyl-4,6-dinitrophenol	0.0595455	0.6597063	0.07	0.57
1,2,3-Trichlorobenzene	0.0042347	0.0242737	0.01	0.02
Lead nitrate	0.0723938	0.0723938	0.09	0.06
Cadmium chloride	0.0444800	0.0444800	0.05	0.04
Zinc chloride	76.9230769	76.9230769	91.83	66.46
Mercuric chloride	0.0099701	0.0099701	0.01	0.01
Potassium chromate (VI)	1.9232249	1.9232249	2.30	1.66
Cobalt chloride	0.0339386	0.0339386	0.04	0.03
Nickel chloride	0.4259452	0.4259452	0.51	0.37

3 Supplementary Figures

3.1 Curve-fitting of single chemical concentration-response

3.1.1 iCell Neurons

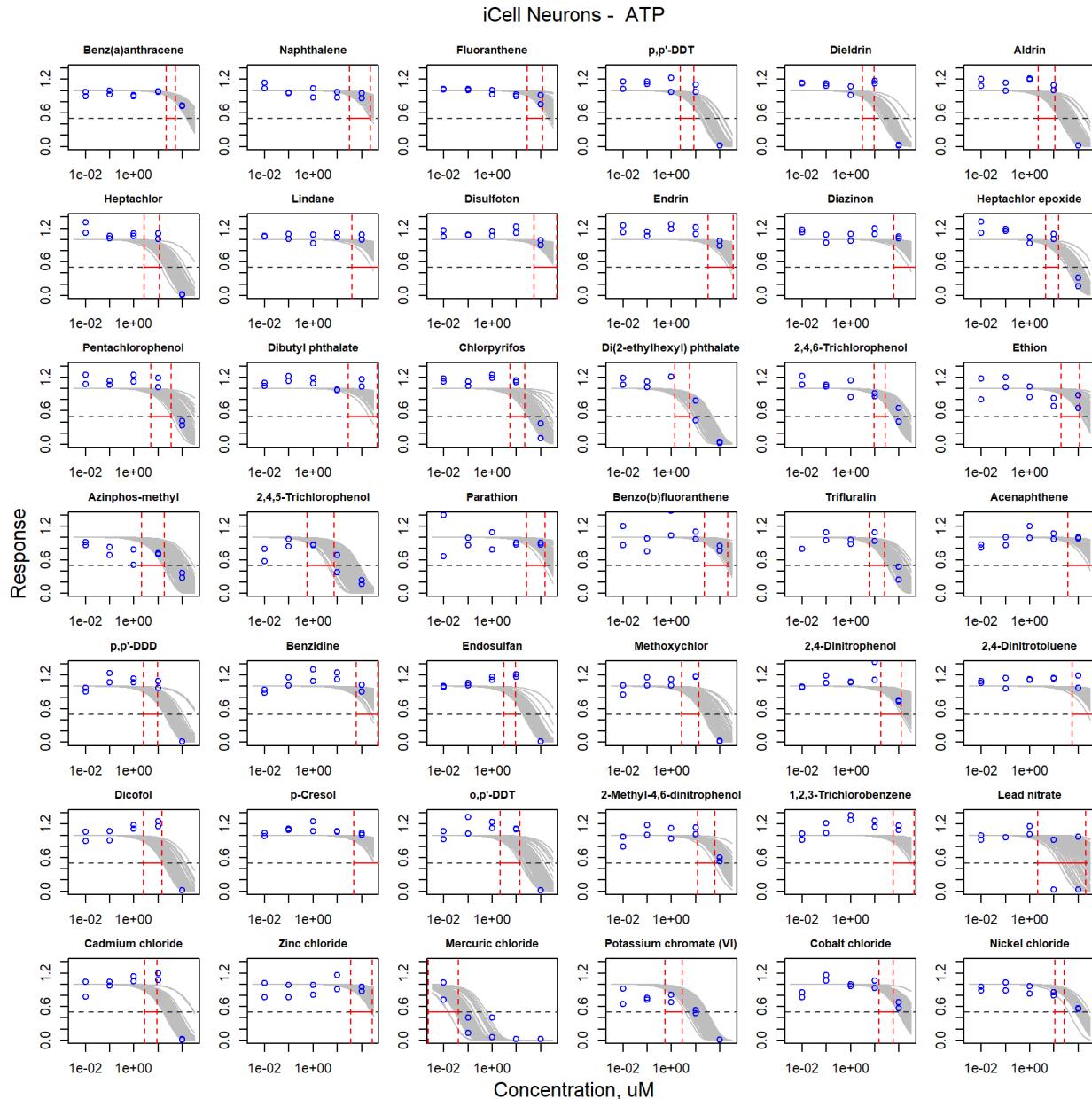


Figure S1. Curve-fitting of single chemical concentration and observed response (ATP) in iCell Neurons.

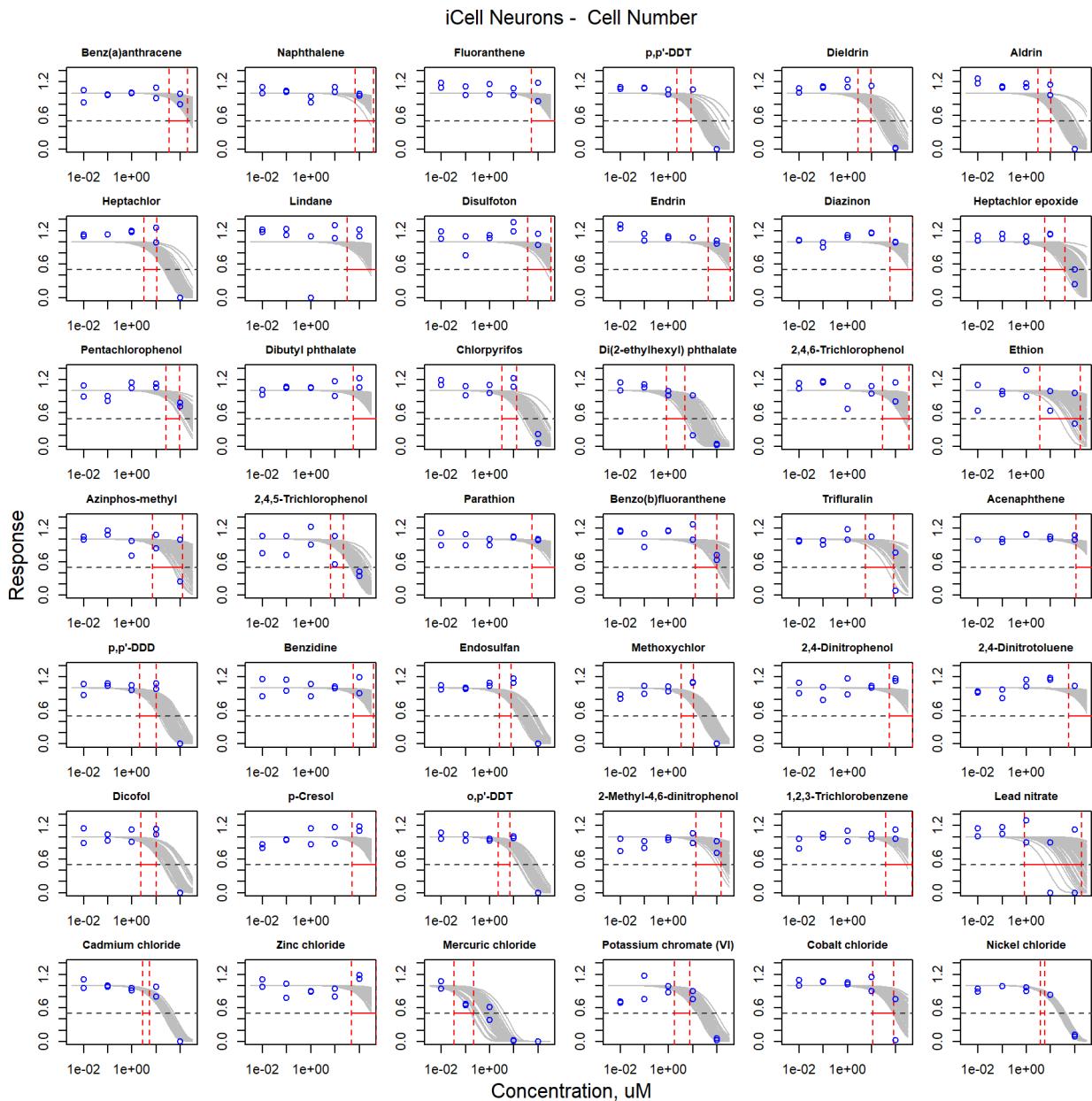


Figure S2. Curve-fitting of single chemical concentration and observed response (Cell Number) in iCell Neurons.

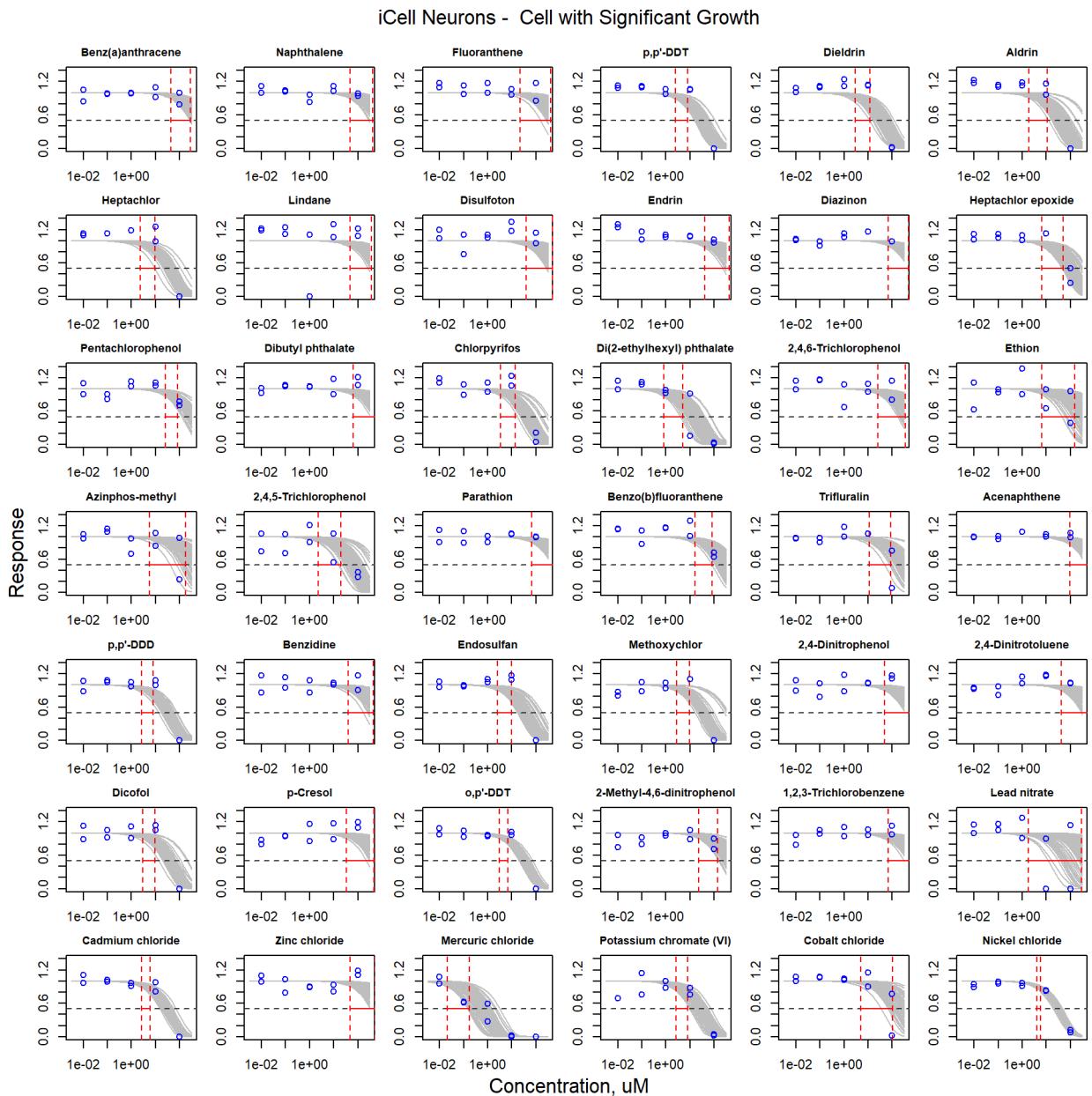


Figure S3. Curve-fitting of single chemical concentration and observed response (Cell with Significant Growth) in iCell Neurons.

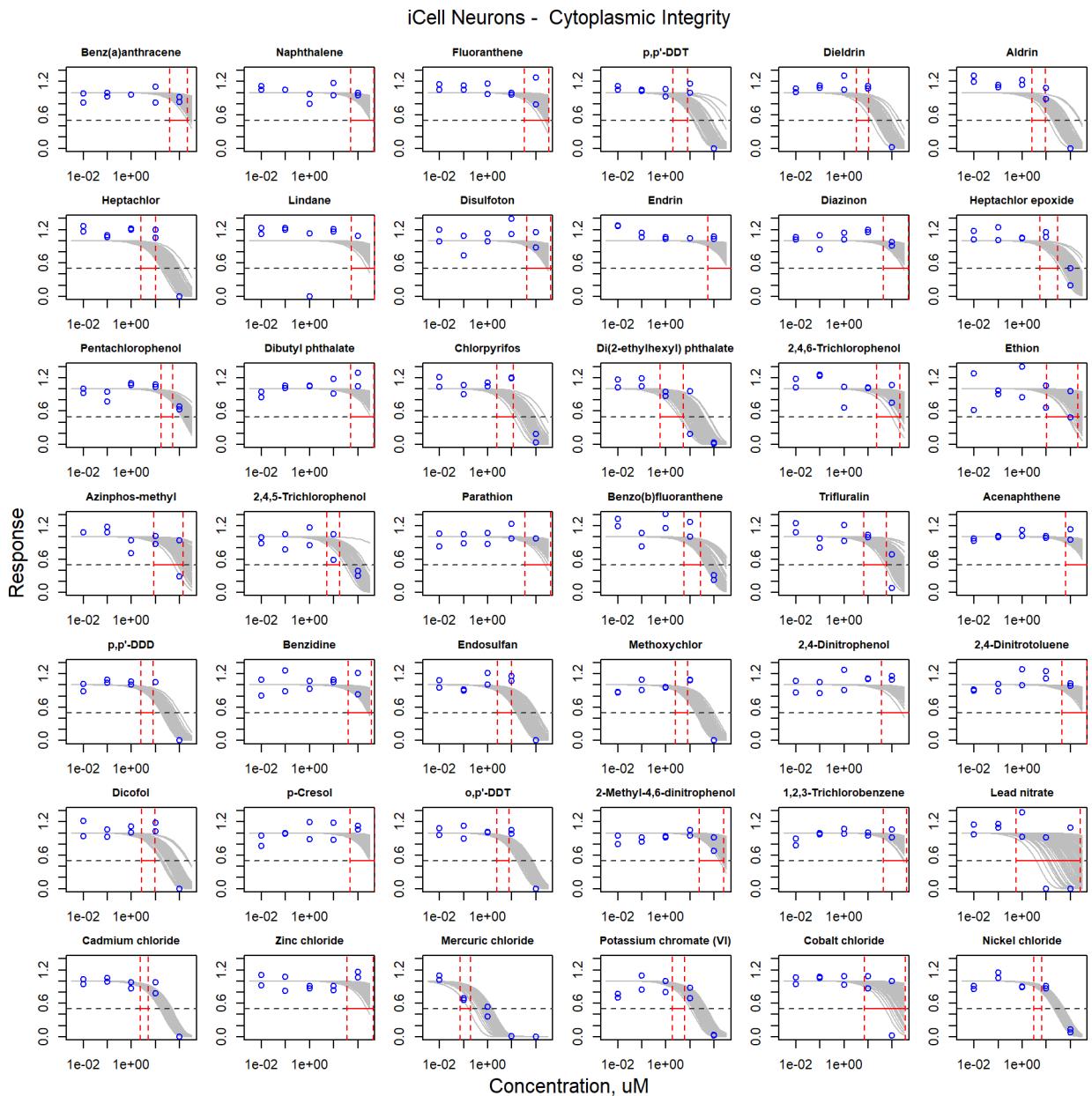


Figure S4. Curve-fitting of single chemical concentration and observed response (Cytoplasmic Integrity) in iCell Neurons.

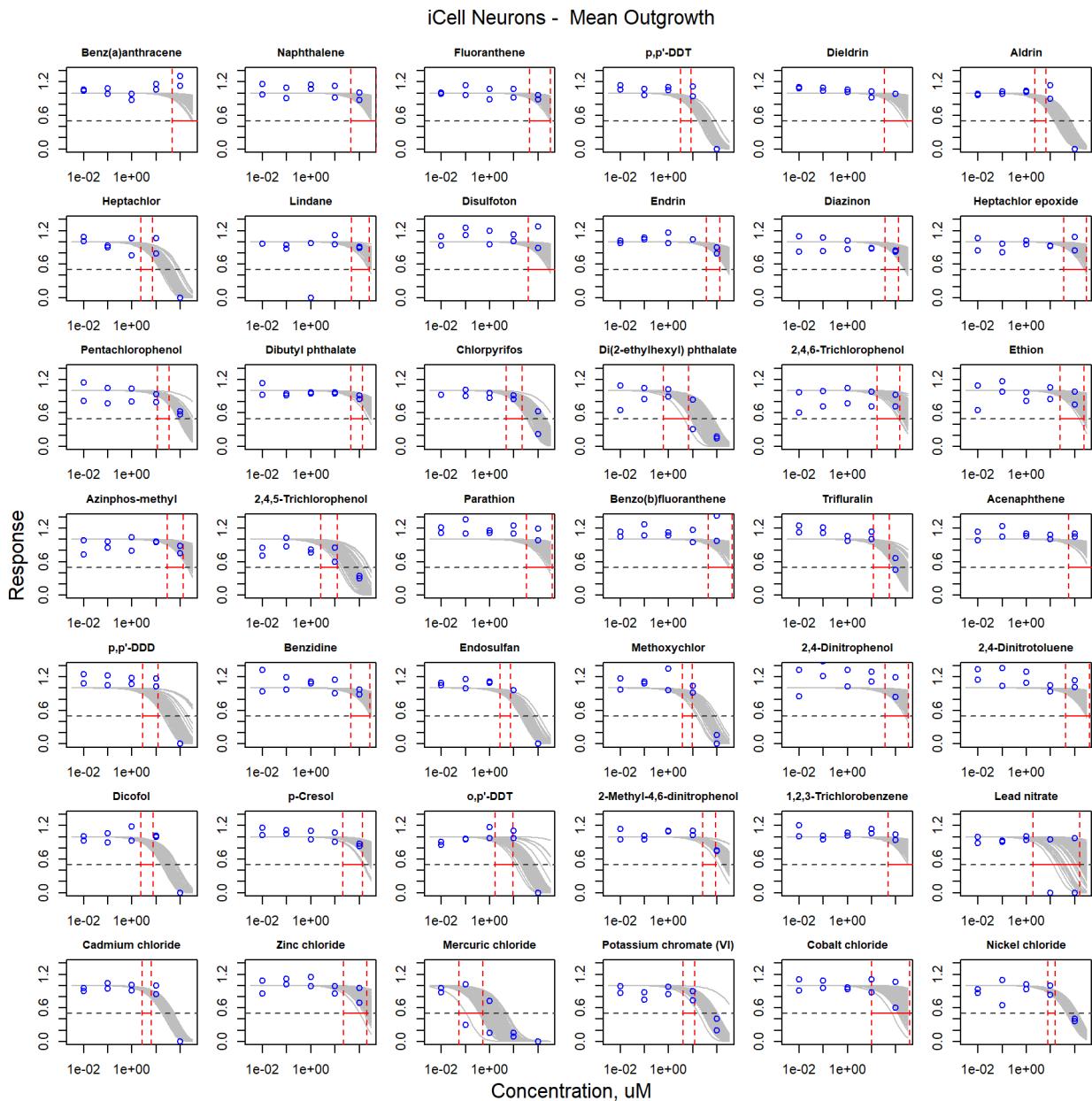


Figure S5. Curve-fitting of single chemical concentration and observed response (Mean Outgrowth) in iCell Neurons.

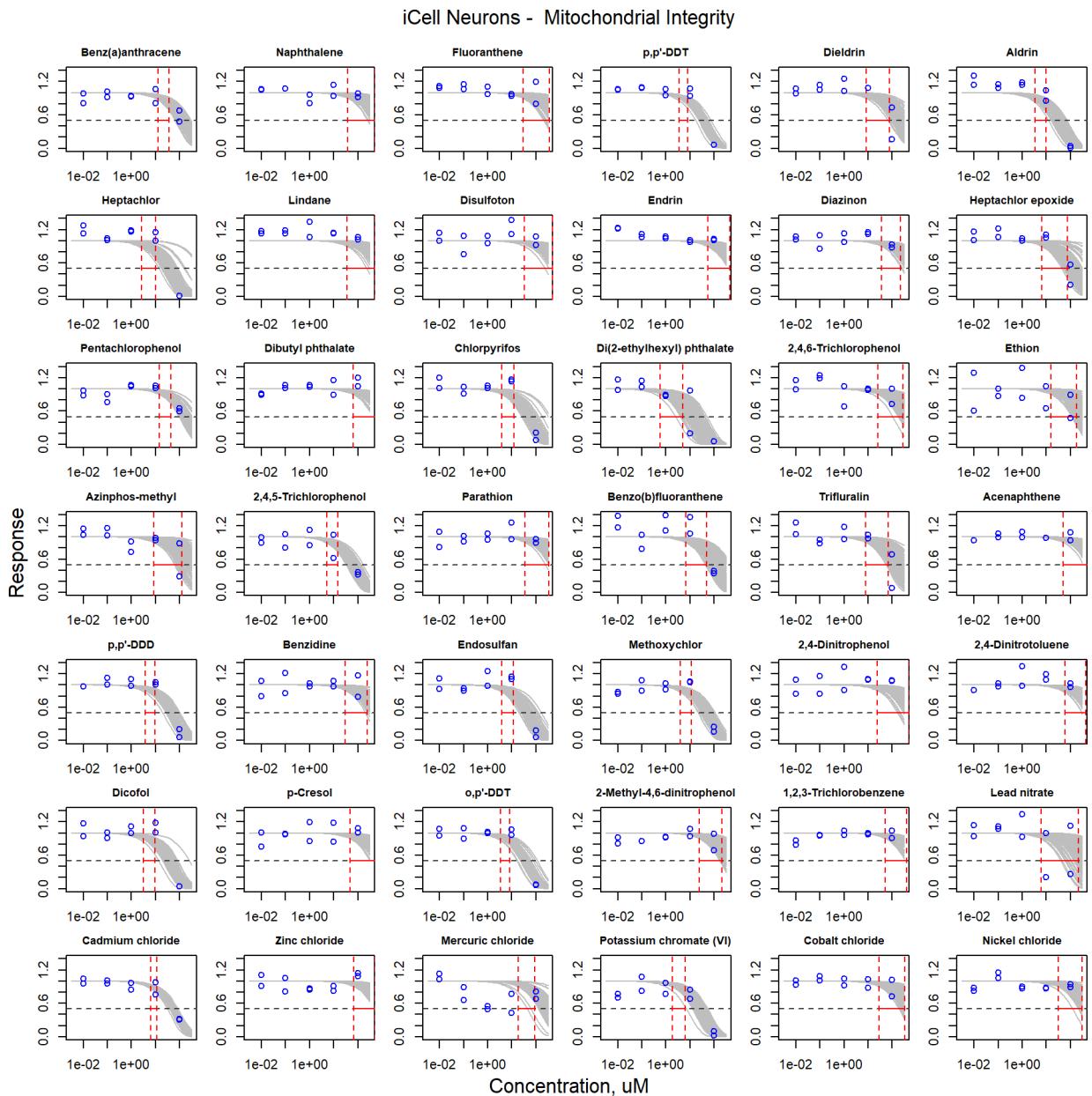


Figure S6. Curve-fitting of single chemical concentration and observed response (Mitochondrial Integrity) in iCell Neurons.

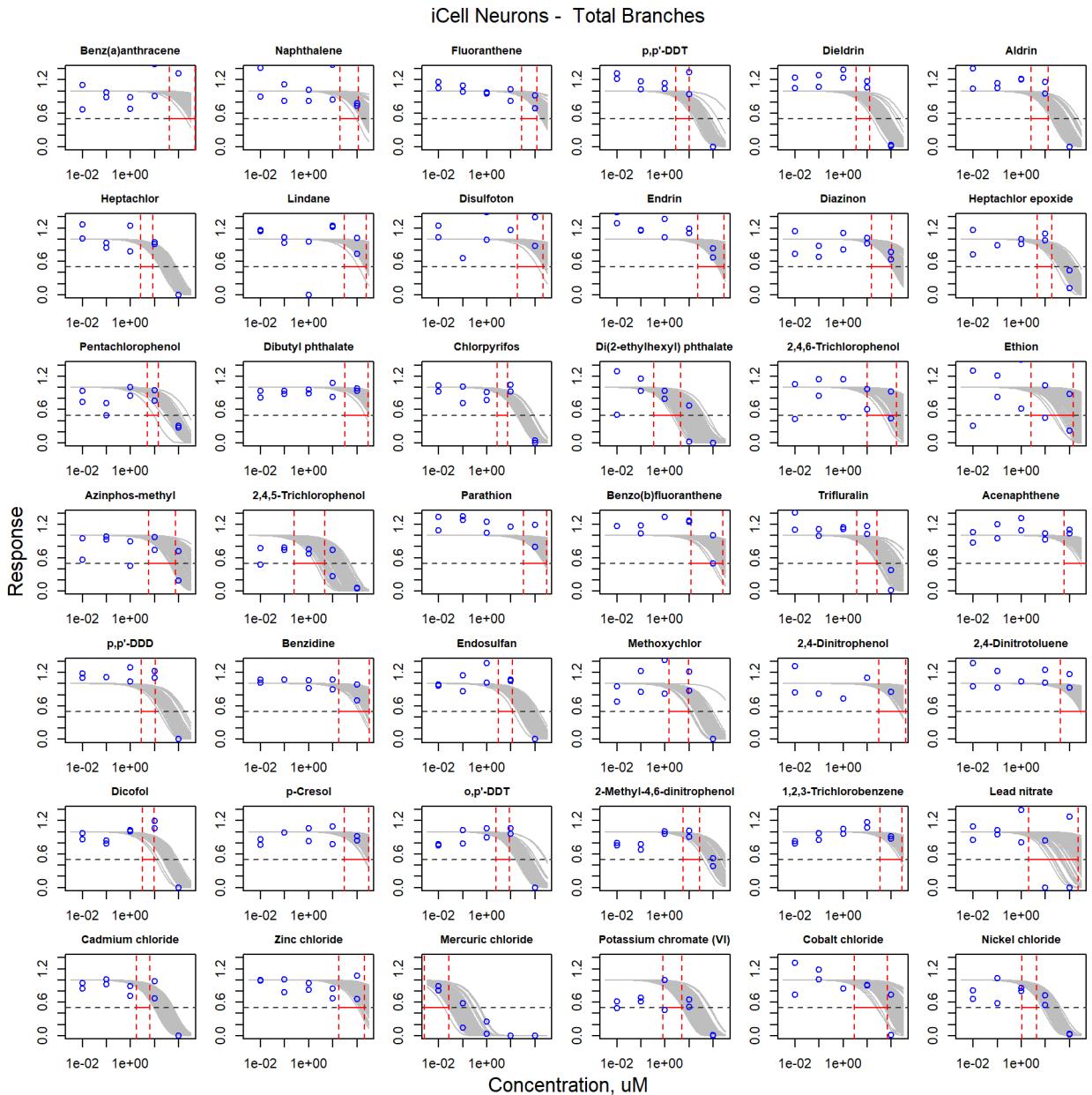


Figure S7. Curve-fitting of single chemical concentration and observed response (Total Branches) in iCell Neurons.

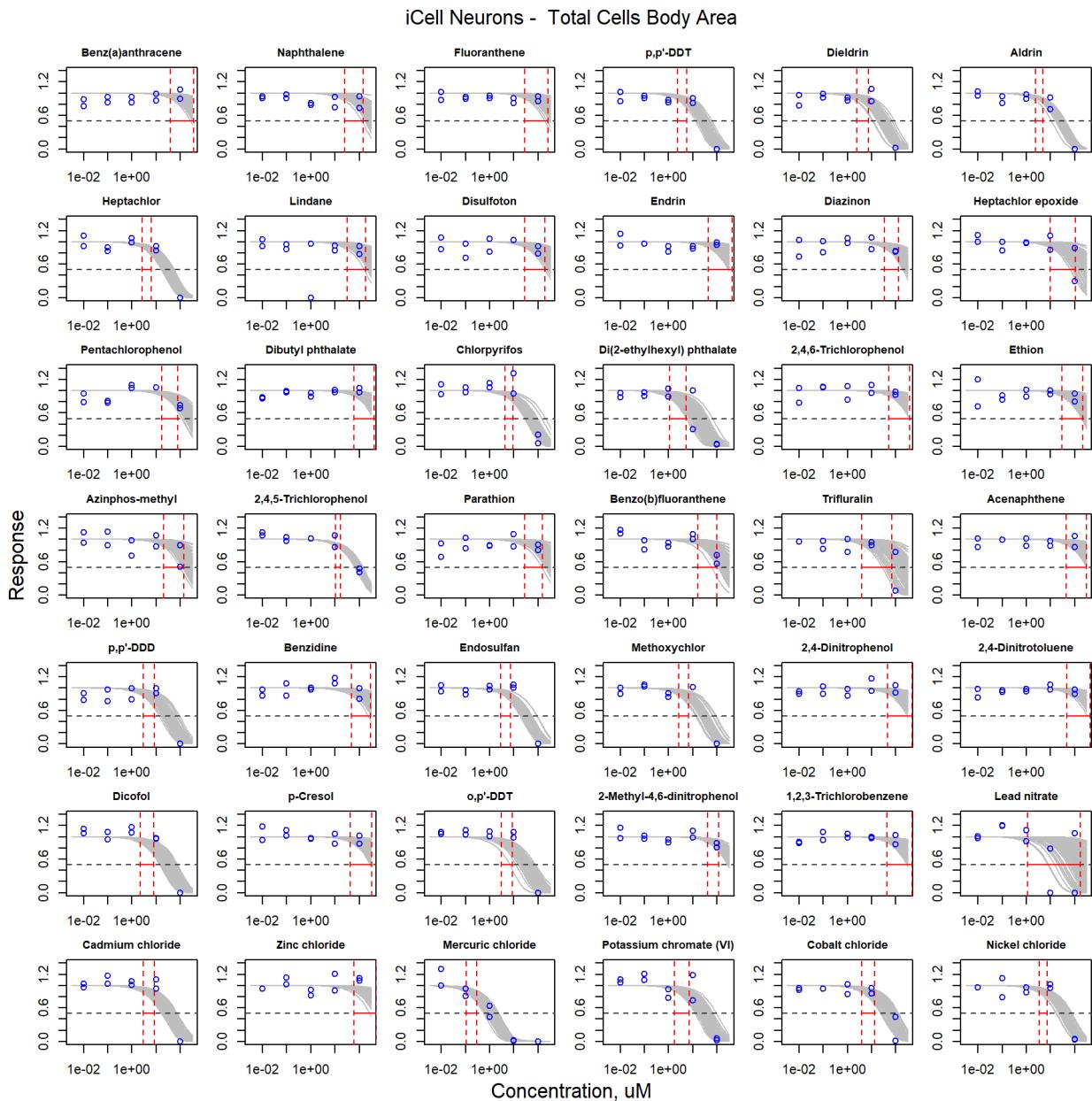


Figure S8. Curve-fitting of single chemical concentration and observed response (Total Cells Body Area) in iCell Neurons.

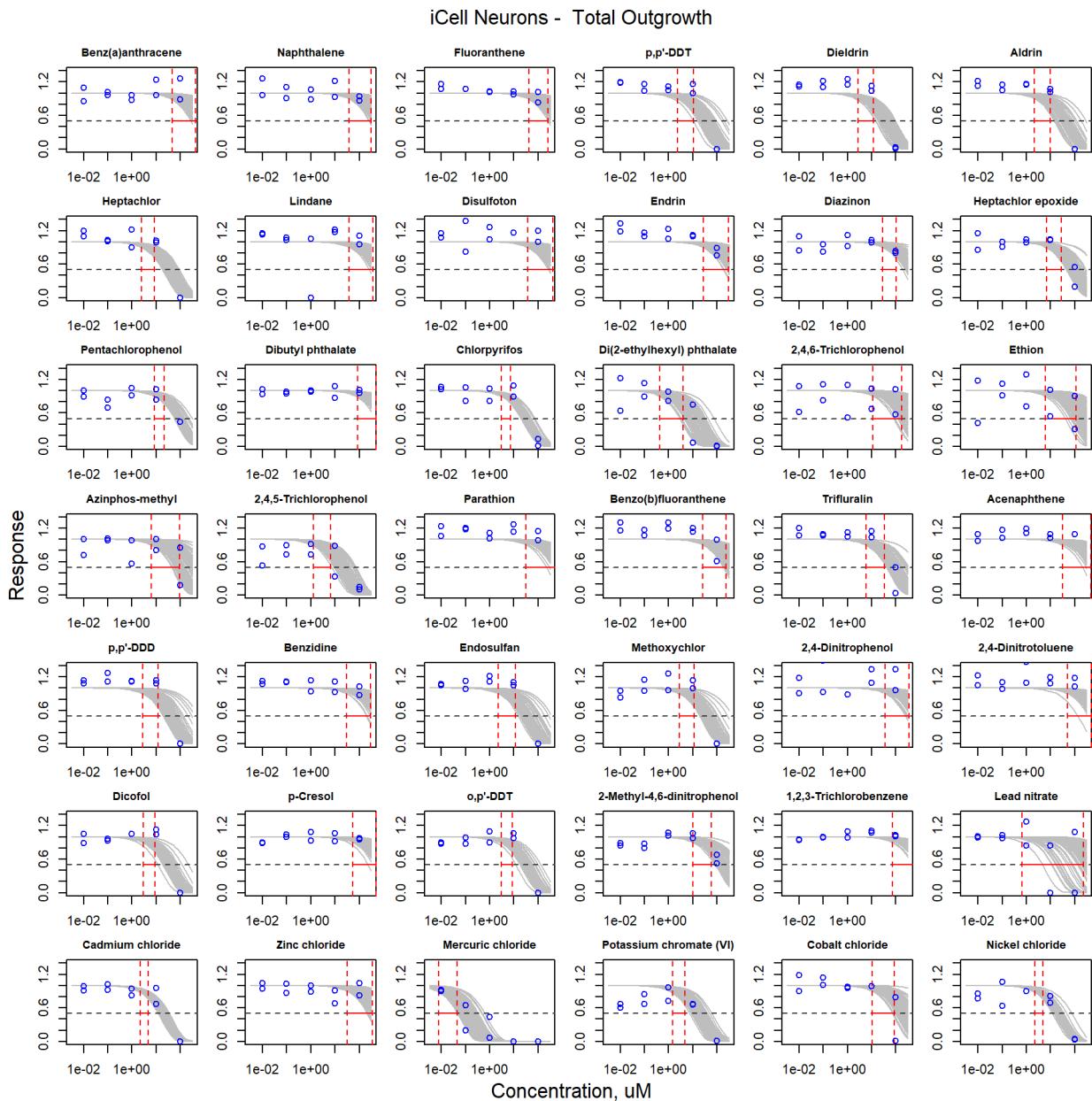


Figure S9. Curve-fitting of single chemical concentration and observed response (Total Outgrowth) in iCell Neurons.

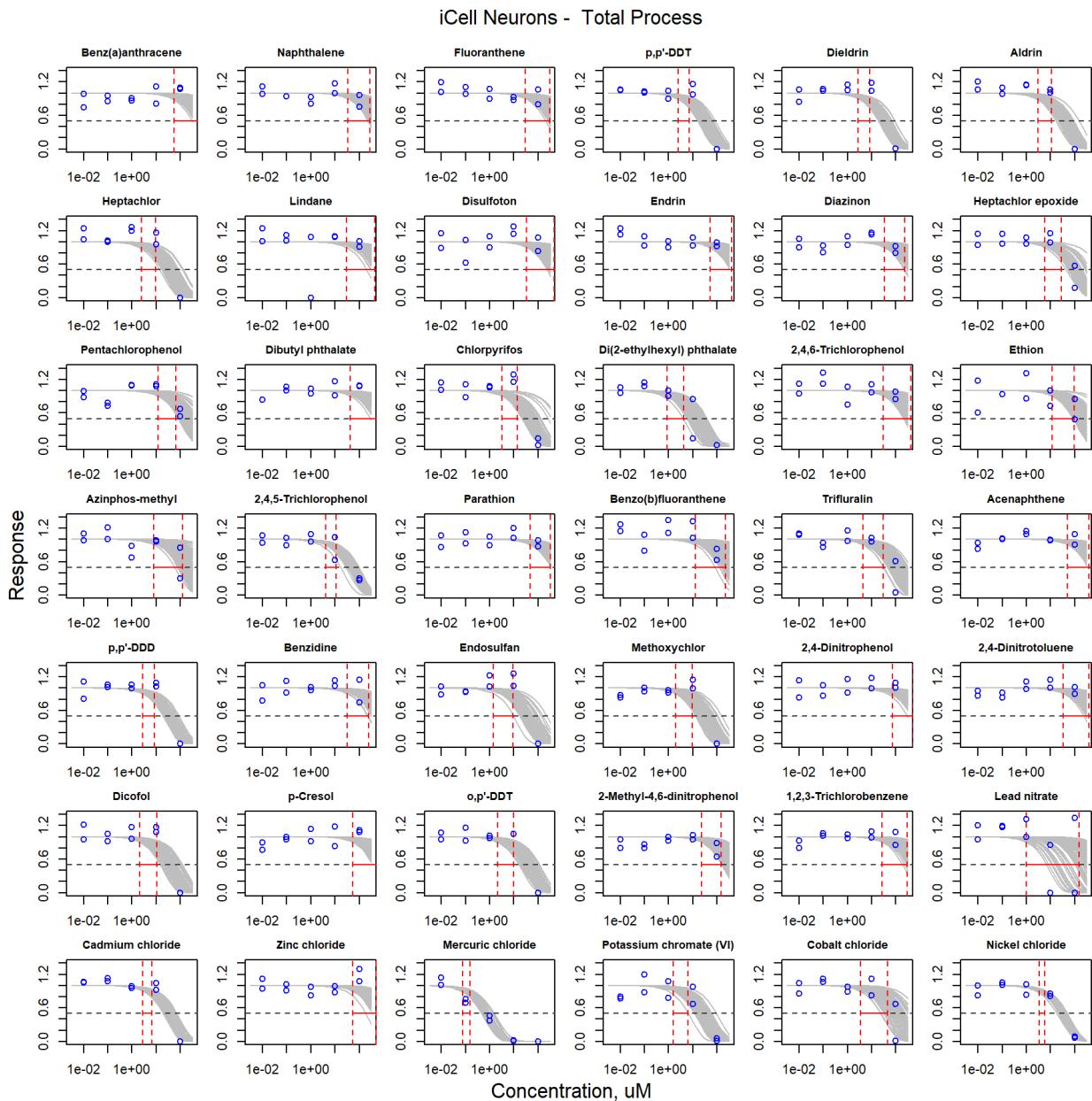


Figure S10. Curve-fitting of single chemical concentration and observed response (Total Process) in iCell Neurons.

3.1.2 HUVECs

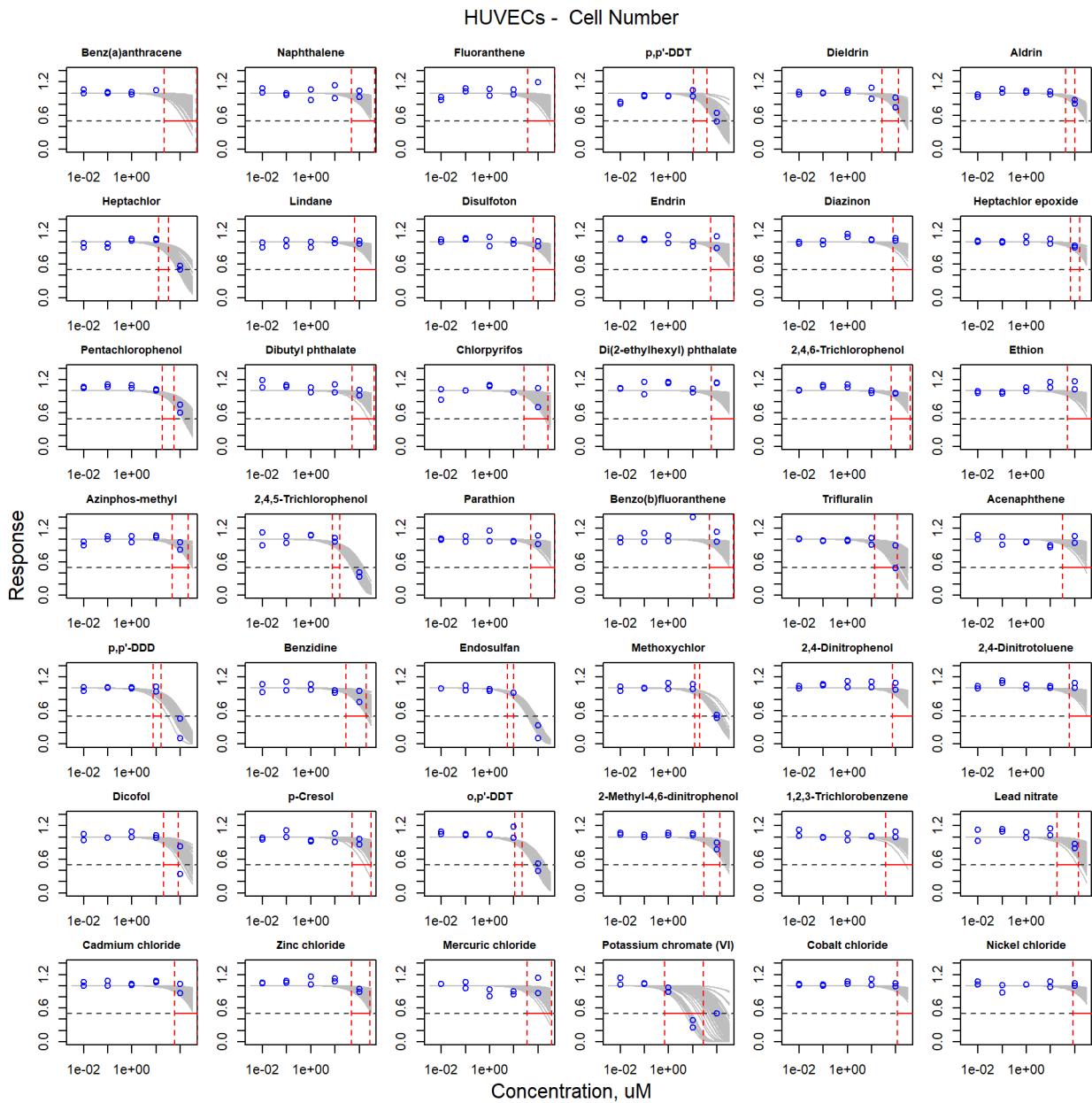


Figure S11. Curve-fitting of single chemical concentration and observed response (Cell Number) in HUVECs.

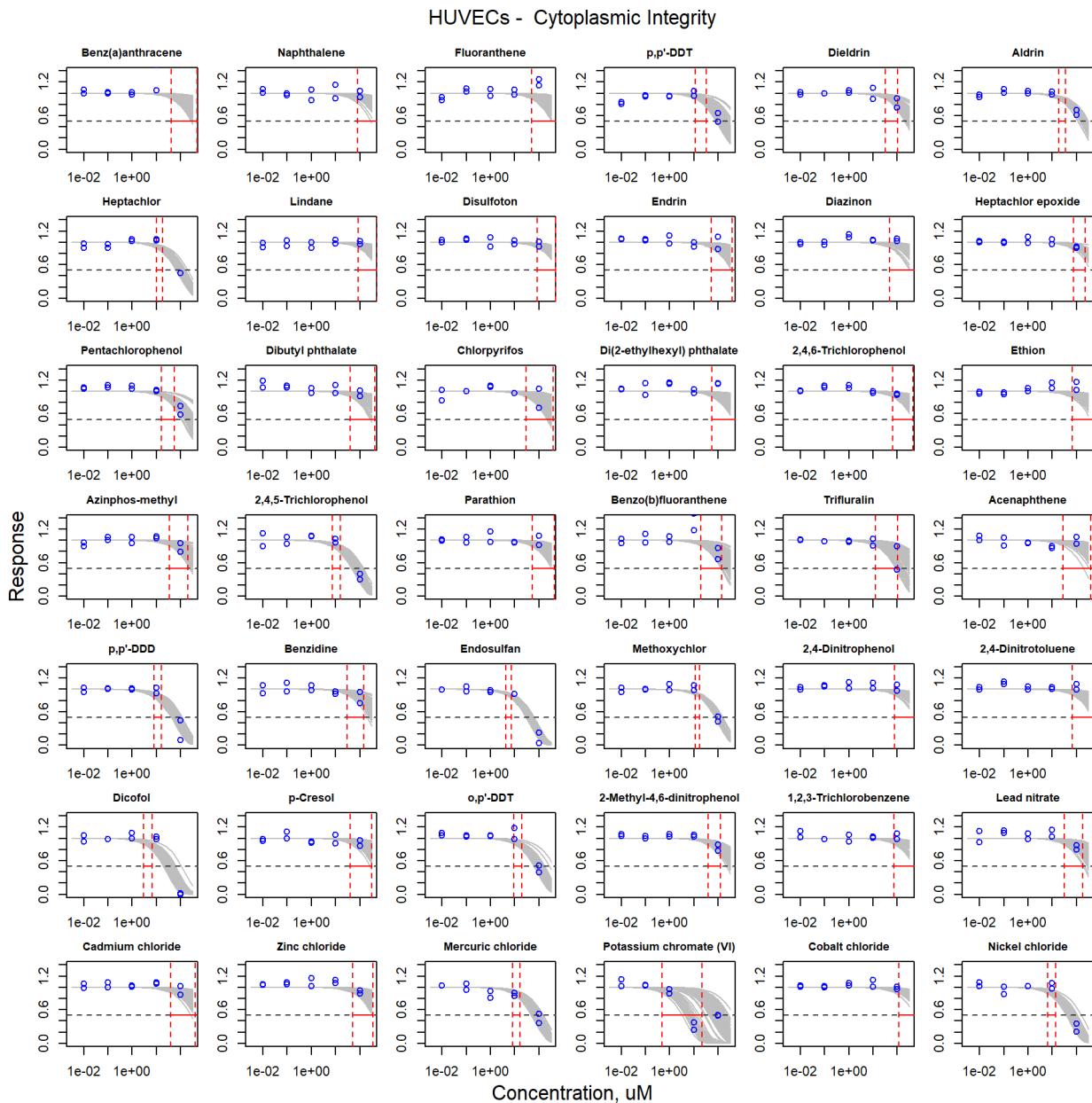


Figure S12. Curve-fitting of single chemical concentration and observed response (Cytoplasmic Integrity) in HUVECs.

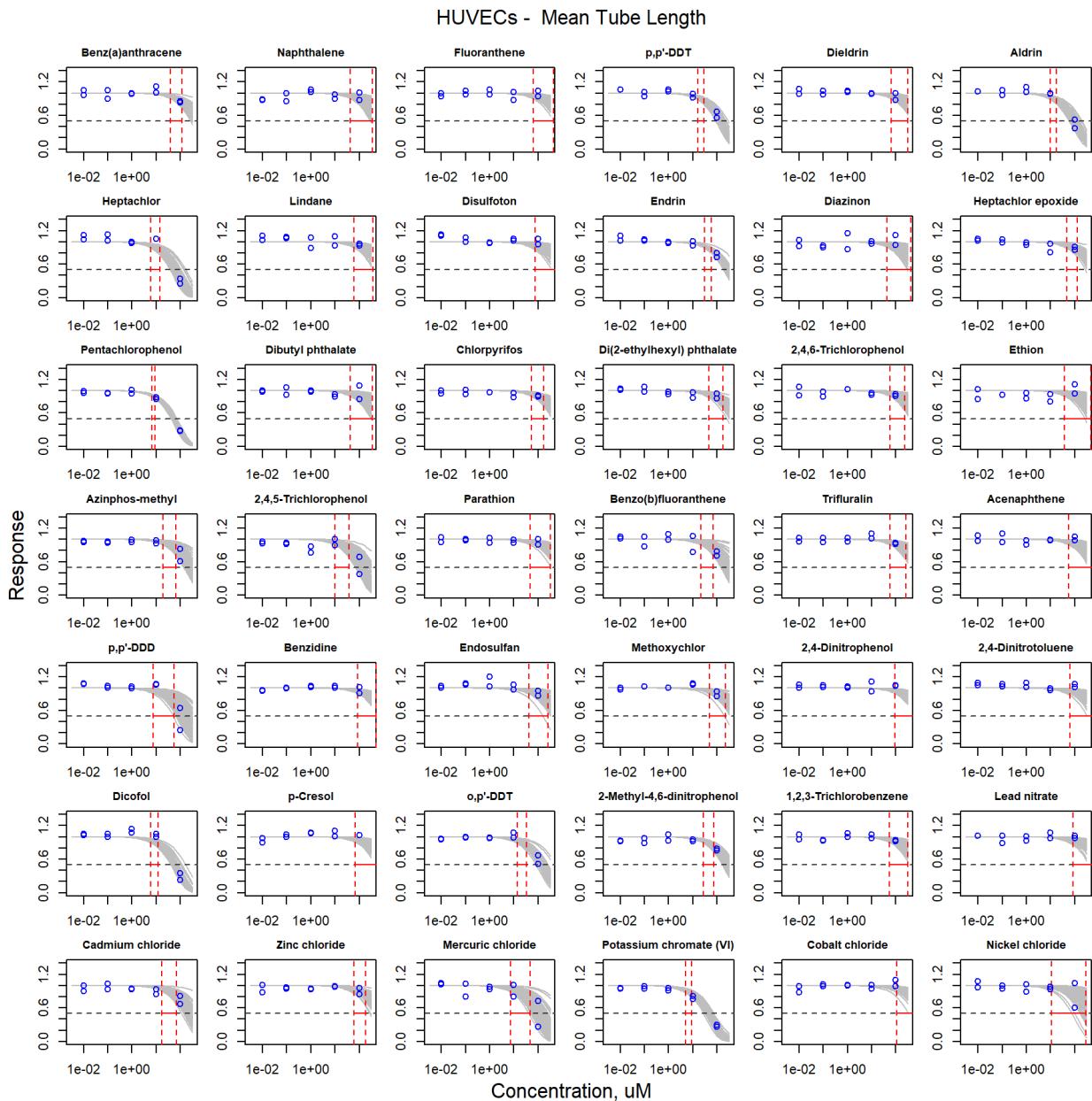


Figure S13. Curve-fitting of single chemical concentration and observed response (Mean Tube Length) in HUVECs.

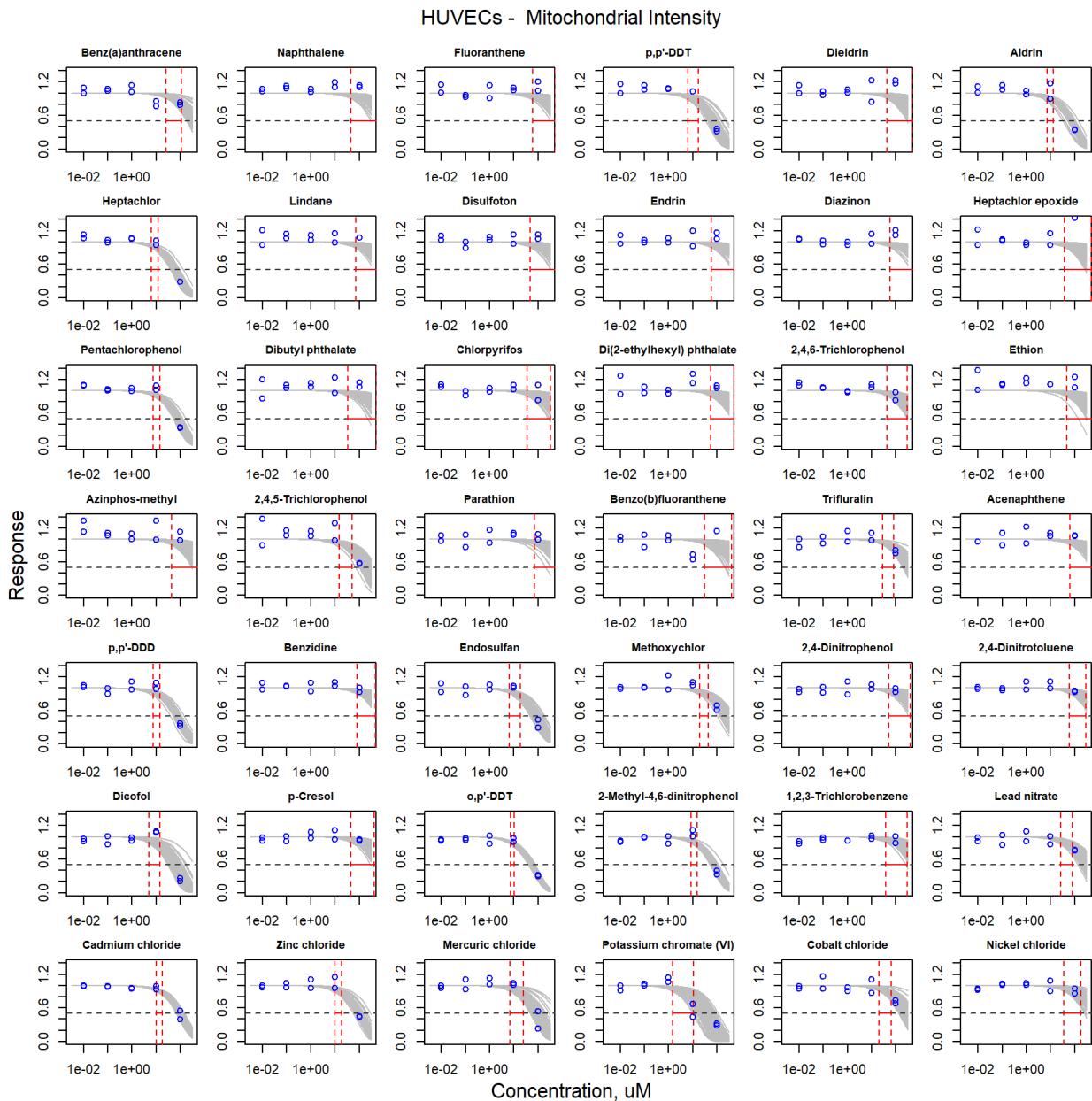


Figure S14. Curve-fitting of single chemical concentration and observed response (Mitochondrial Intensity) in HUVECs.

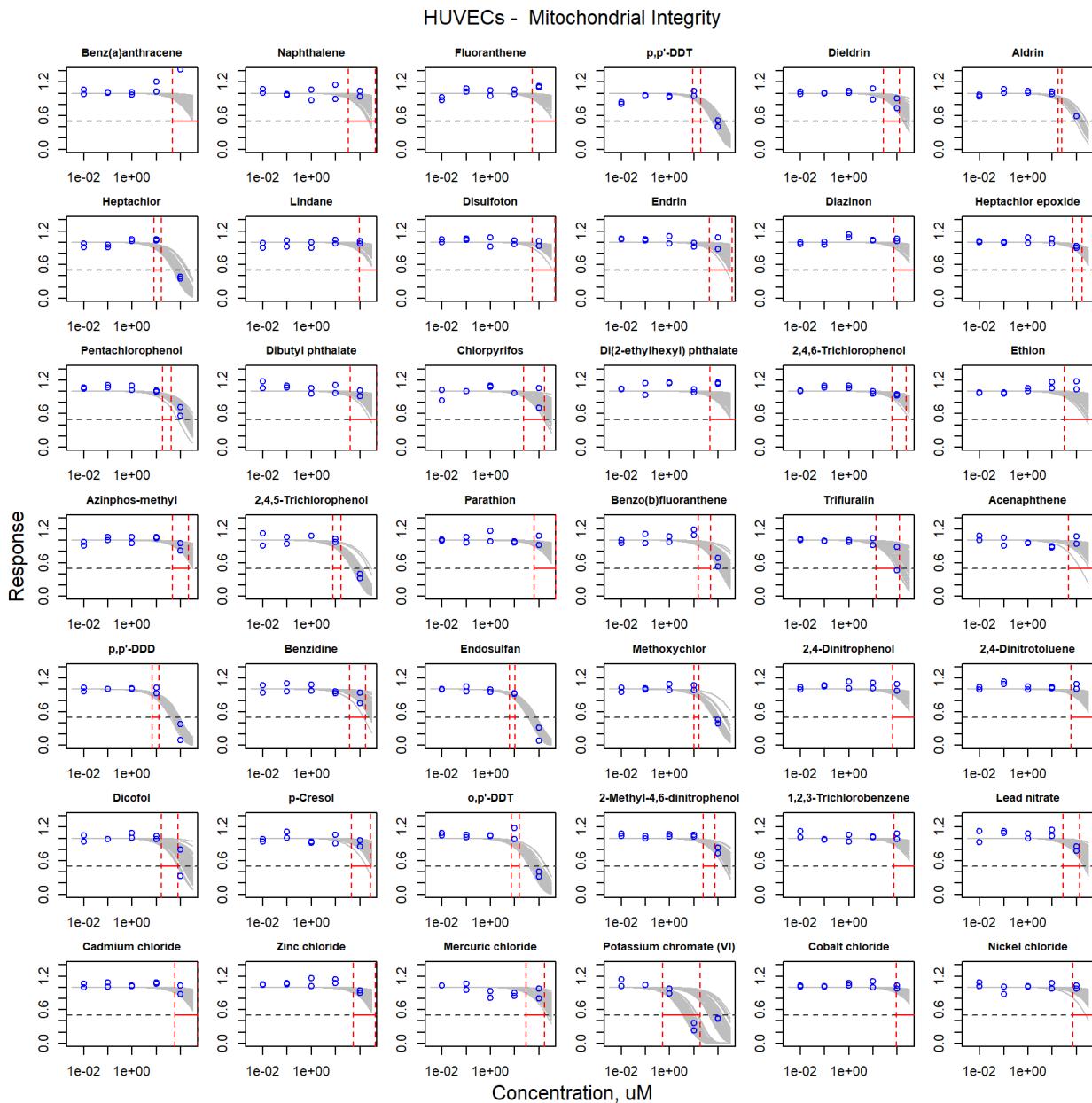


Figure S15. Curve-fitting of single chemical concentration and observed response (Mitochondrial Integrity) in HUVECs.

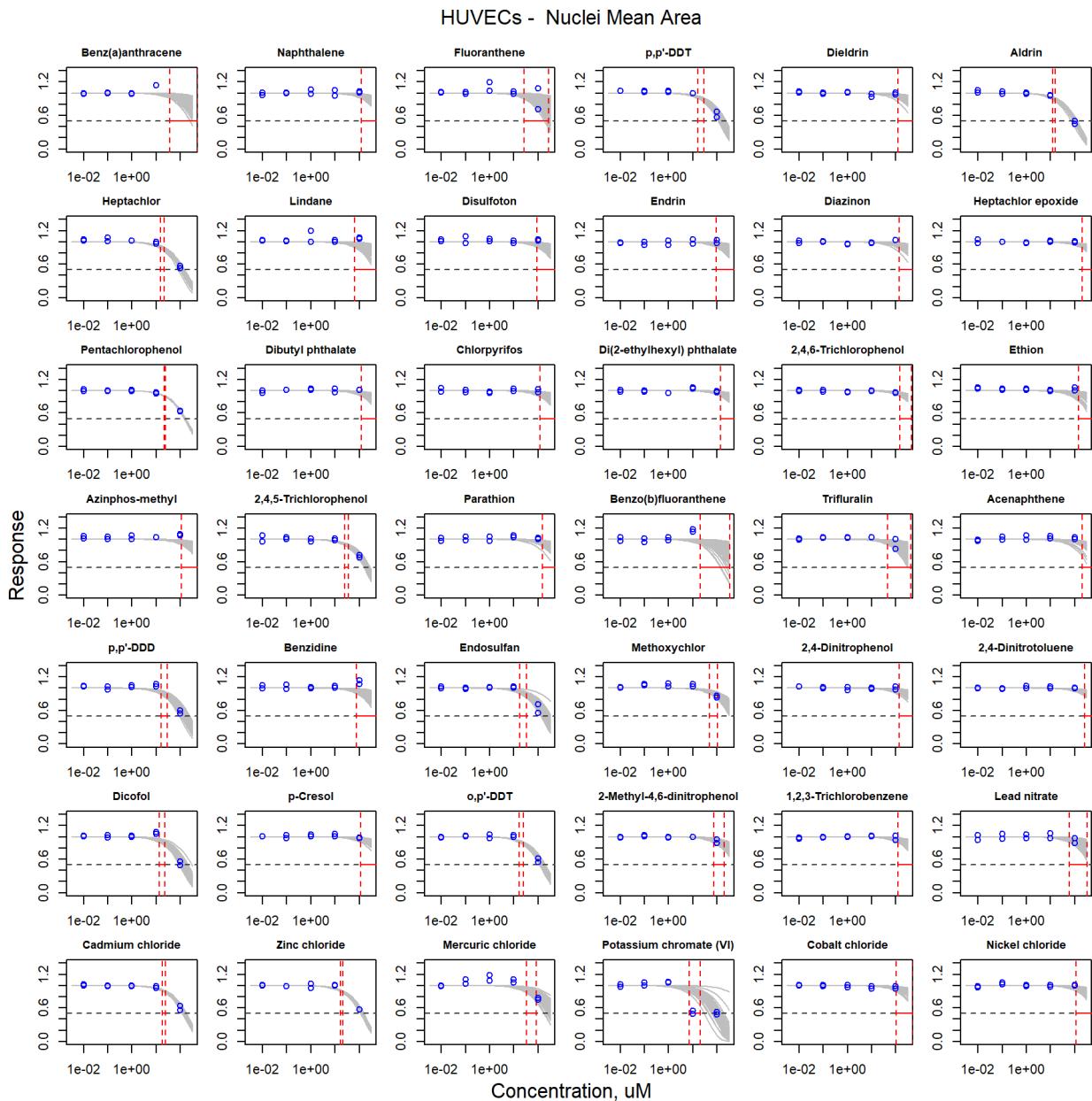


Figure S16. Curve-fitting of single chemical concentration and observed response (Nuclei Mean Area) in HUVECs.

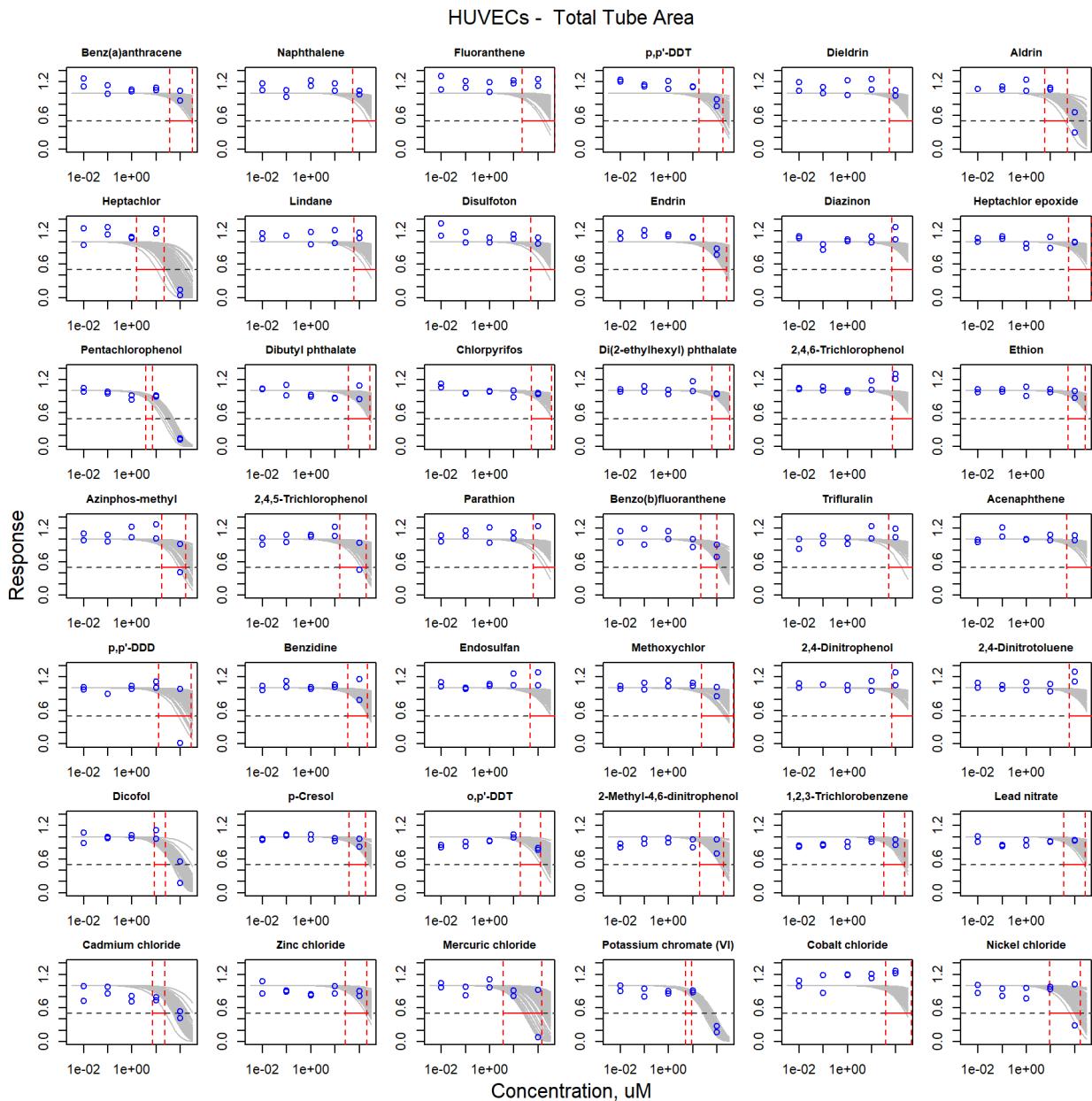


Figure S17. Curve-fitting of single chemical concentration and observed response (Total Tube Area) in HUVECs.

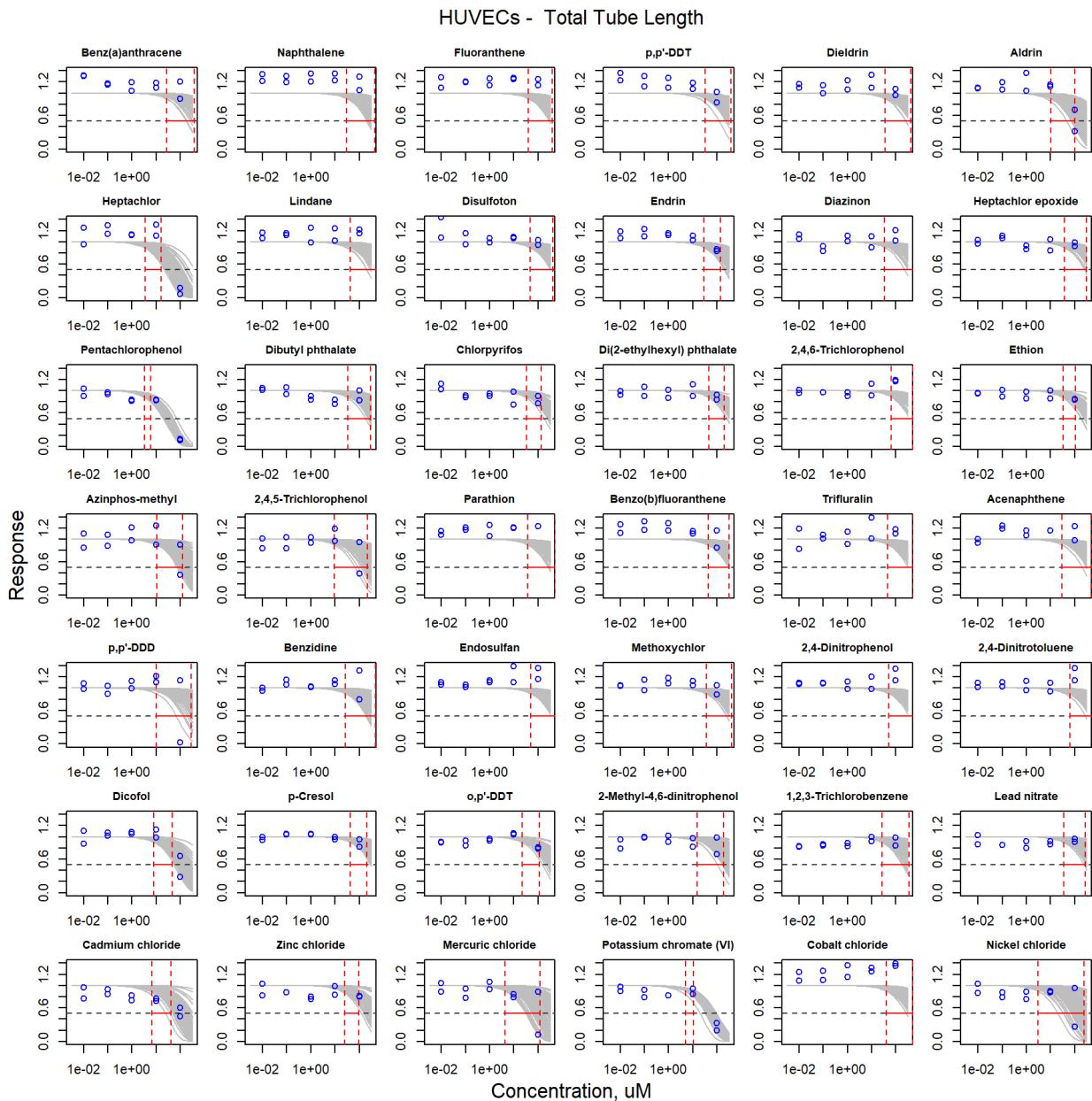


Figure S18. Curve-fitting of single chemical concentration and observed response (Total Tube Length) in HUVECs.

3.1.3 iCell Hepatocytes

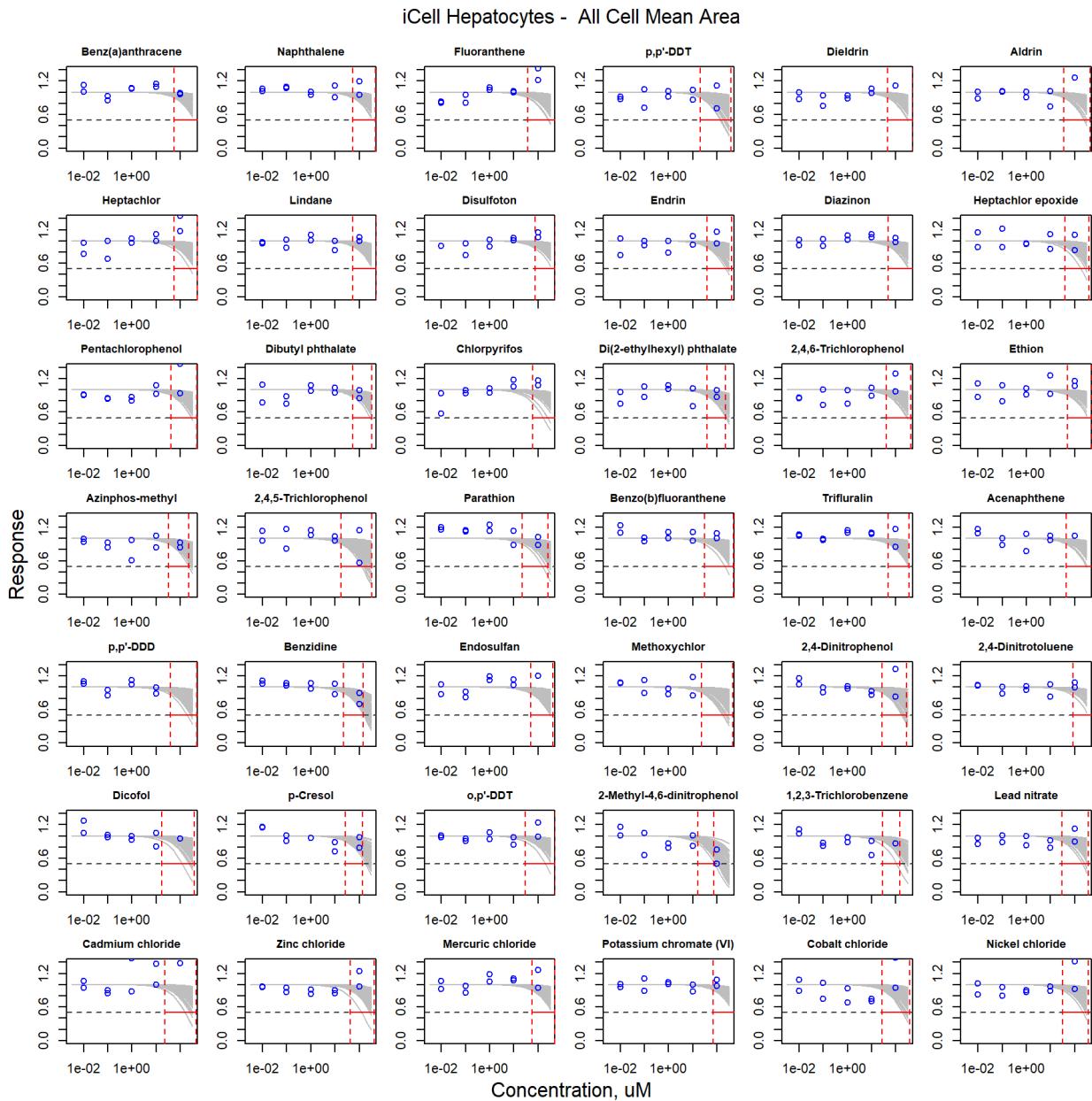


Figure S19. Curve-fitting of single chemical concentration and observed response (All Cell Mean Area) in iCell Hepatocytes.

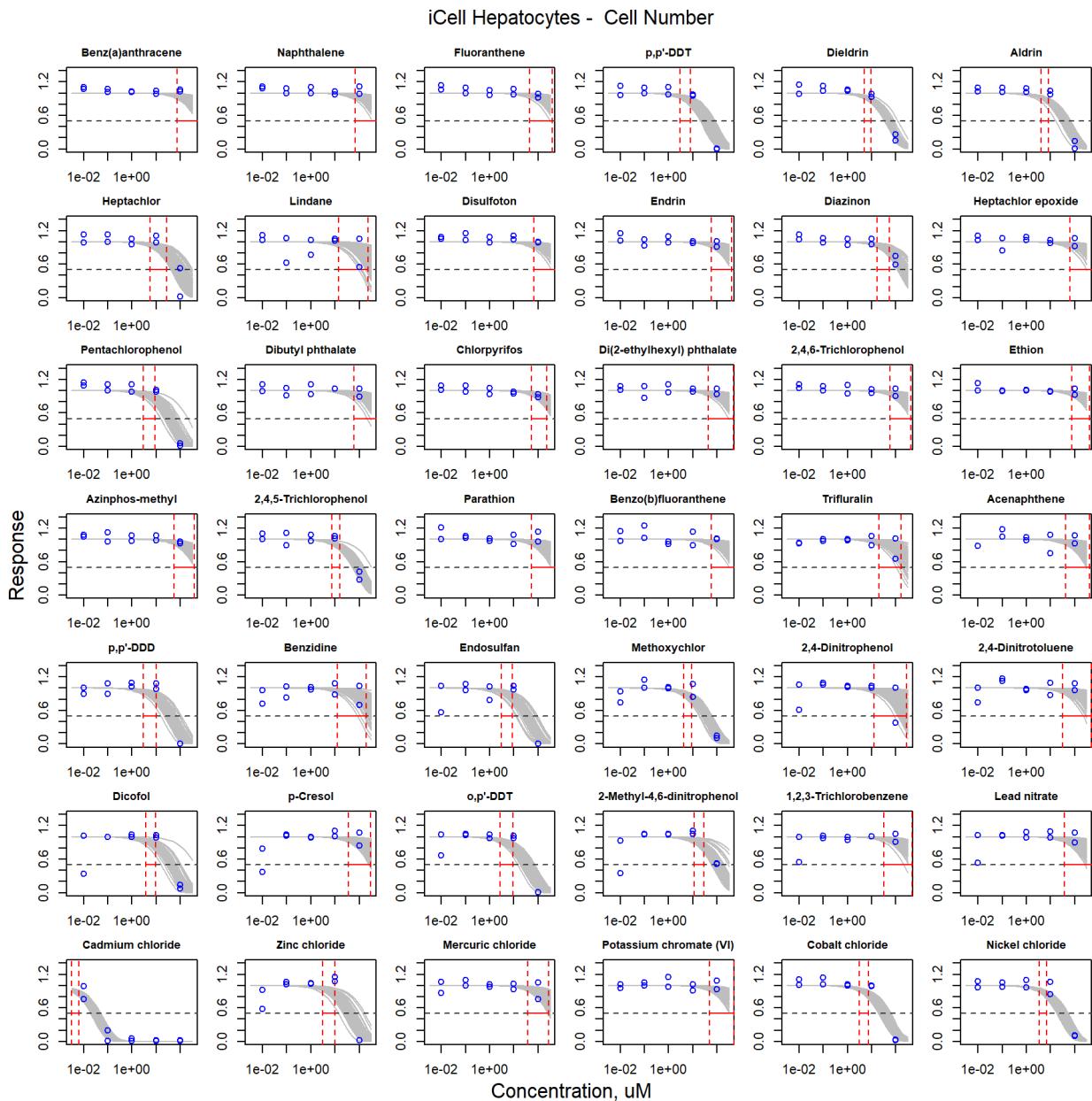


Figure S20. Curve-fitting of single chemical concentration and observed response (Cell Number) in iCell Hepatocytes.

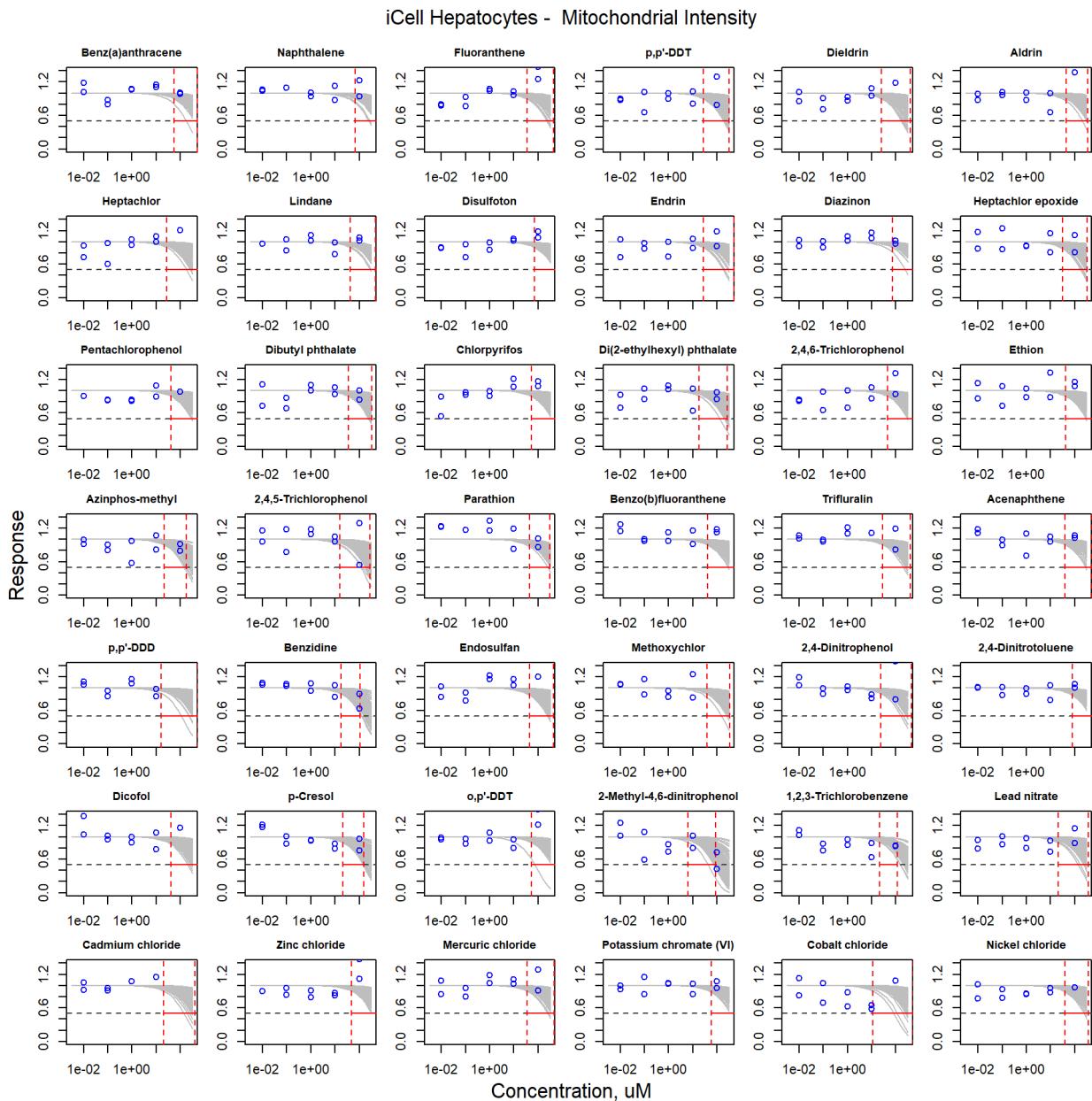


Figure S21. Curve-fitting of single chemical concentration and observed response (Mitochondrial Intensity) in iCell Hepatocytes.

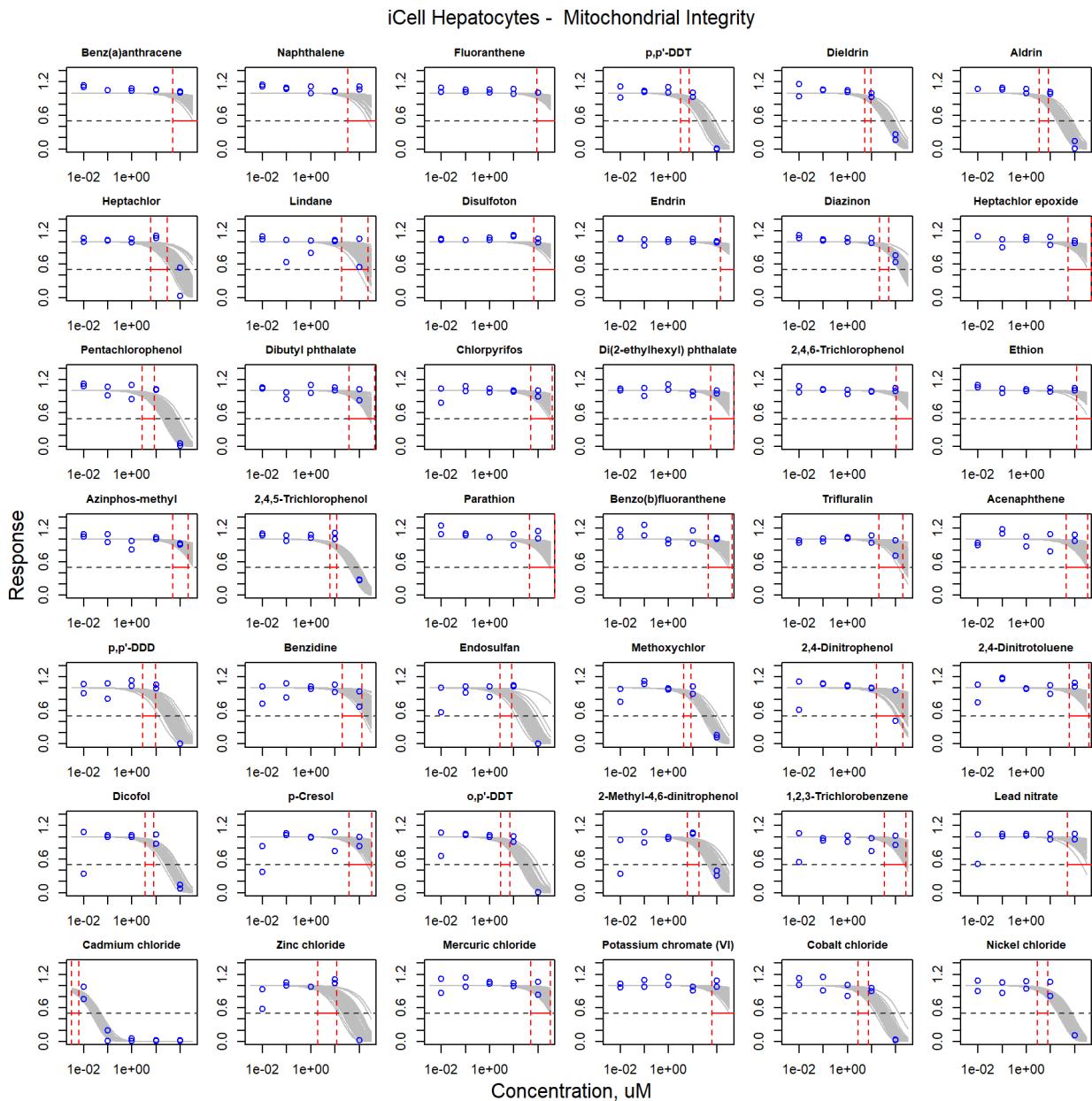


Figure S22. Curve-fitting of single chemical concentration and observed response (Mitochondrial Integrity) in iCell Hepatocytes.

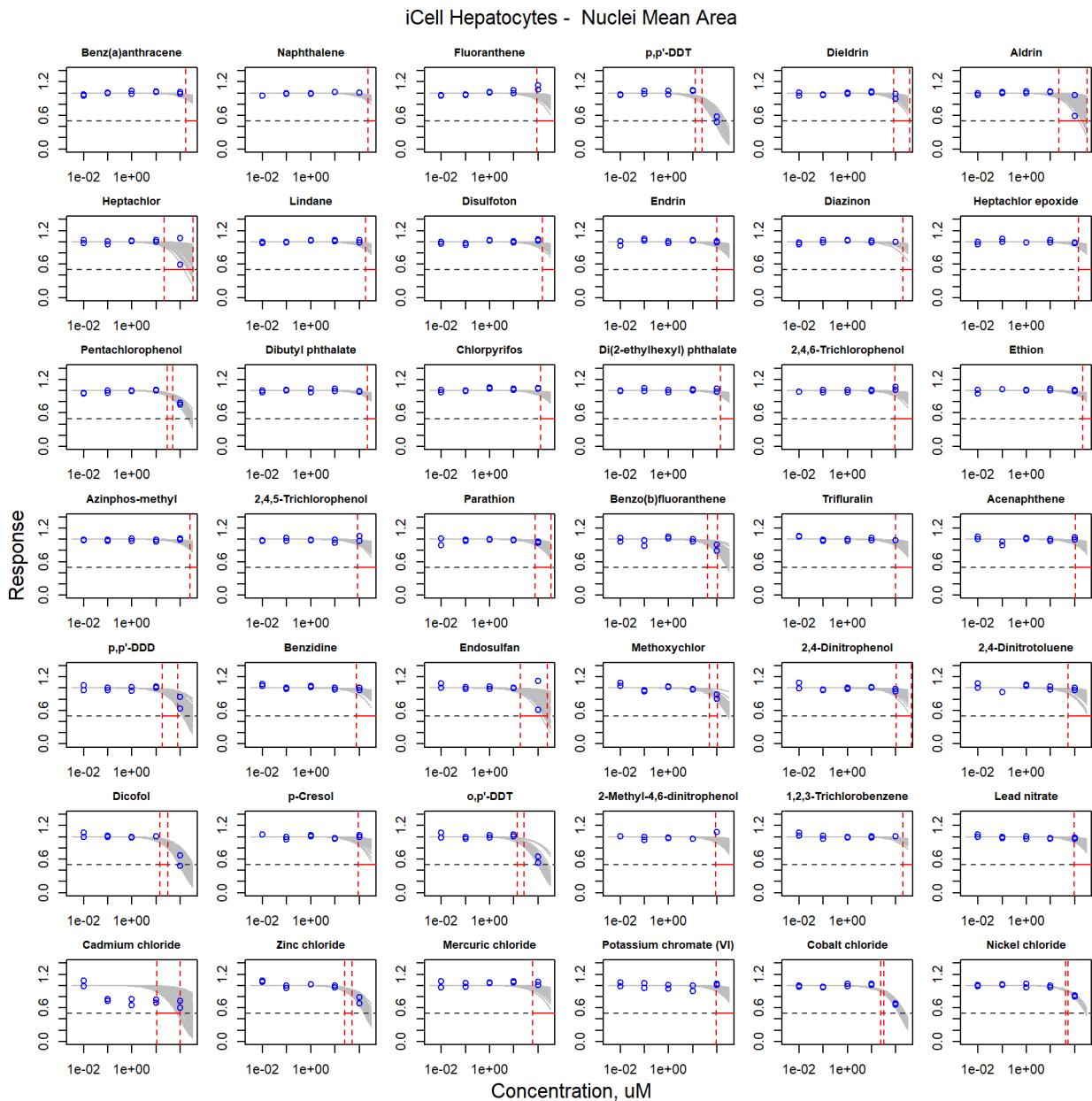


Figure S23. Curve-fitting of single chemical concentration and observed response (Nuclei Mean Area) in iCell Hepatocytes.

3.1.4 iCell Endothelial cells

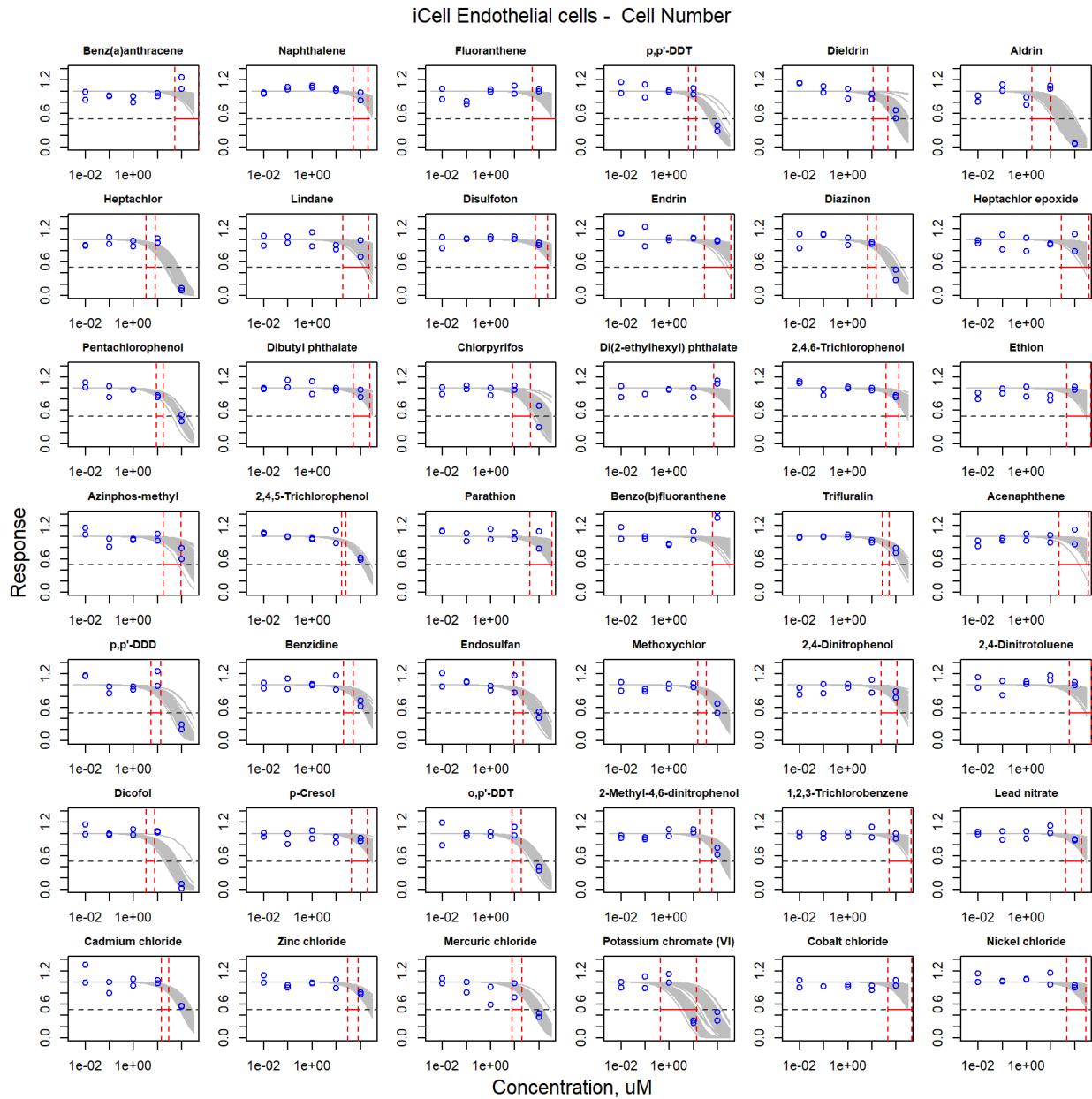


Figure S24. Curve-fitting of single chemical concentration and observed response (Cell Number) in iCell Endothelial cells.

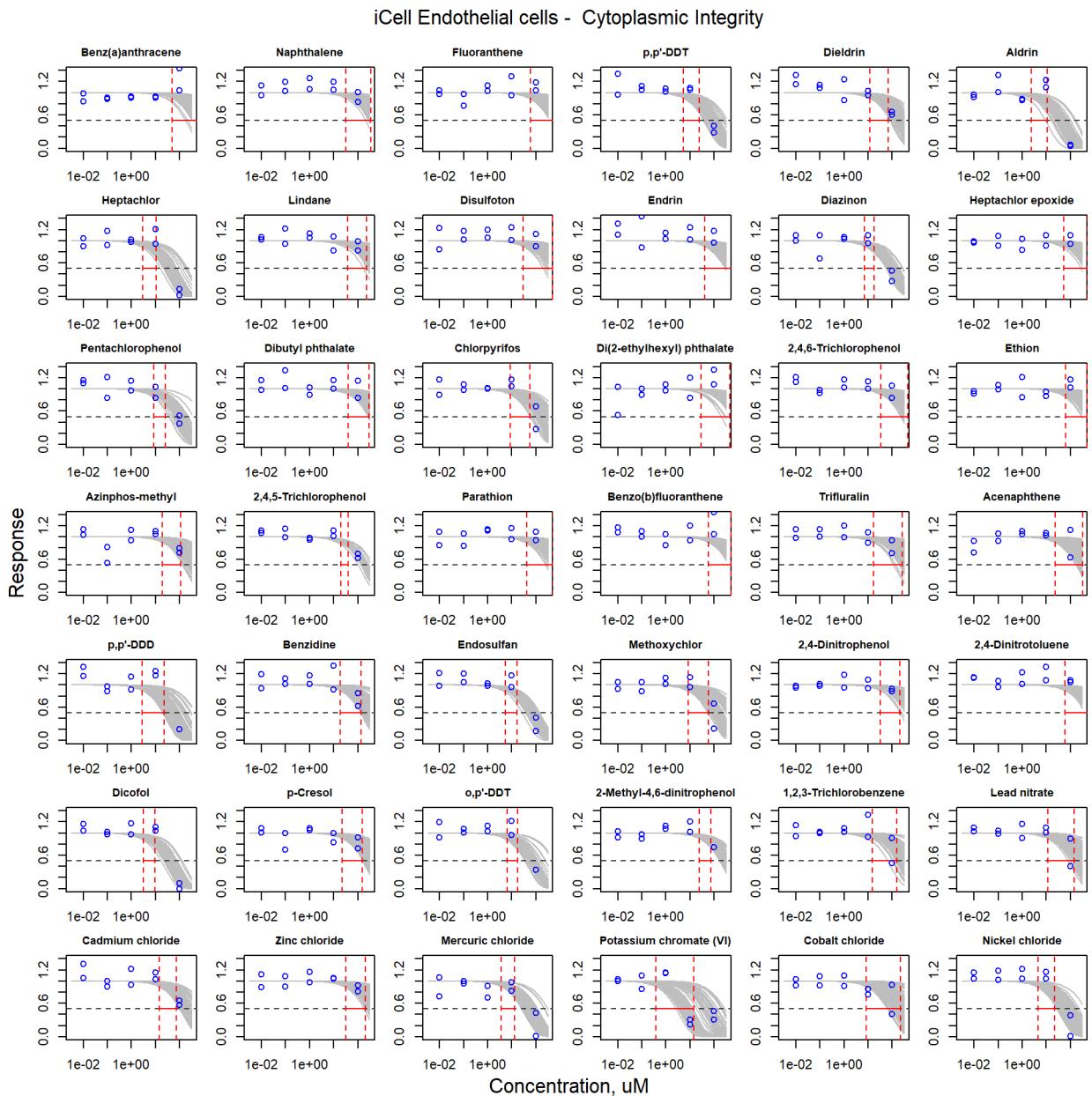


Figure S25. Curve-fitting of single chemical concentration and observed response (Cytoplasmic Integrity) in iCell Endothelial cells.

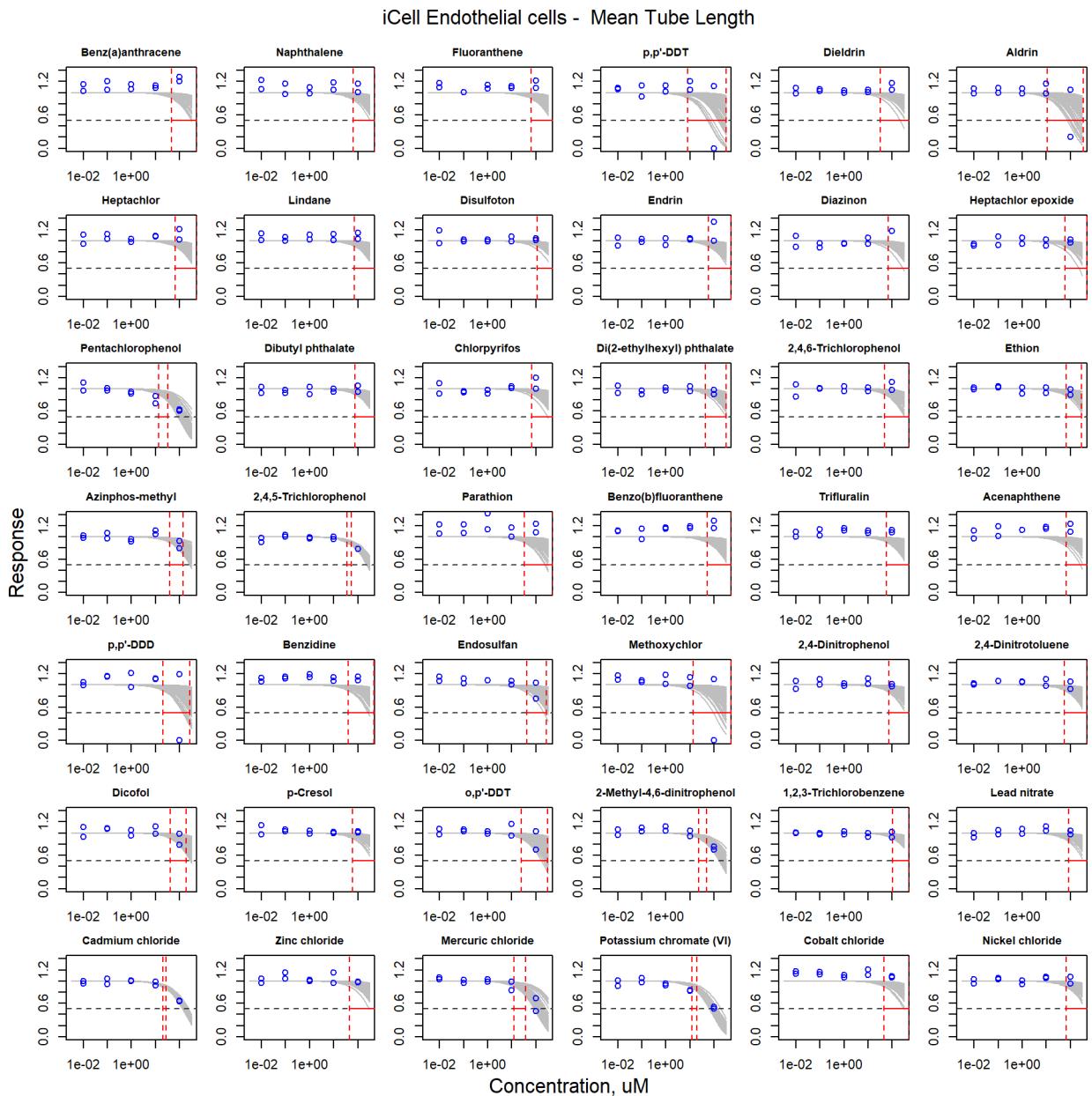


Figure S26. Curve-fitting of single chemical concentration and observed response (Mean Tube Length) in iCell Endothelial cells.

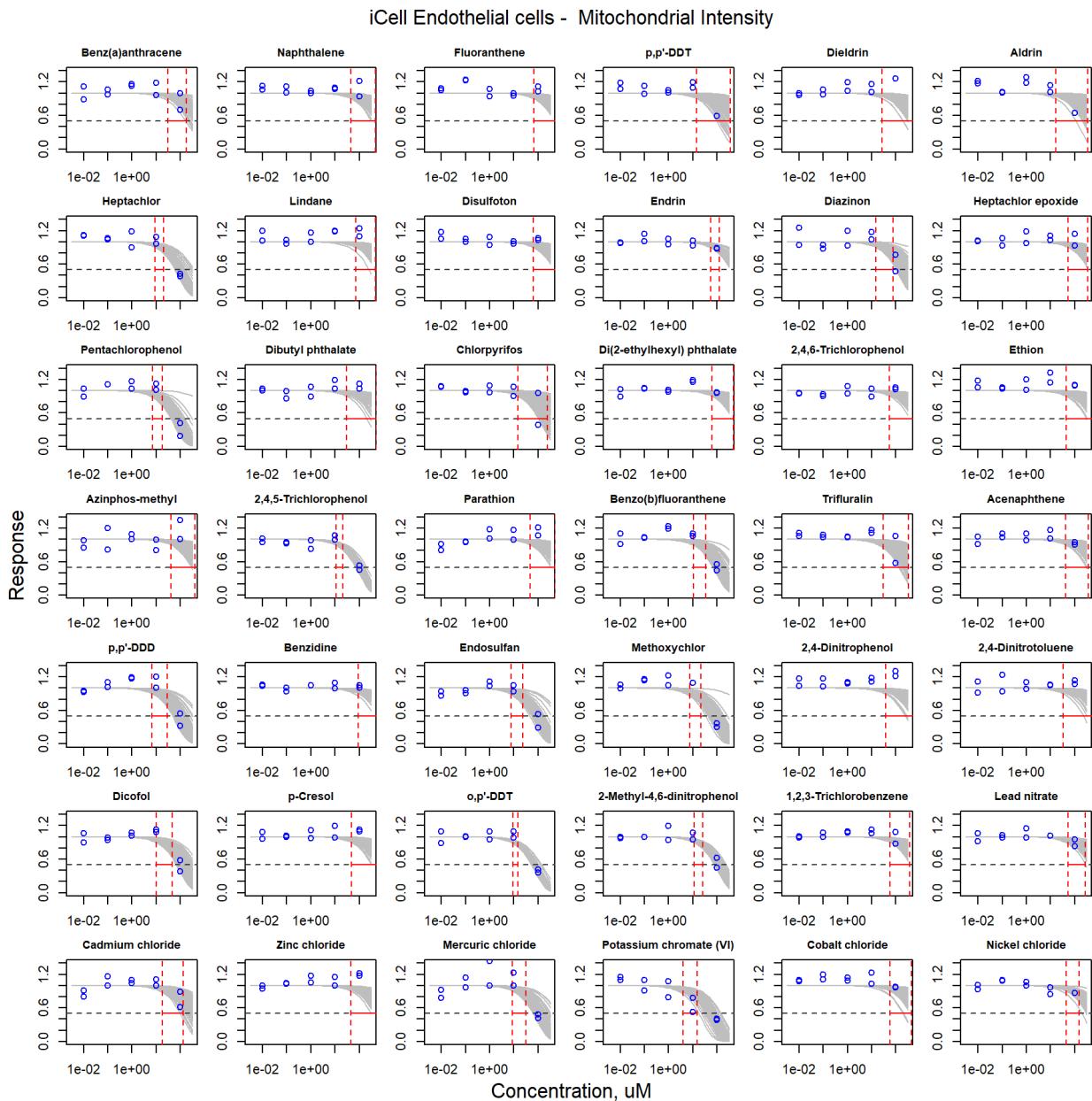


Figure S27. Curve-fitting of single chemical concentration and observed response (Mitochondrial Intensity) in iCell Endothelial cells.

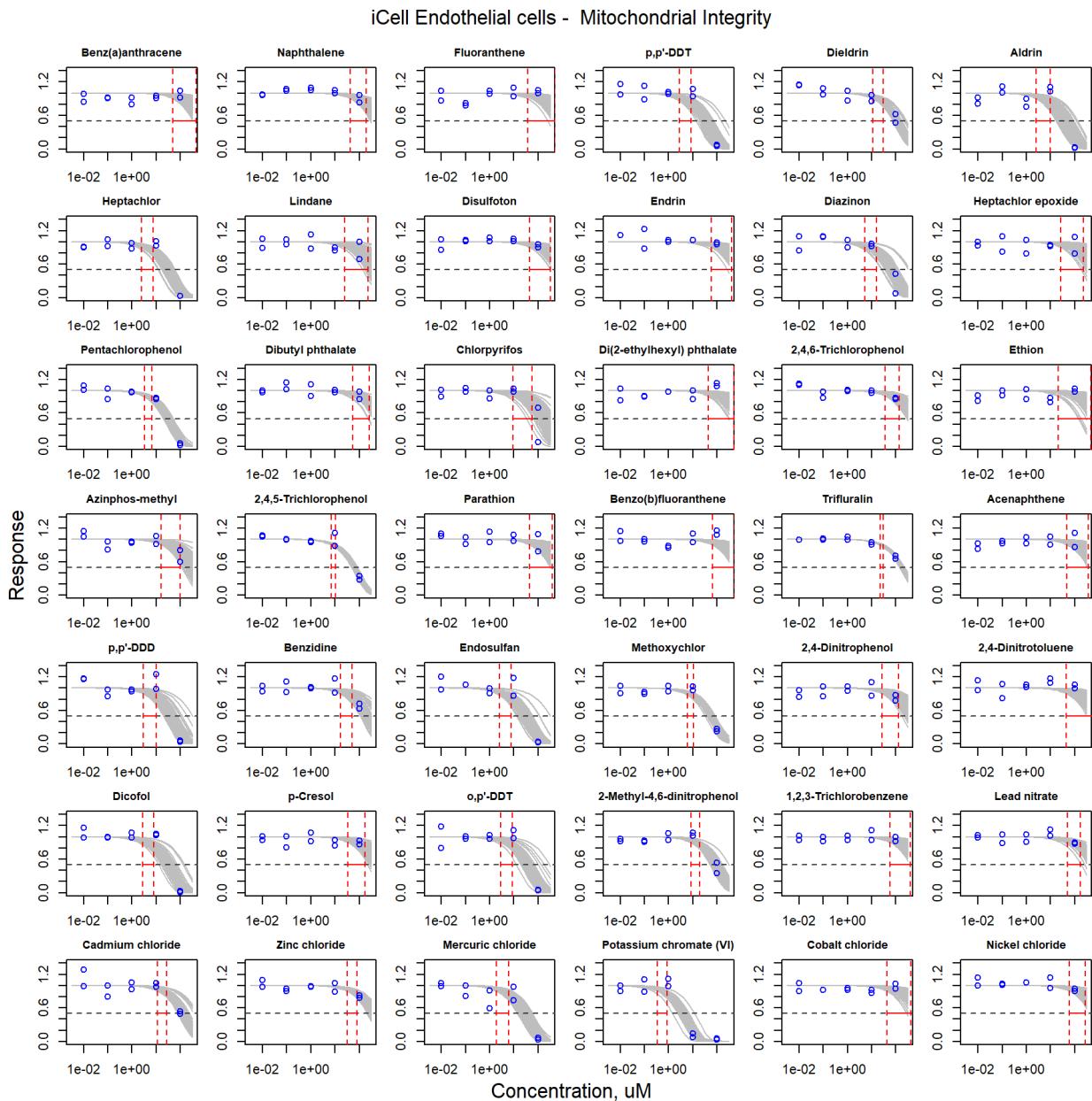


Figure S28. Curve-fitting of single chemical concentration and observed response (Mitochondrial Integrity) in iCell Endothelial cells.

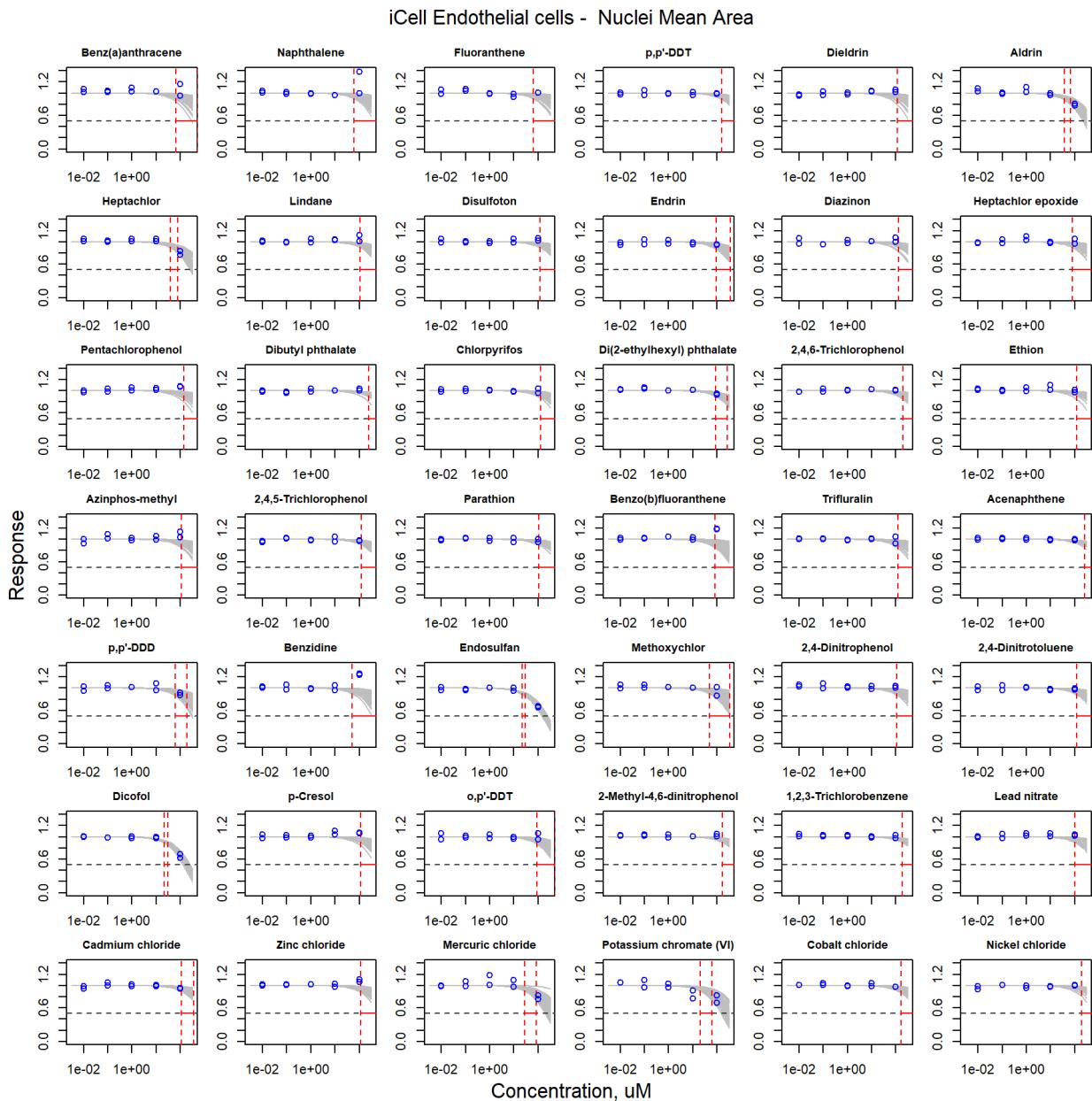


Figure S29. Curve-fitting of single chemical concentration and observed response (Nuclei Mean Area) in iCell Endothelial cells.

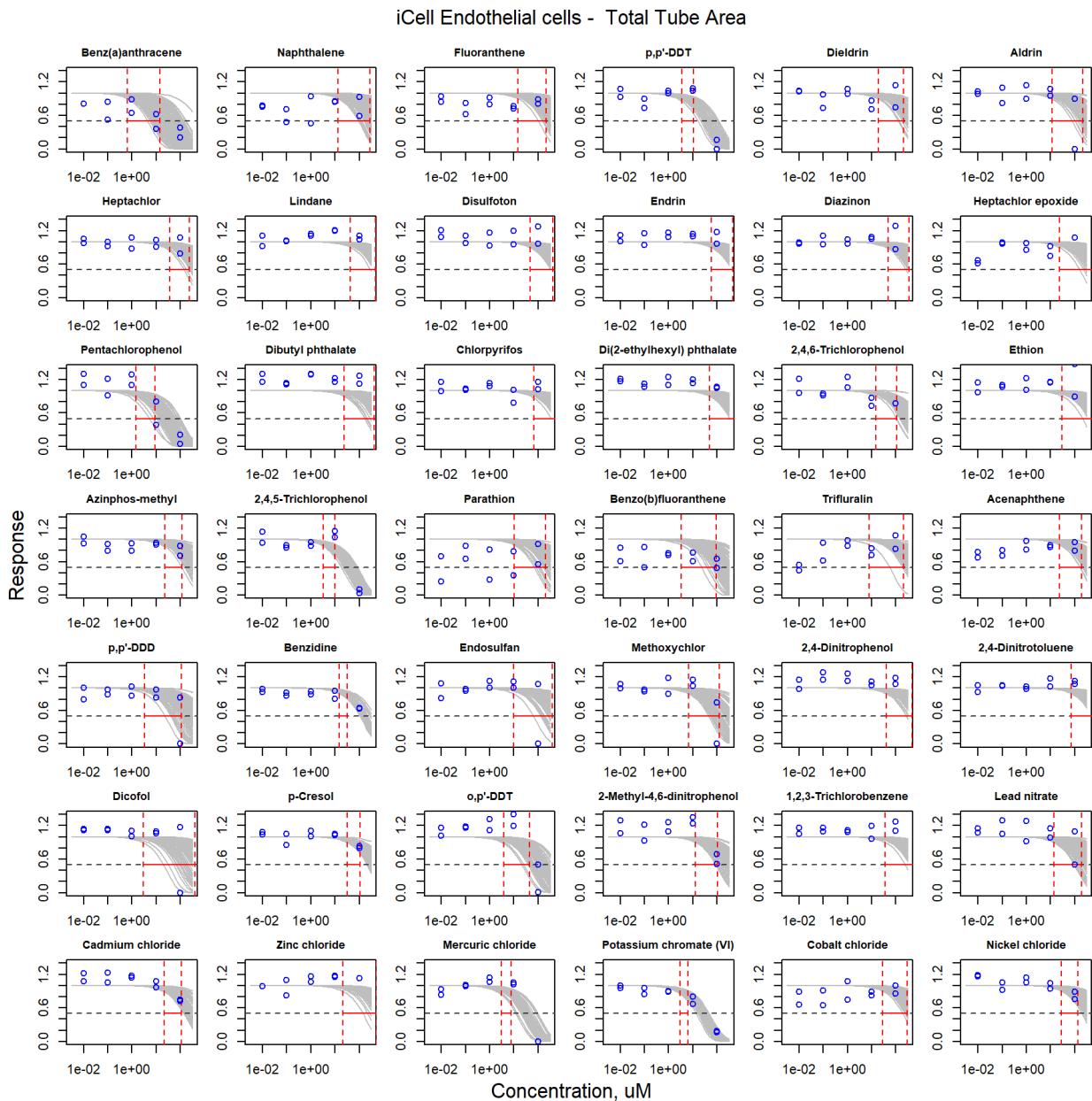


Figure S30. Curve-fitting of single chemical concentration and observed response (Total Tube Area) in iCell Endothelial cells.

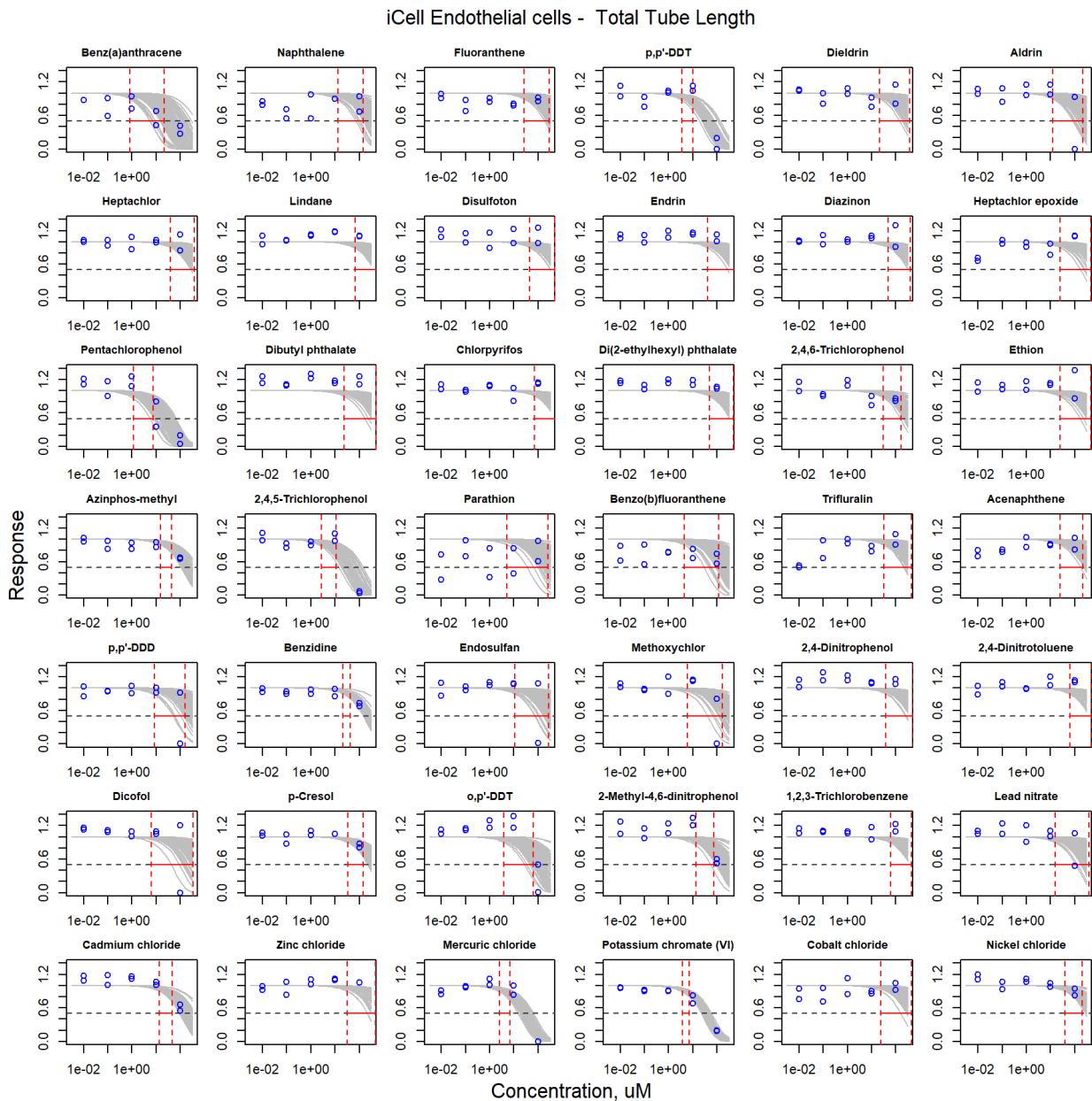


Figure S31. Curve-fitting of single chemical concentration and observed response (Total Tube Length) in iCell Endothelial cells.

3.1.5 iCell Cardiomyocytes

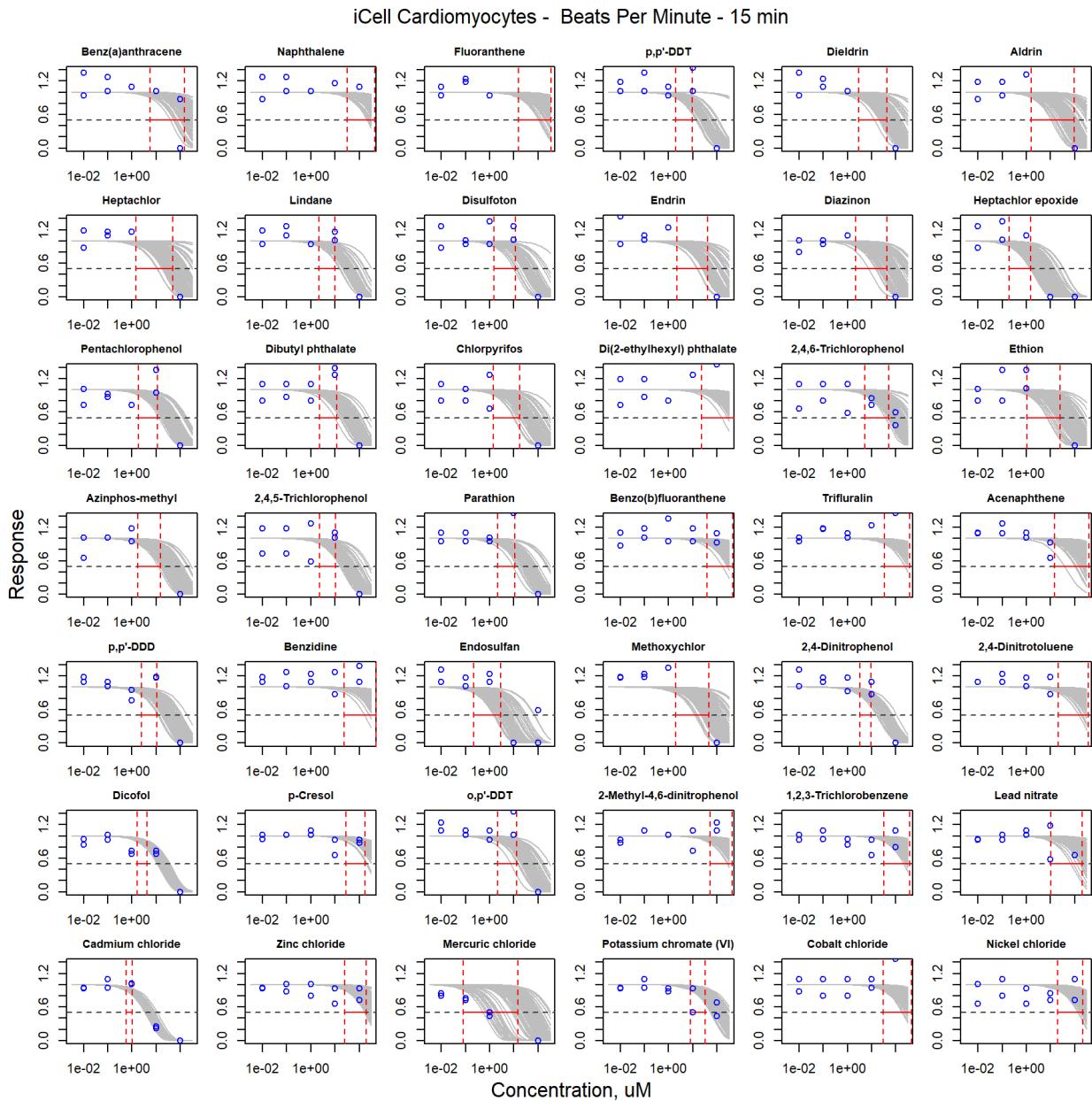


Figure S32. Curve-fitting of single chemical concentration and observed response (Beats Per Minute - 15 min) in iCell Cardiomyocytes.

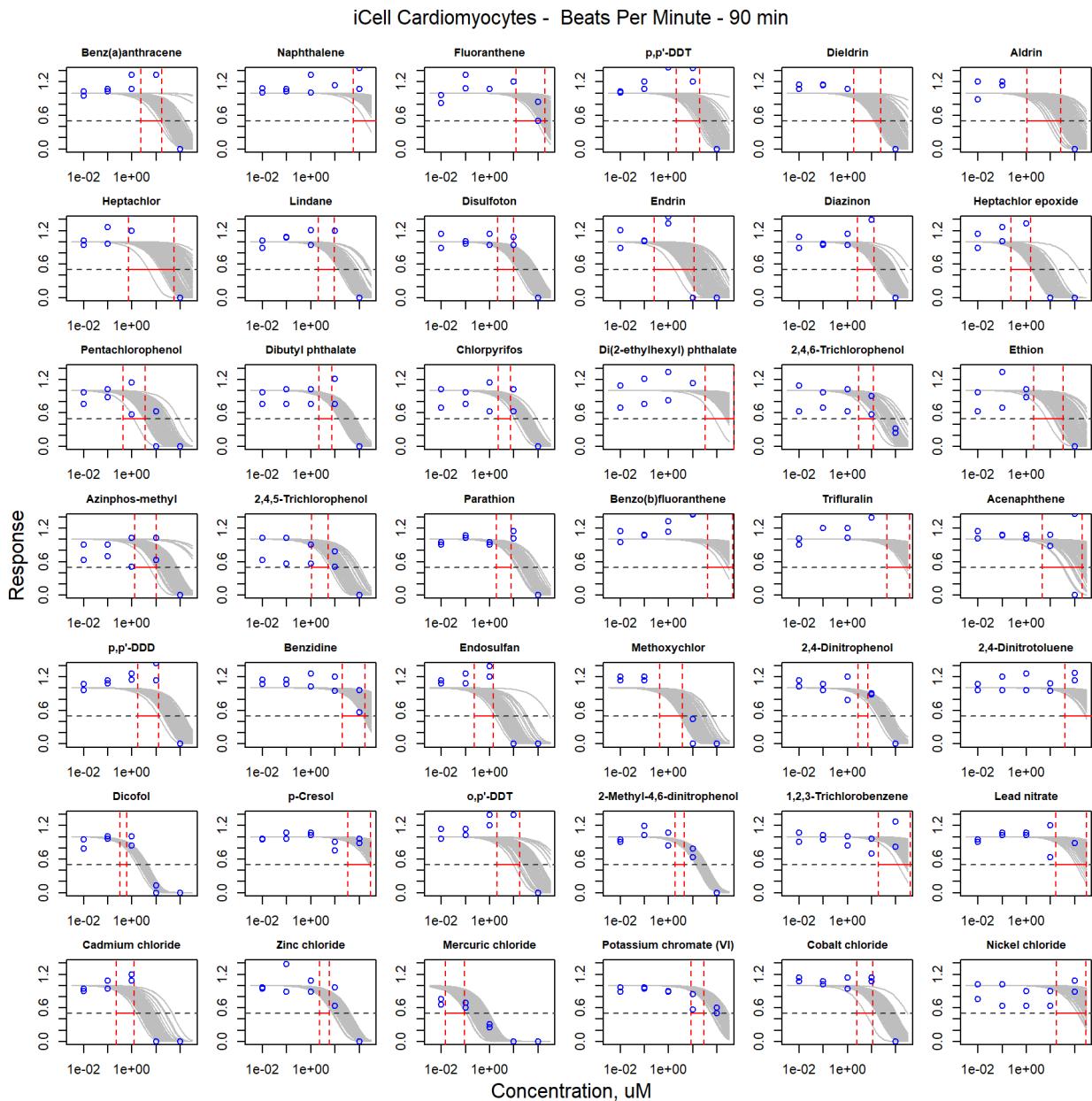


Figure S33. Curve-fitting of single chemical concentration and observed response (Beats Per Minute - 90 min) in iCell Cardiomyocytes.

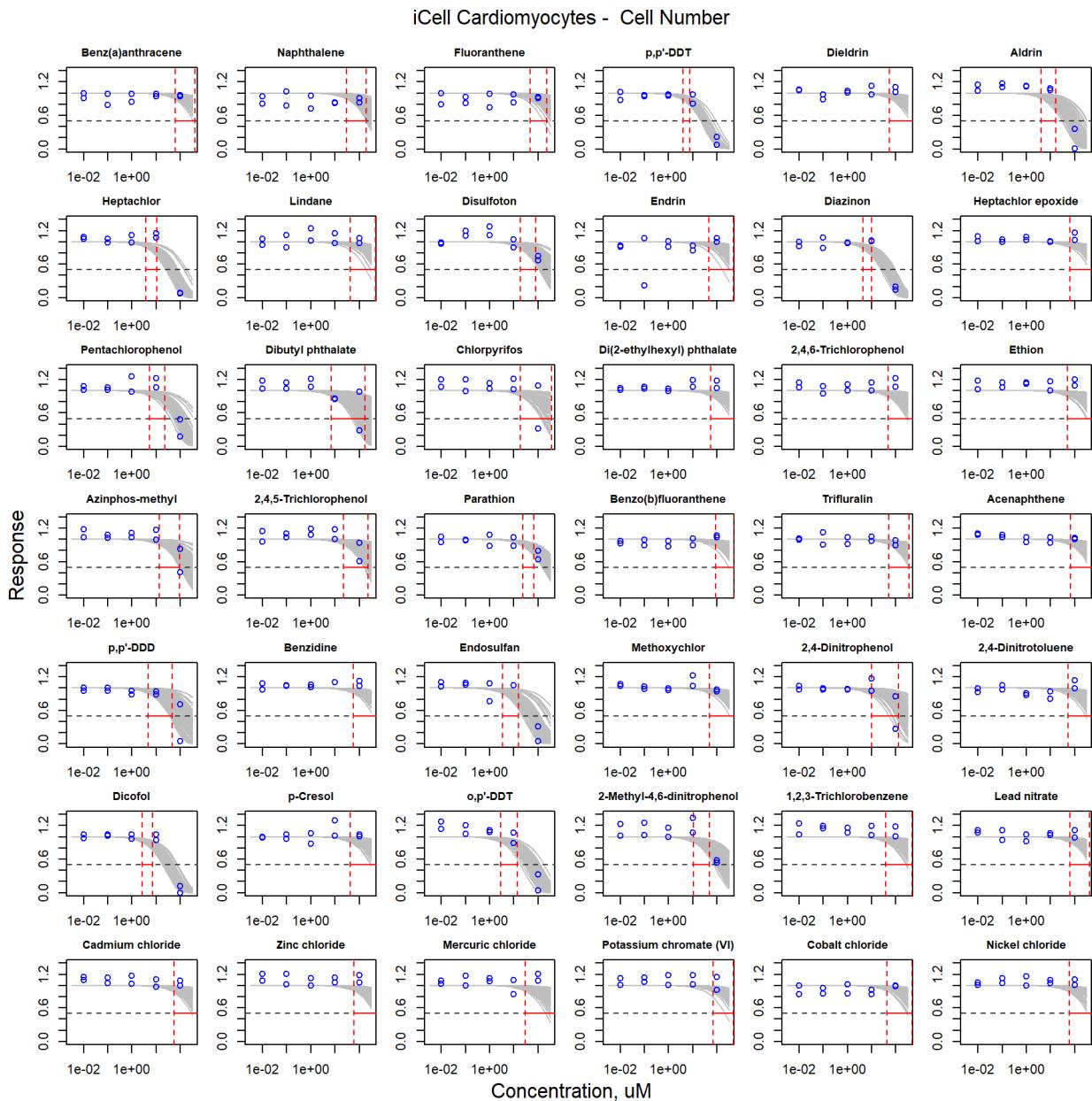


Figure S34. Curve-fitting of single chemical concentration and observed response (Cell Number) in iCell Cardiomyocytes.

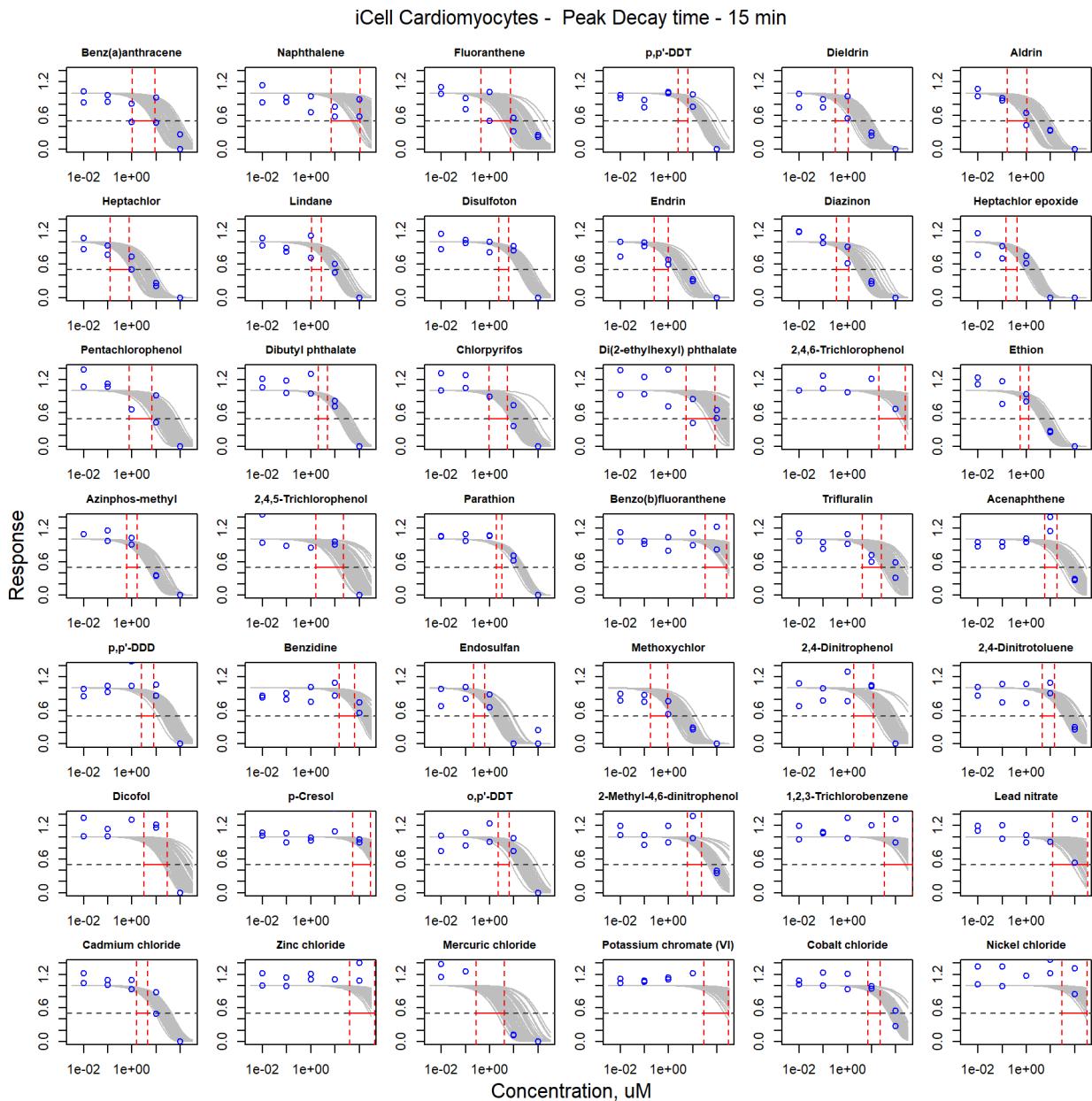


Figure S35. Curve-fitting of single chemical concentration and observed response (Peak Decay time - 15 min) in iCell Cardiomyocytes.

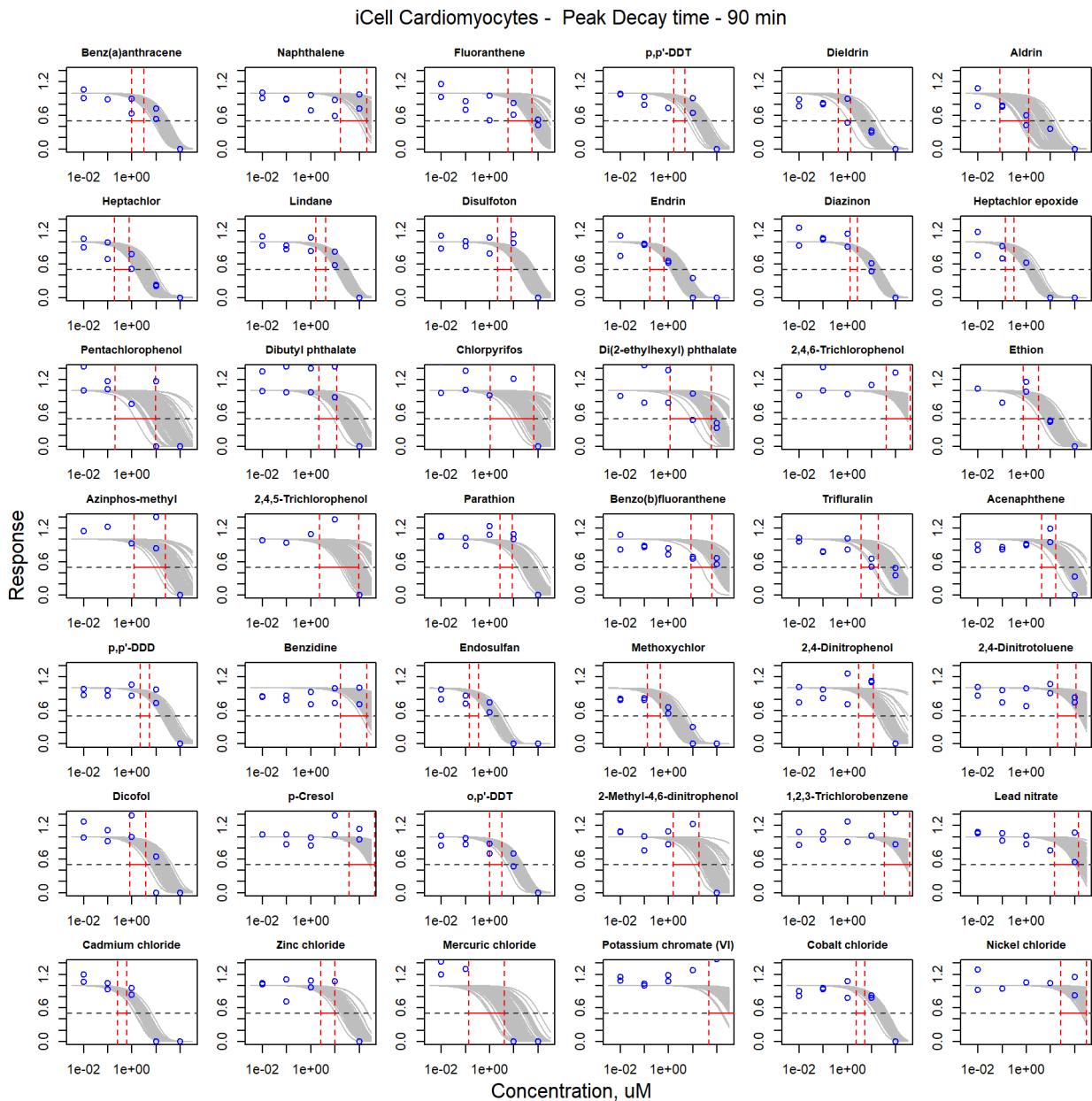


Figure S36. Curve-fitting of single chemical concentration and observed response (Peak Decay time - 90 min) in iCell Cardiomyocytes.

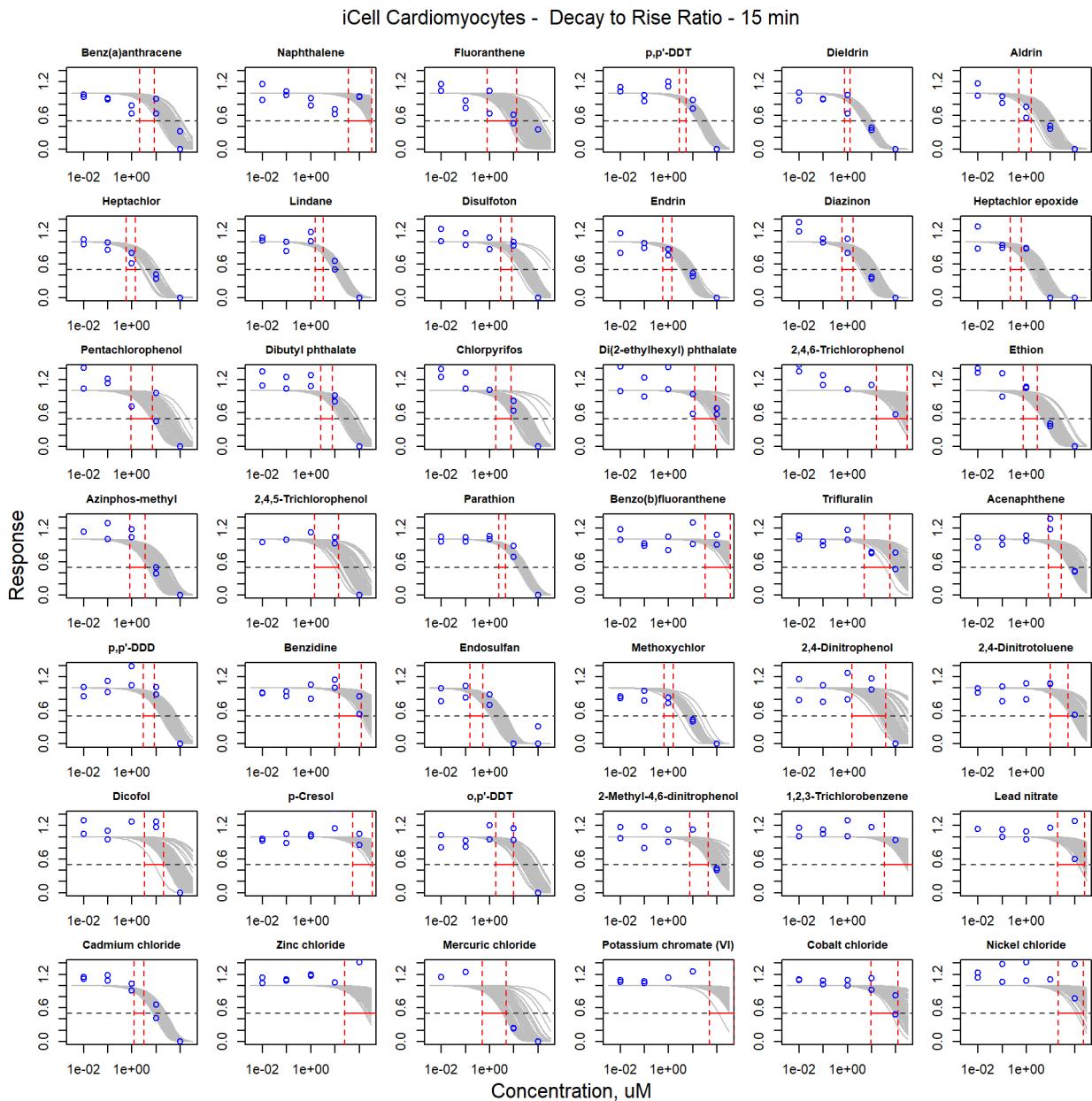


Figure S37. Curve-fitting of single chemical concentration and observed response (Decay to Rise Ratio - 15 min) in iCell Cardiomyocytes.

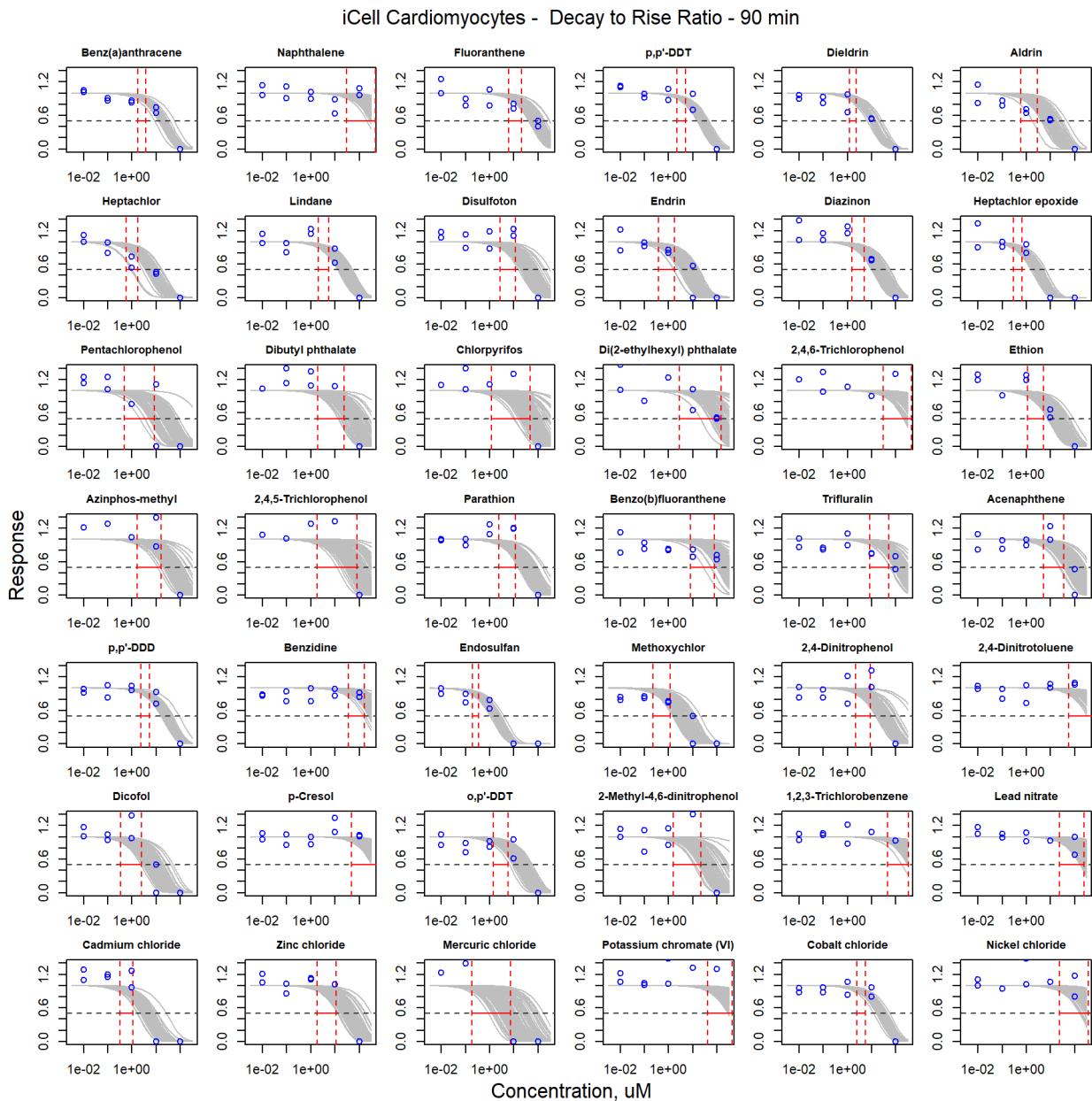


Figure S38. Curve-fitting of single chemical concentration and observed response (Decay to Rise Ratio - 90 min) in iCell Cardiomyocytes.

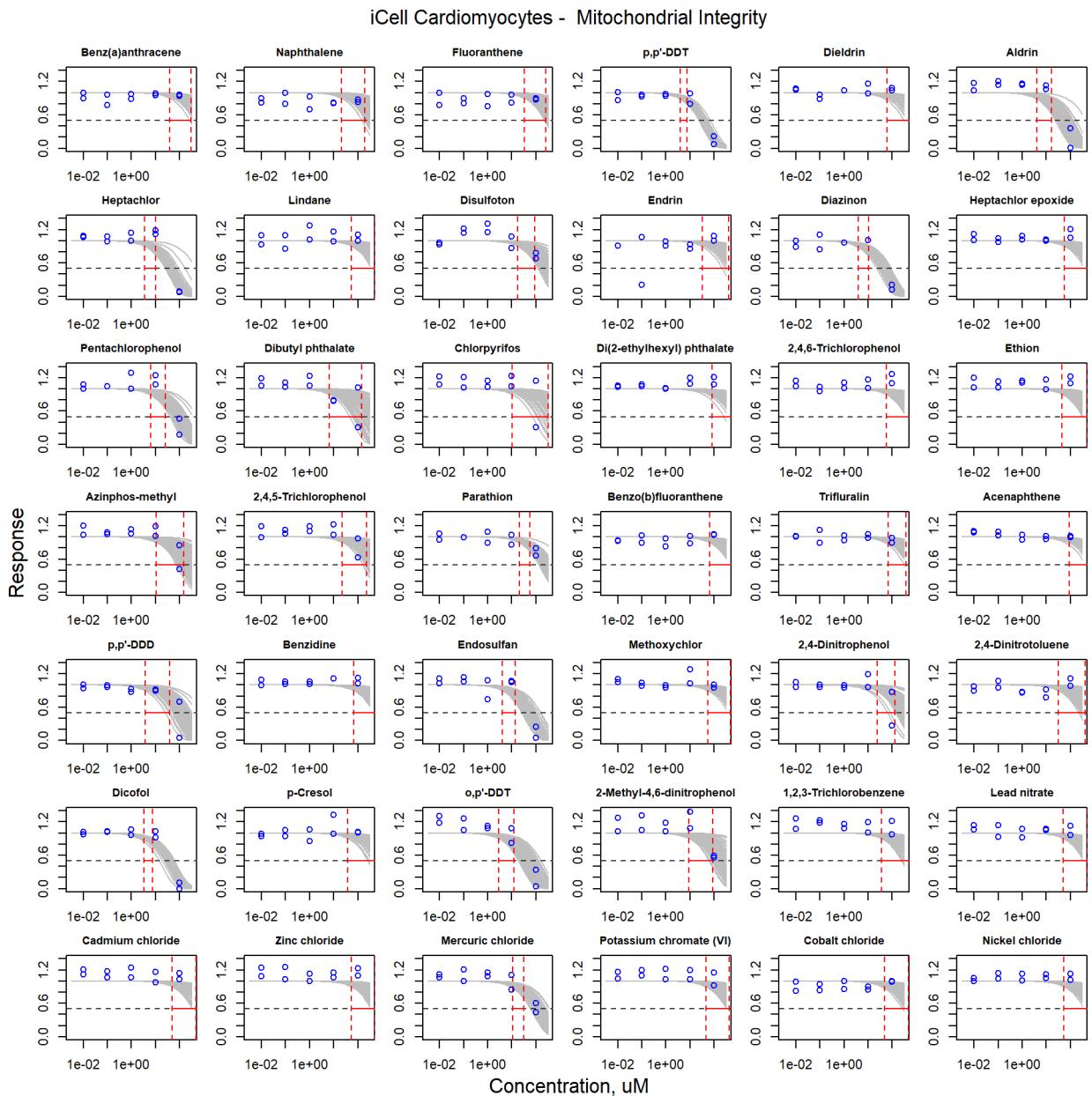


Figure S39. Curve-fitting of single chemical concentration and observed response (Mitochondrial Integrity) in iCell Cardiomyocytes.

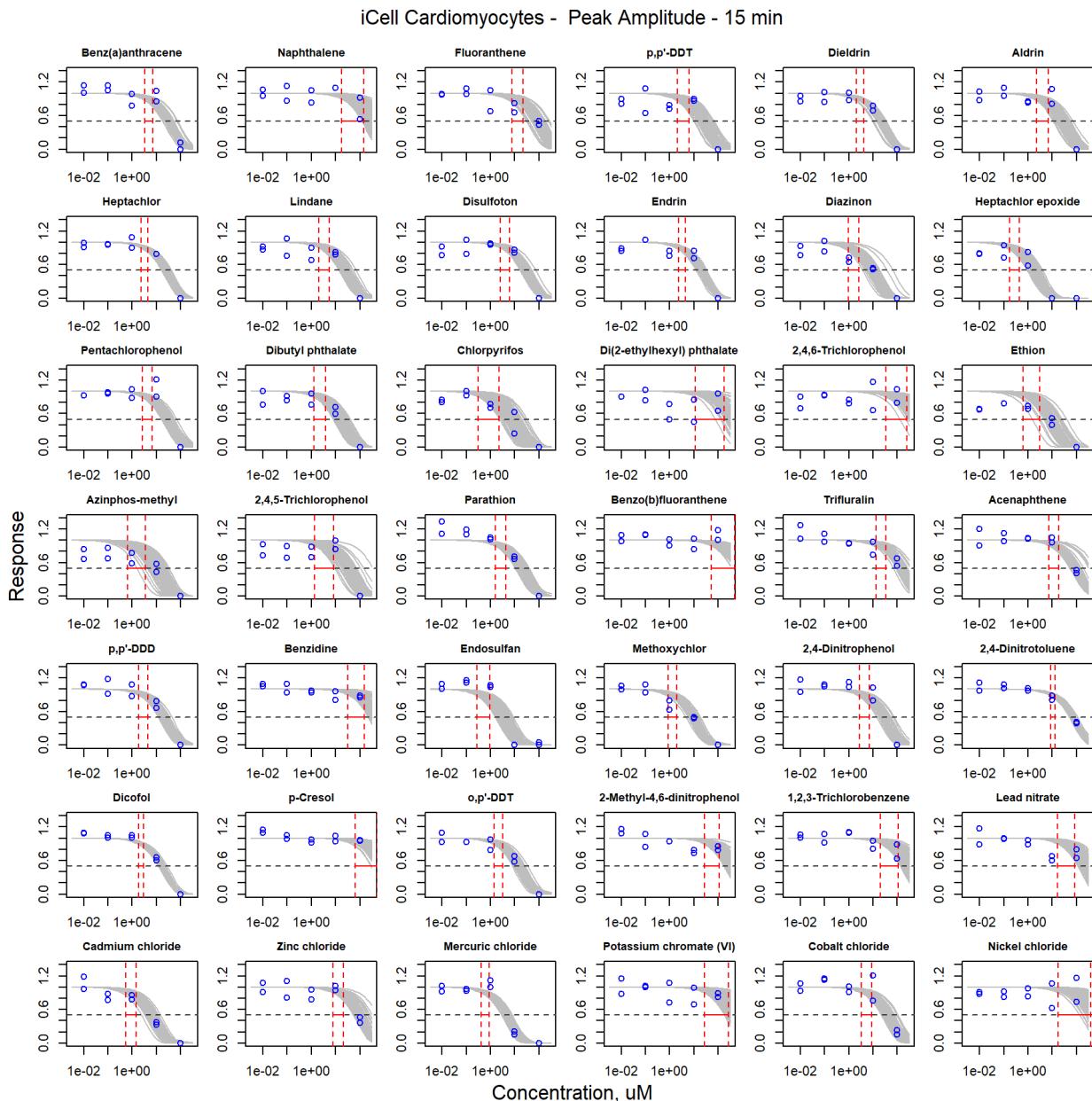


Figure S40. Curve-fitting of single chemical concentration and observed response (Peak Amplitude - 15 min) in iCell Cardiomyocytes.

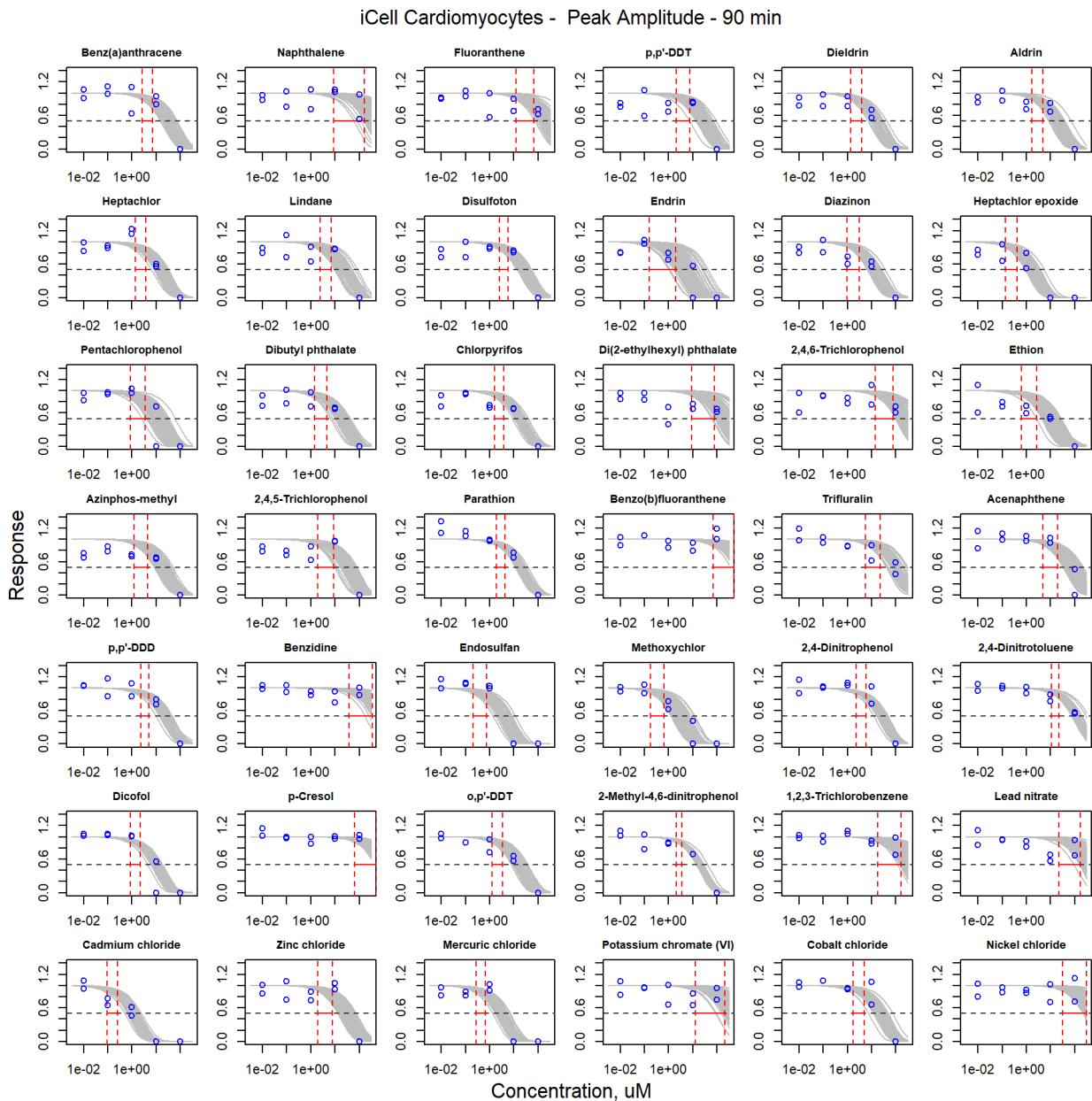


Figure S41. Curve-fitting of single chemical concentration and observed response (Peak Amplitude - 90 min) in iCell Cardiomyocytes.

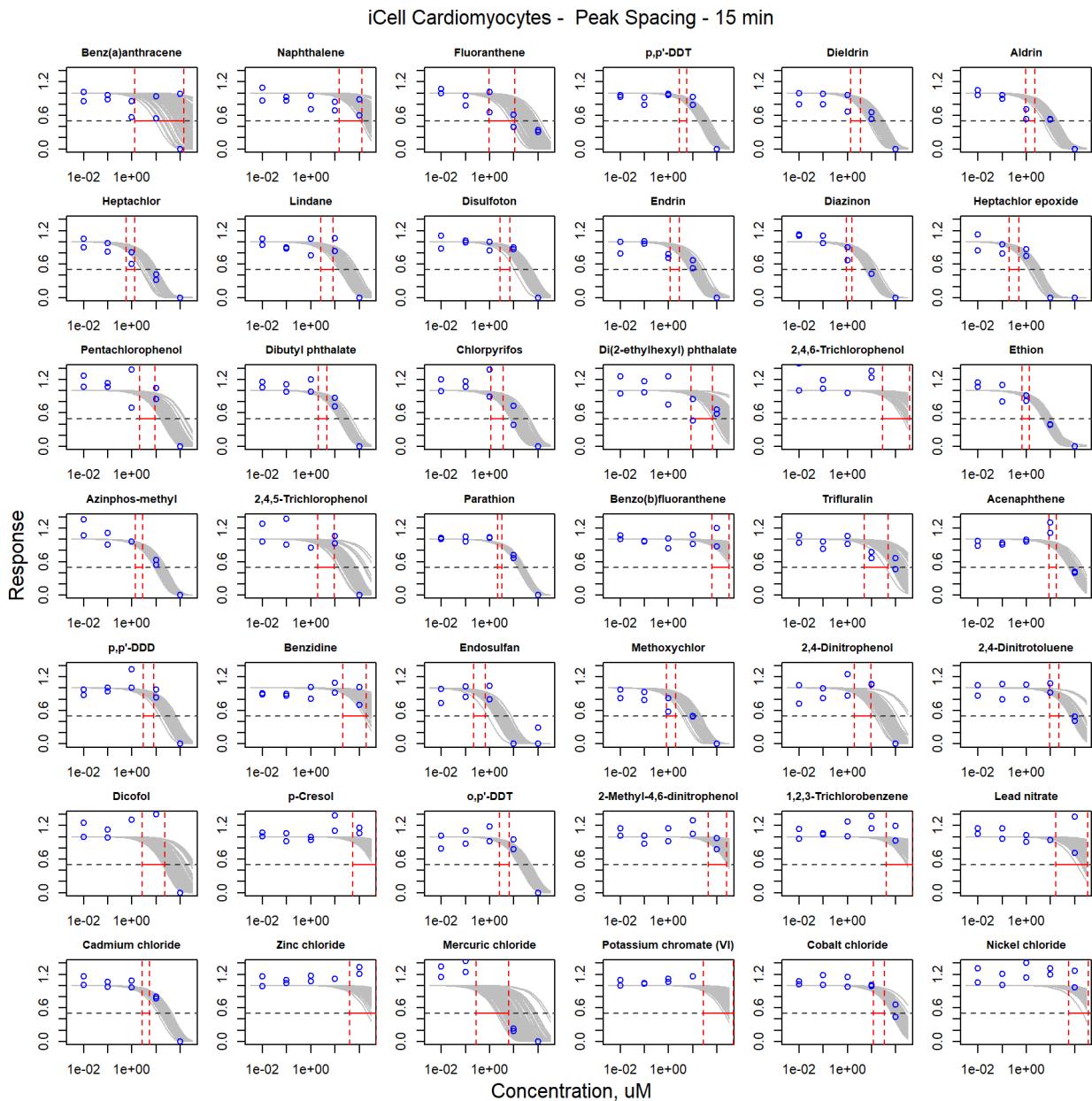


Figure S42. Curve-fitting of single chemical concentration and observed response (Peak Spacing - 15 min) in iCell Cardiomyocytes.

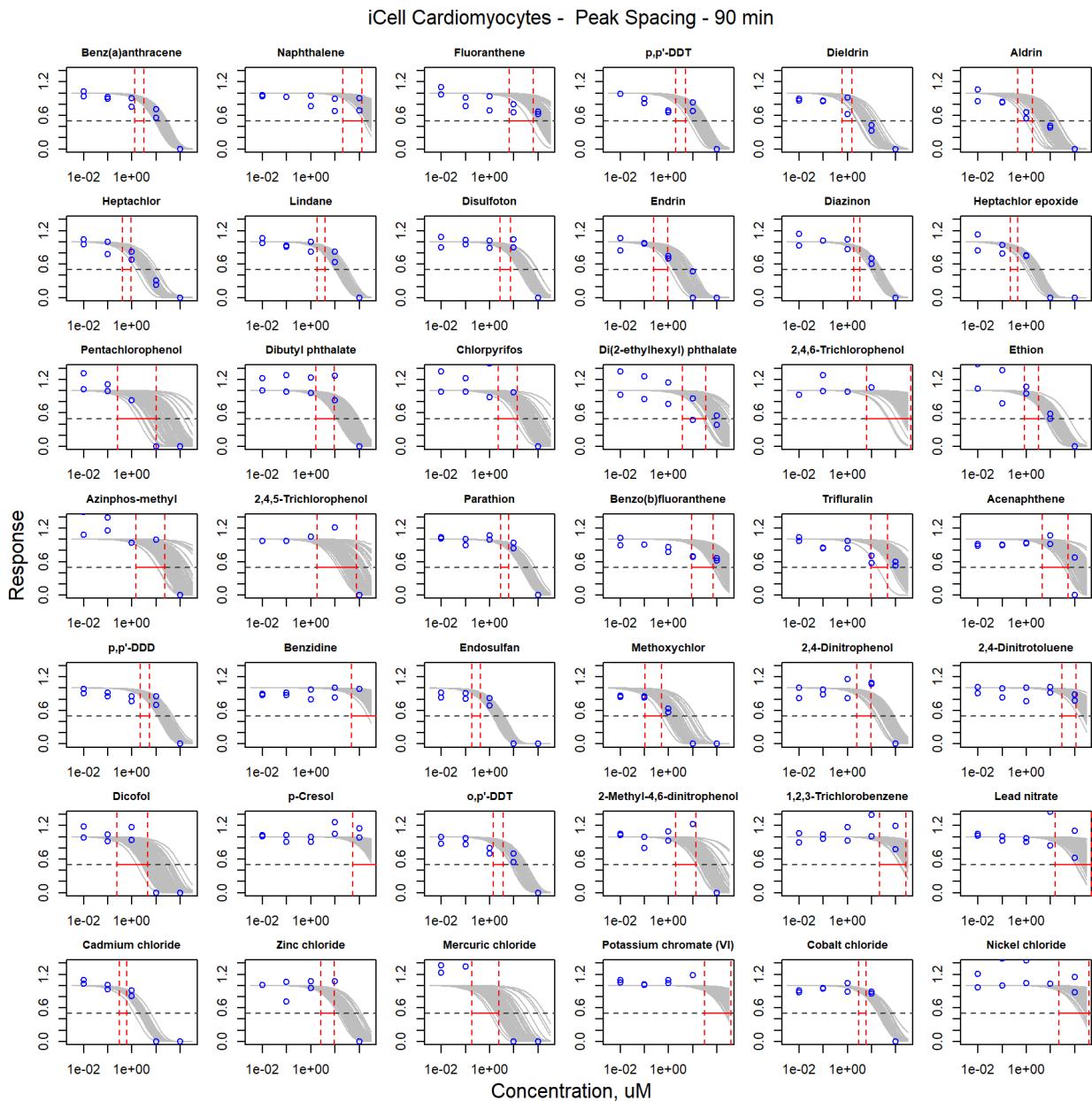


Figure S43. Curve-fitting of single chemical concentration and observed response (Peak Spacing - 90 min) in iCell Cardiomyocytes.

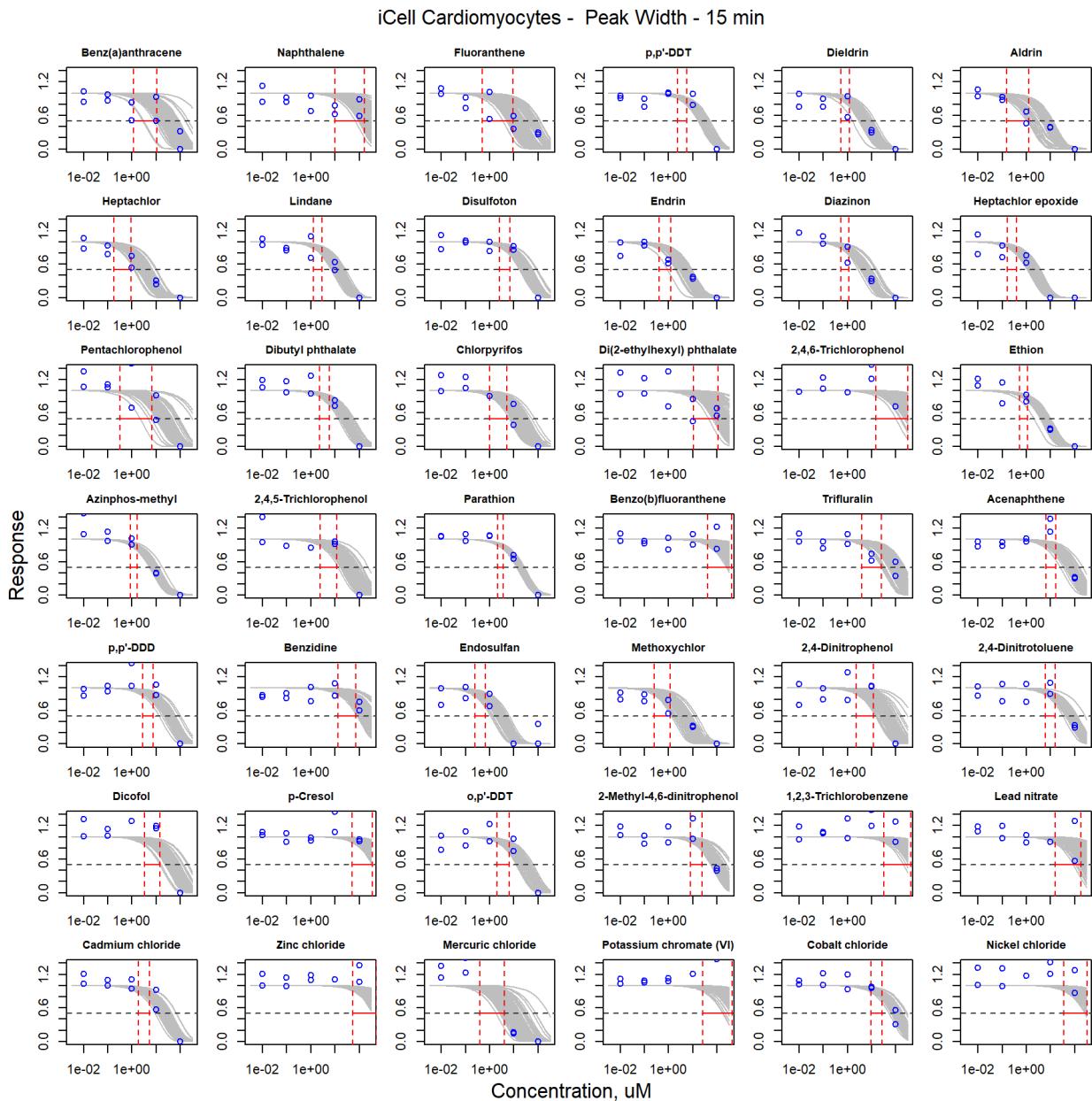


Figure S44. Curve-fitting of single chemical concentration and observed response (Peak Width - 15 min) in iCell Cardiomyocytes.

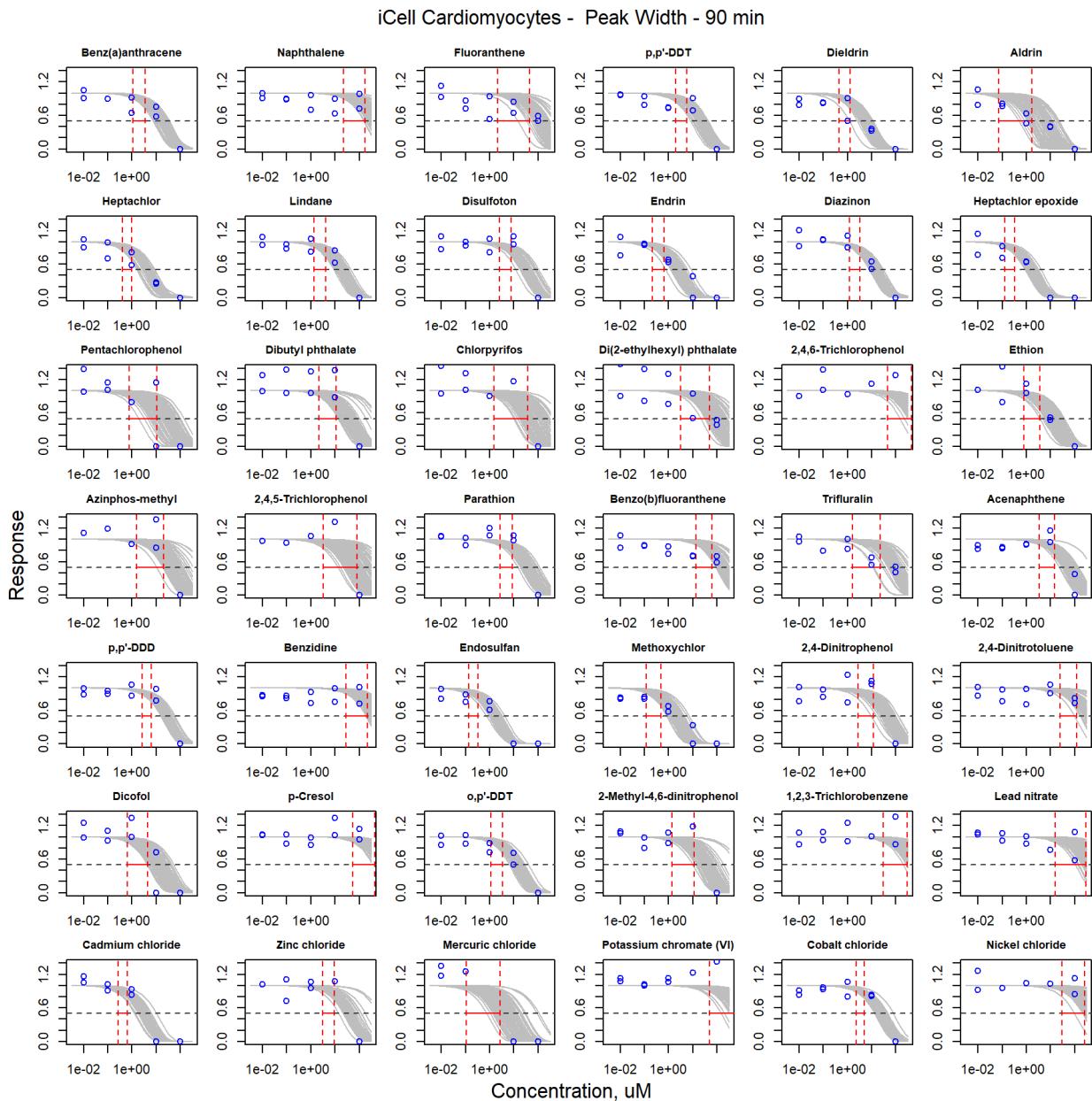


Figure S45. Curve-fitting of single chemical concentration and observed response (Peak Width - 90 min) in iCell Cardiomyocytes.

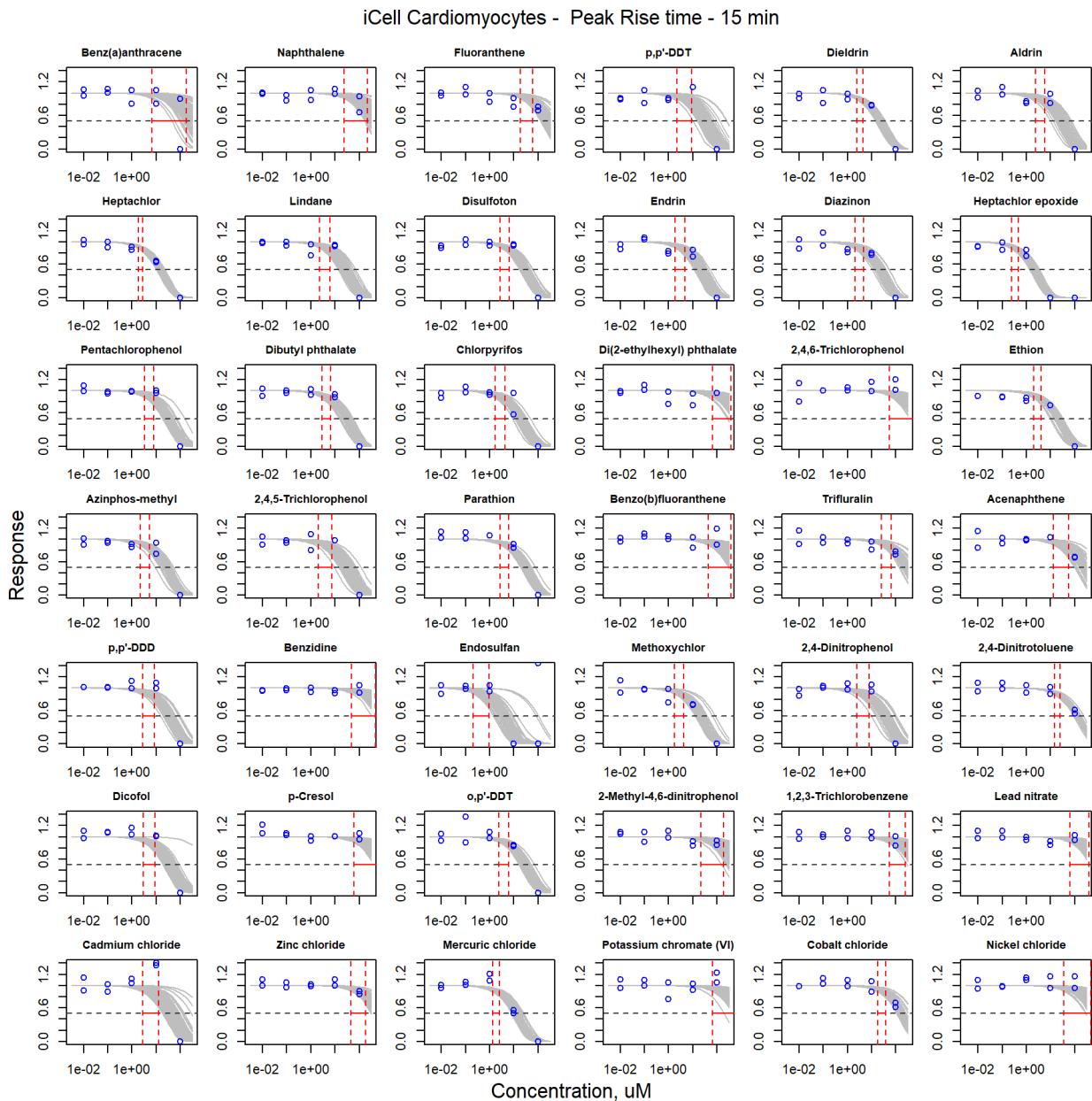


Figure S46. Curve-fitting of single chemical concentration and observed response (Peak Rise time - 15 min) in iCell Cardiomyocytes.

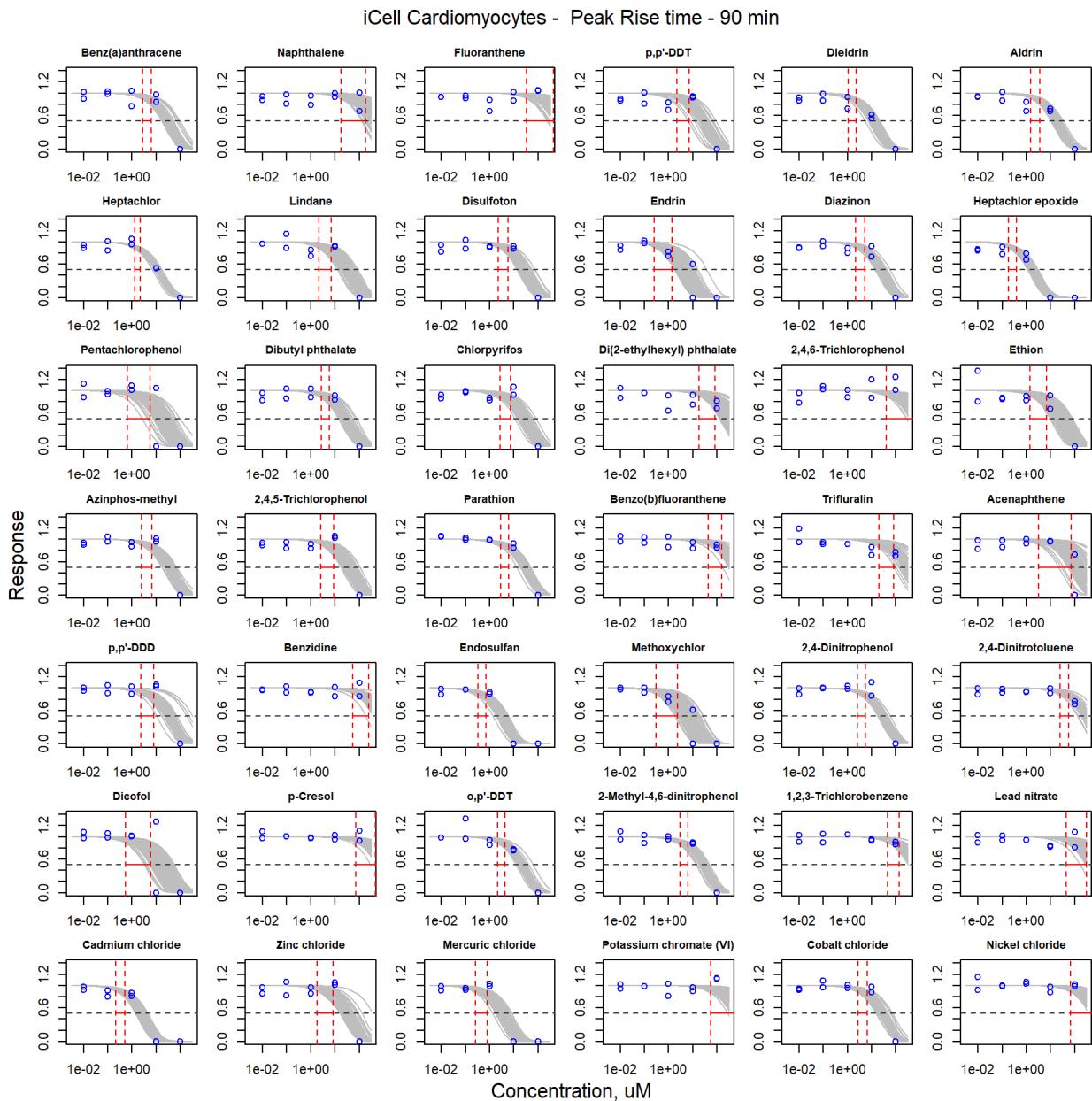


Figure S47. Curve-fitting of single chemical concentration and observed response (Peak Rise time - 90 min) in iCell Cardiomyocytes.

3.2 Curve-fitting of mixture concentration-response

3.2.1 iCell Neurons

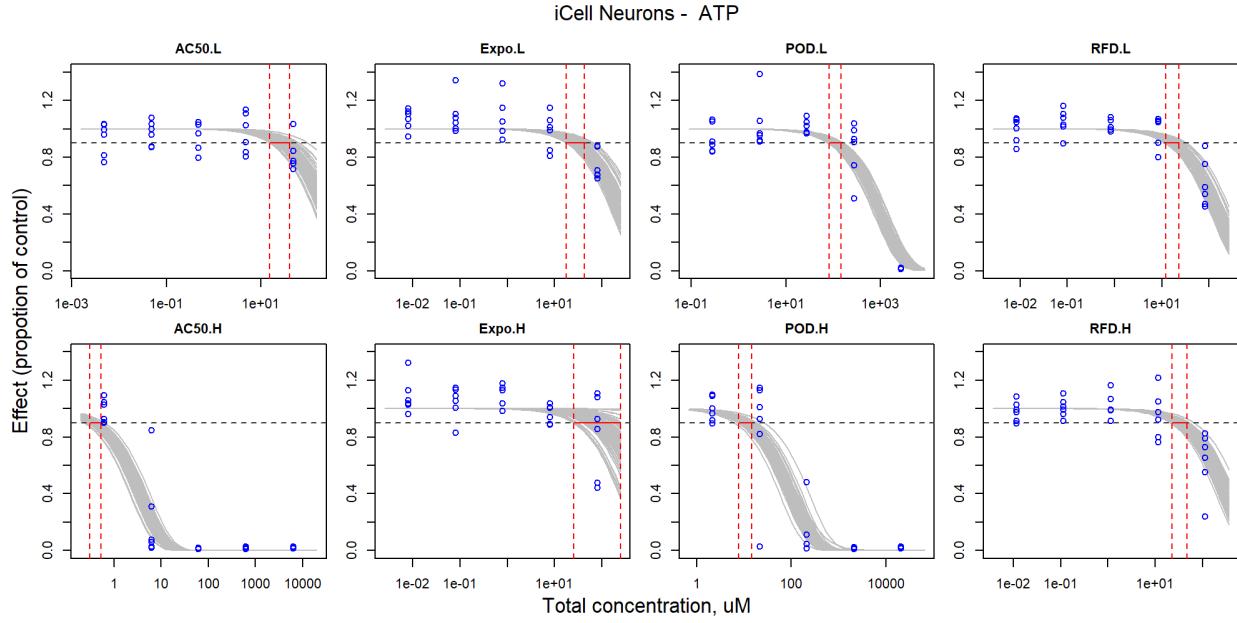


Figure S48. Curve-fitting of mixture concentration and observed response (ATP) in iCell Neurons.

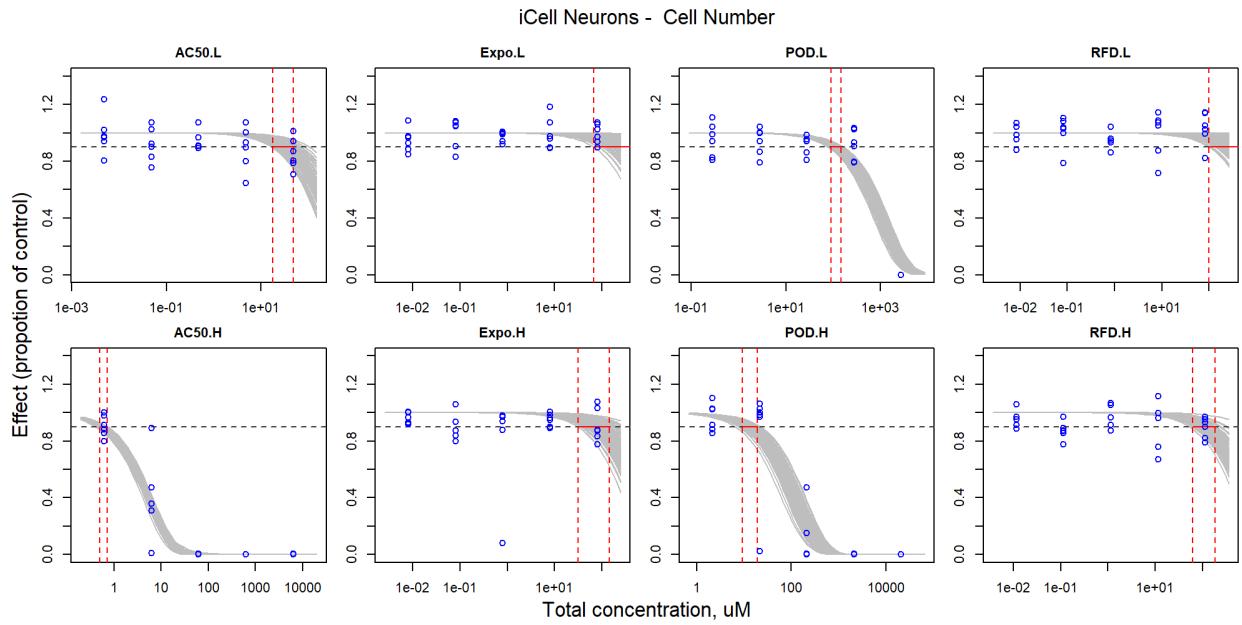


Figure S49. Curve-fitting of mixture concentration and observed response (Cell Number) in iCell Neurons.

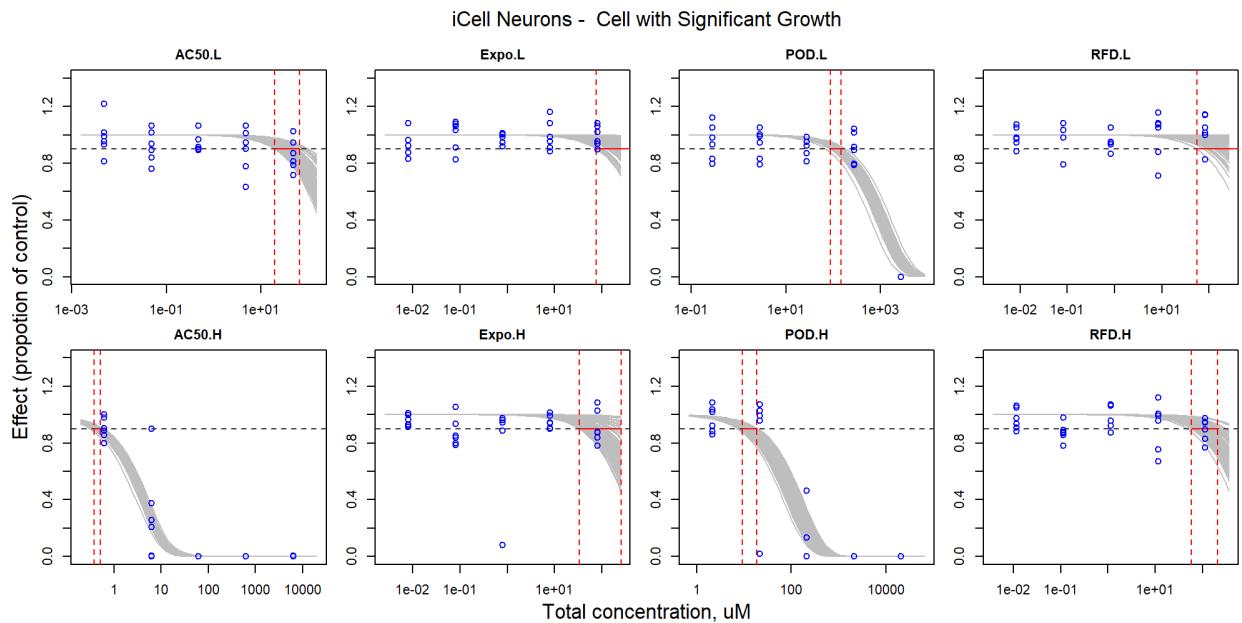


Figure S50. Curve-fitting of mixture concentration and observed response (Cell with Significant Growth) in iCell Neurons.

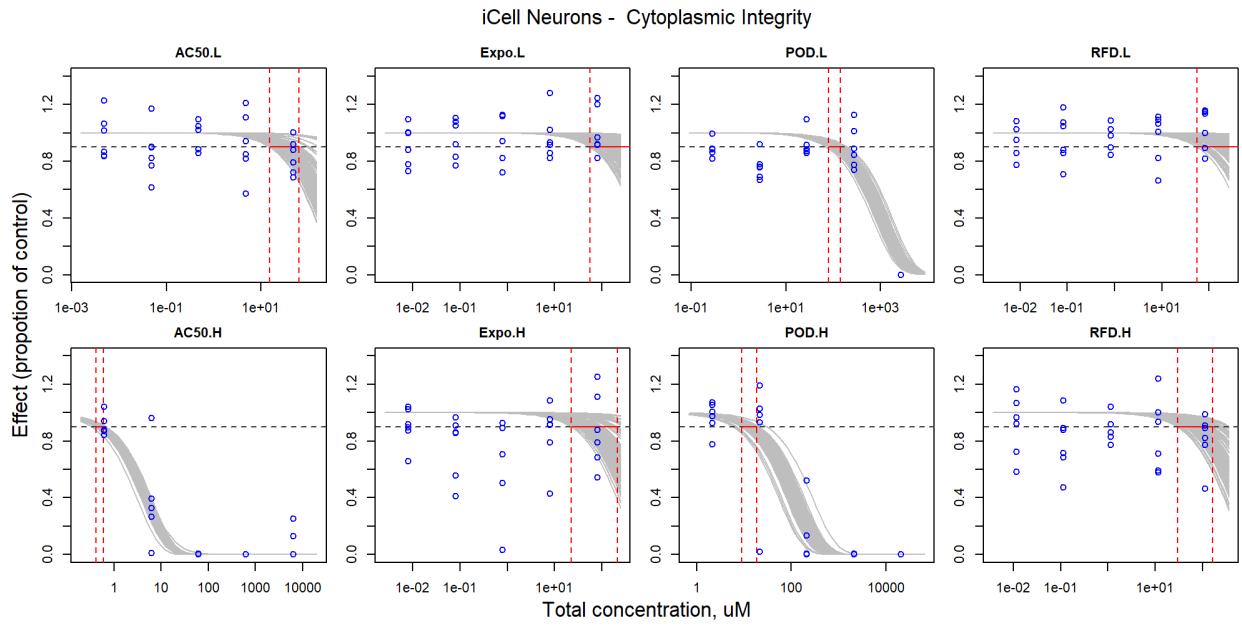


Figure S51. Curve-fitting of mixture concentration and observed response (Cytoplasmic Integrity) in iCell Neurons.

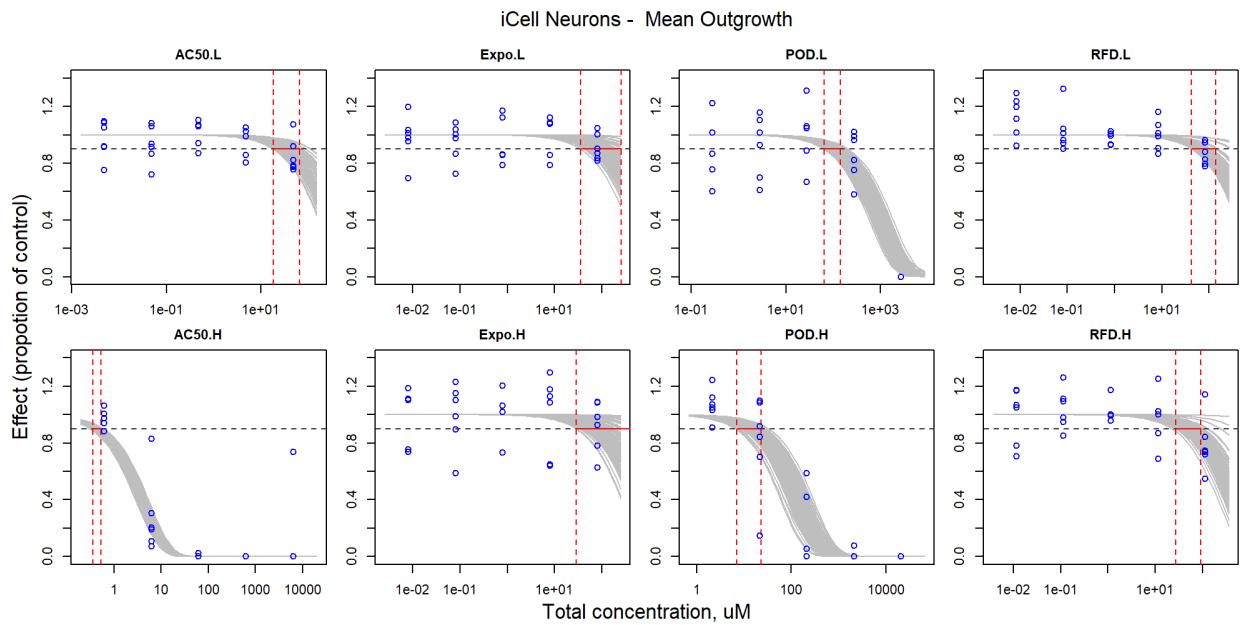


Figure S52. Curve-fitting of mixture concentration and observed response (Mean Outgrowth) in iCell Neurons.

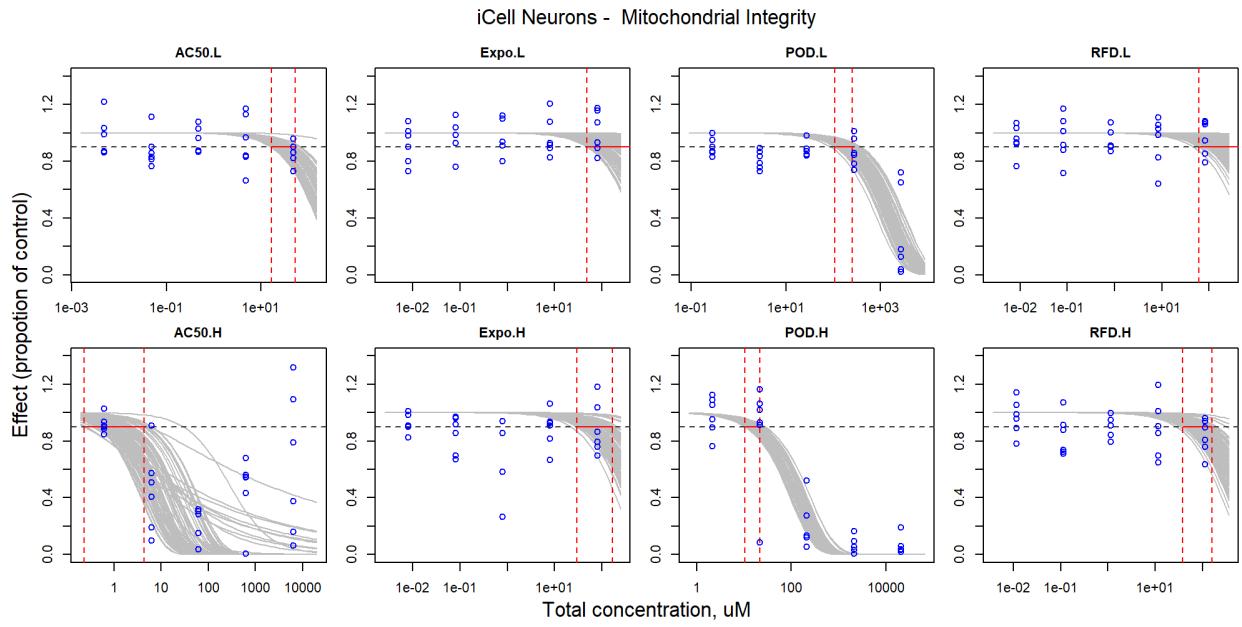


Figure S53. Curve-fitting of mixture concentration and observed response (Mitochondrial Integrity) in iCell Neurons.

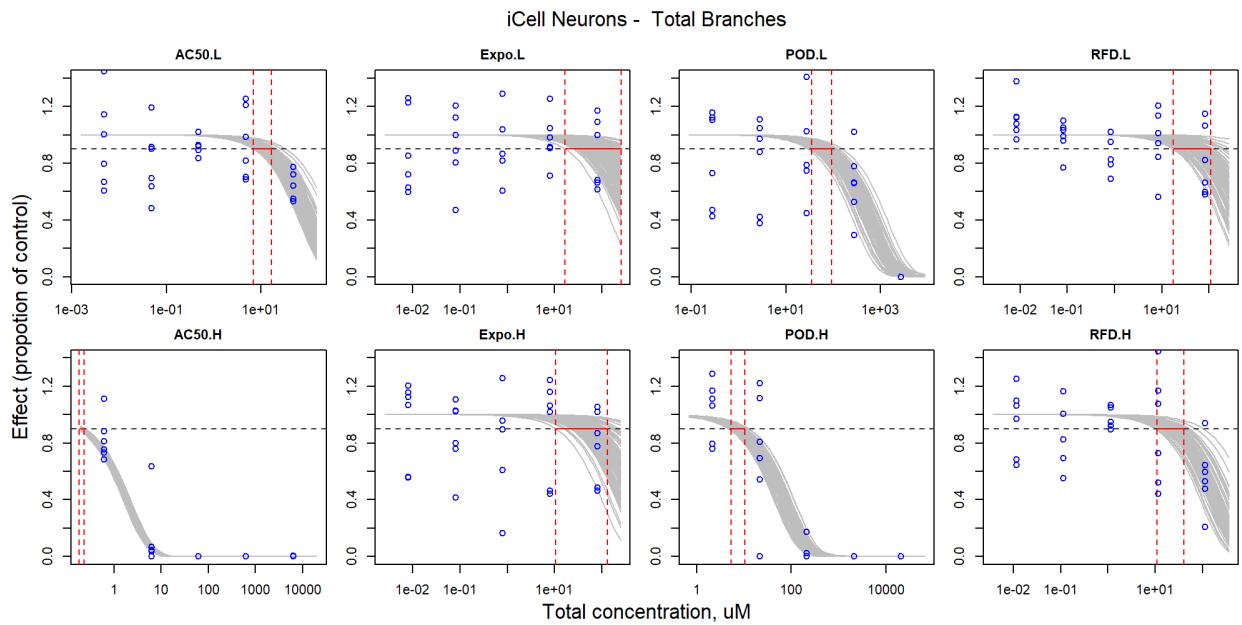


Figure S54. Curve-fitting of mixture concentration and observed response (Total Branches) in iCell Neurons.

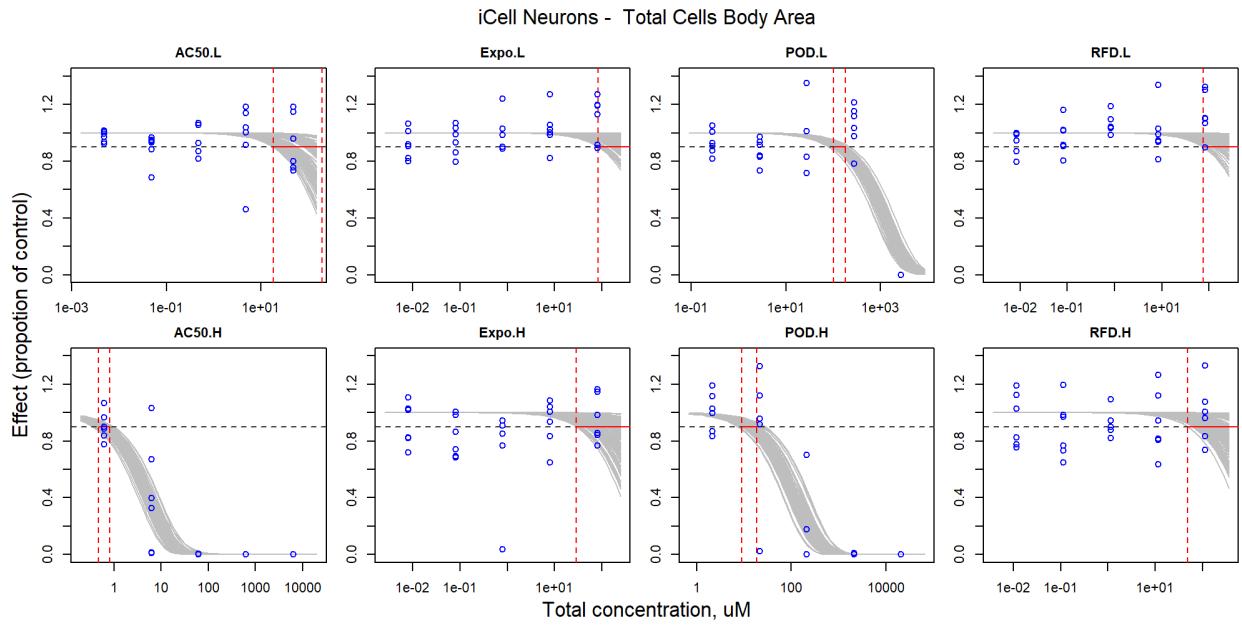


Figure S55. Curve-fitting of mixture concentration and observed response (Total Cells Body Area) in iCell Neurons.

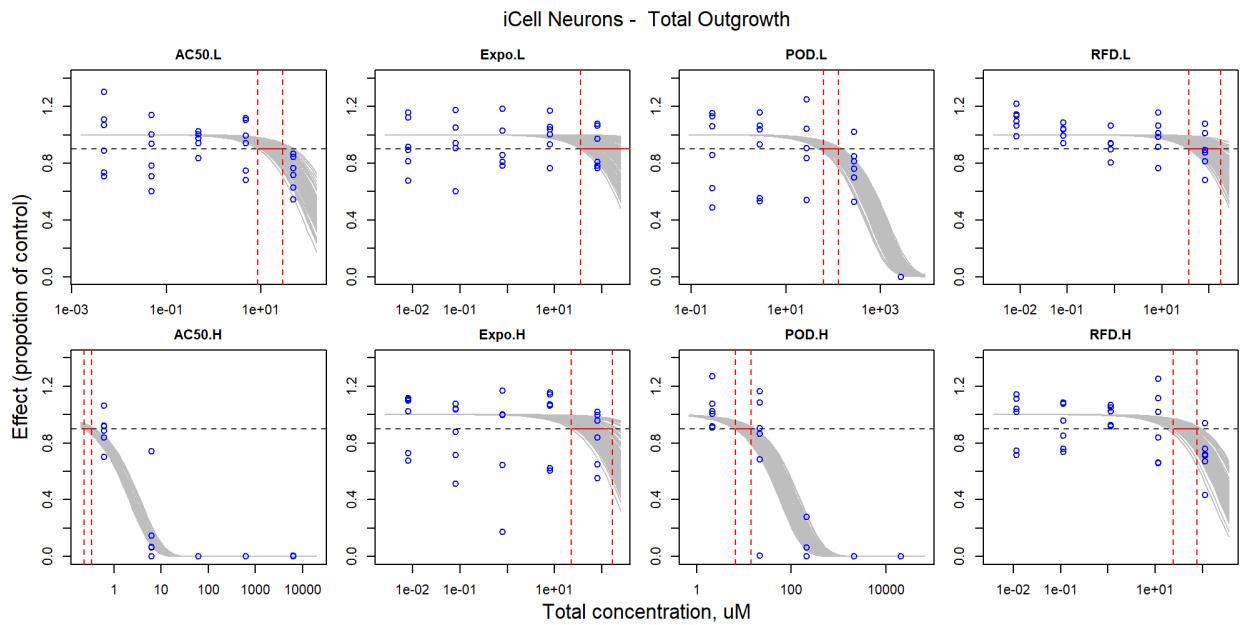


Figure S56. Curve-fitting of mixture concentration and observed response (Total Outgrowth) in iCell Neurons.

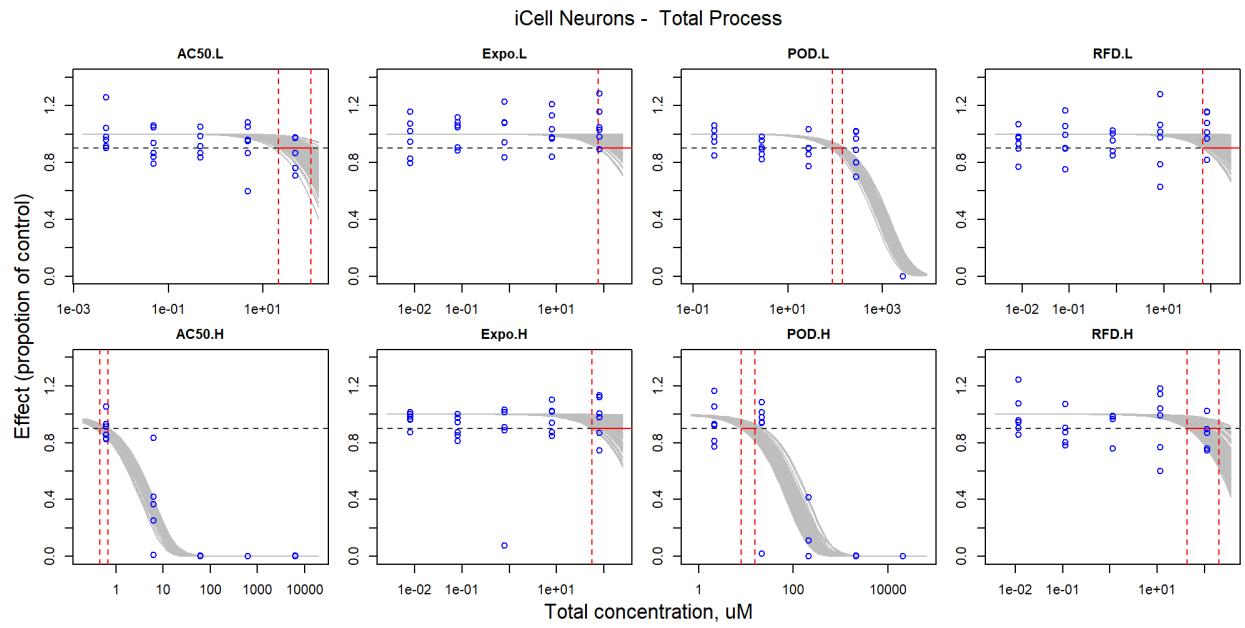


Figure S57. Curve-fitting of mixture concentration and observed response (Total Process) in iCell Neurons.

3.2.2 HUVECs

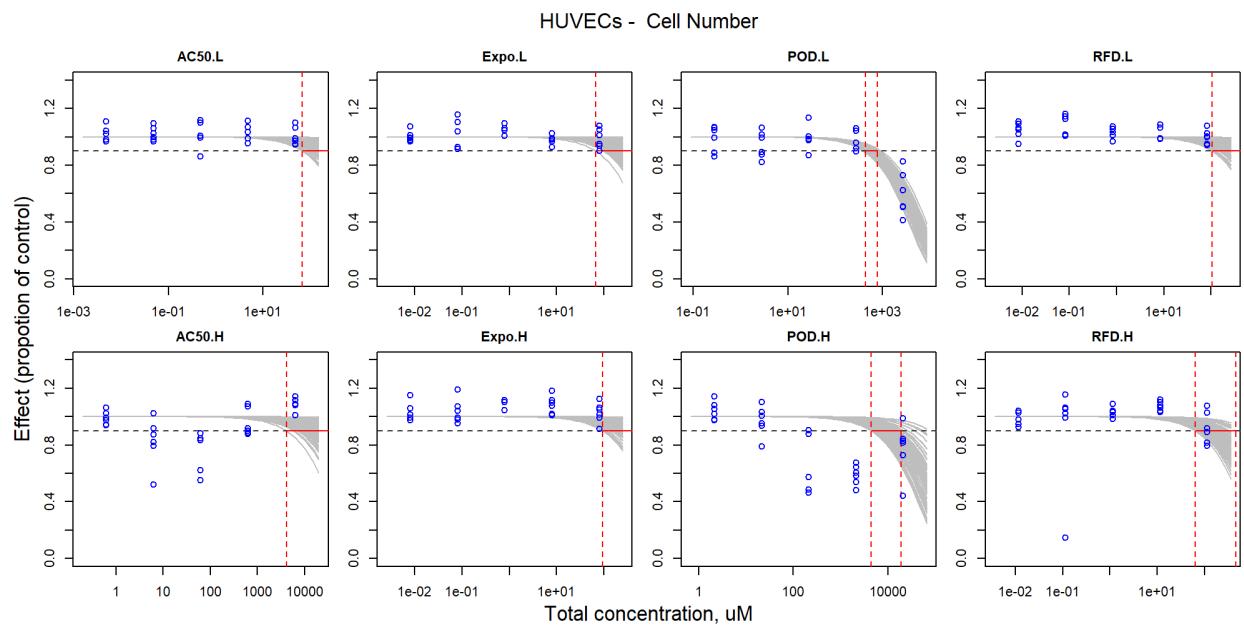


Figure S58. Curve-fitting of mixture concentration and observed response (Cell Number) in HUVECs.

HUVECs - Cytoplasmic Integrity

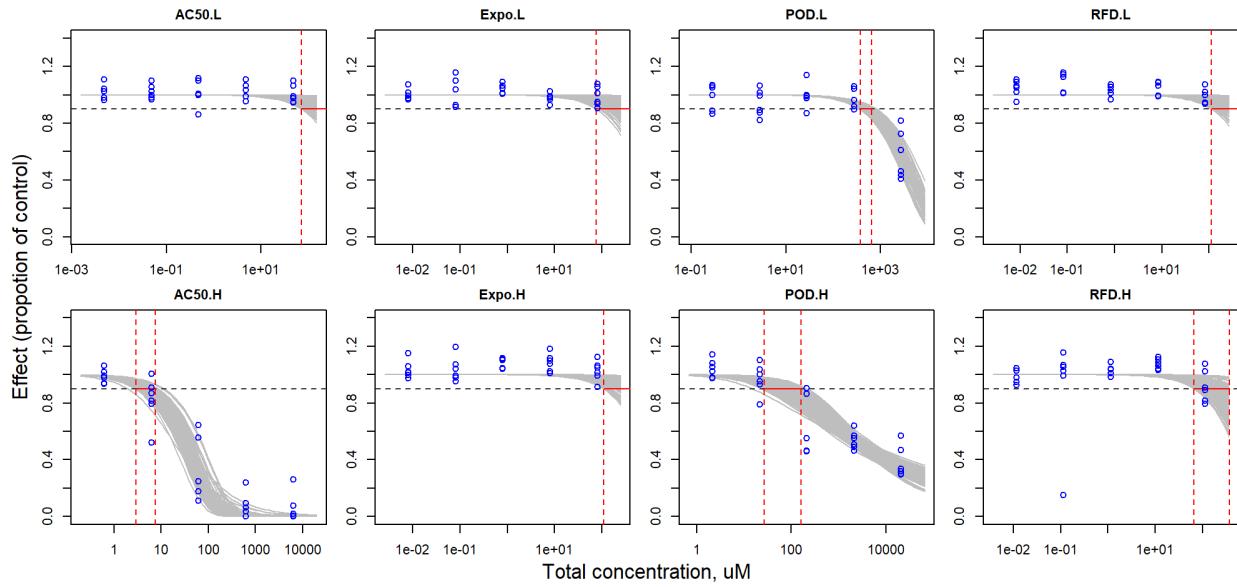


Figure S59. Curve-fitting of mixture concentration and observed response (Cytoplasmic Integrity) in HUVECs.

HUVECs - Mean Tube Length

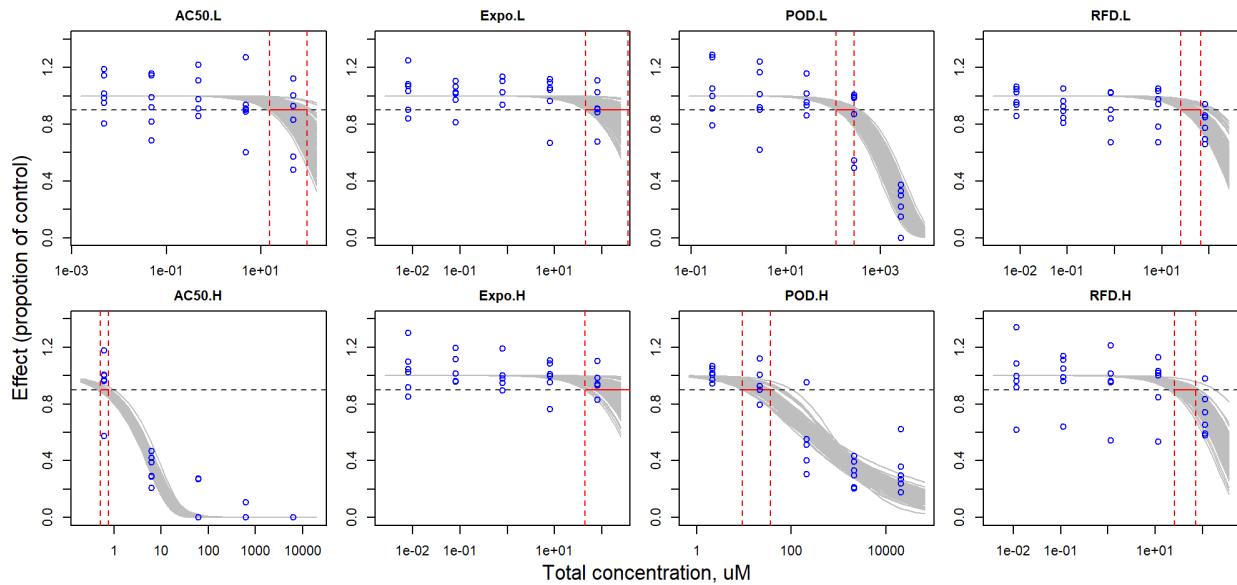


Figure S60. Curve-fitting of mixture concentration and observed response (Mean Tube Length) in HUVECs.

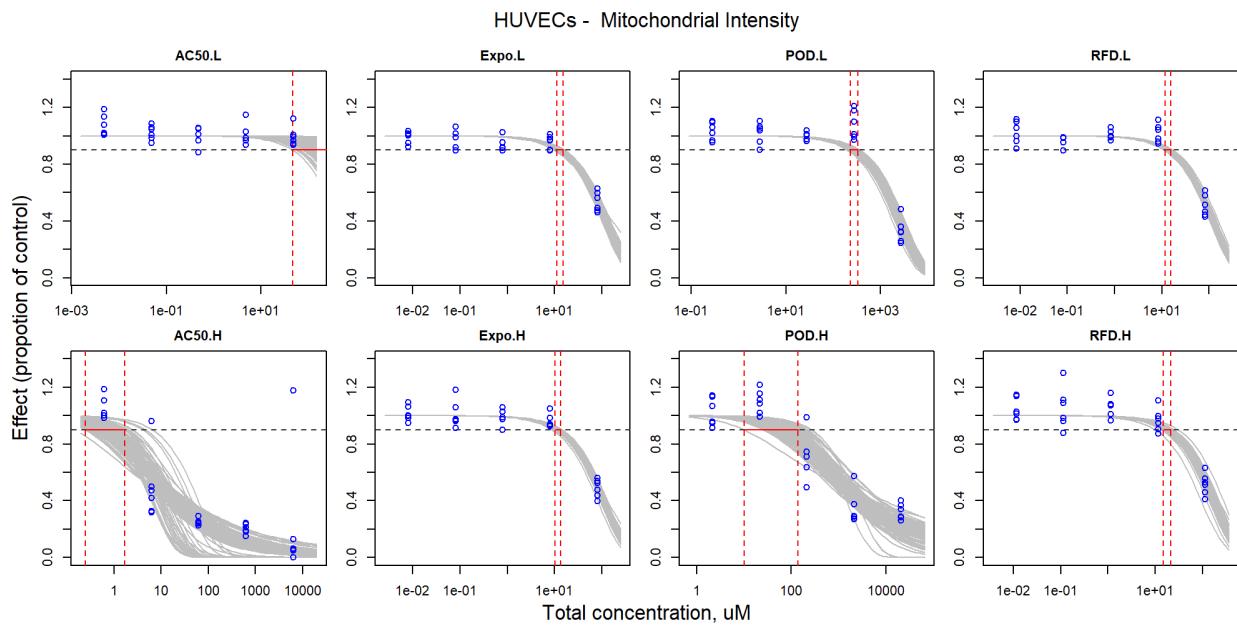


Figure S61. Curve-fitting of mixture concentration and observed response (Mitochondrial Intensity) in HUVECs.

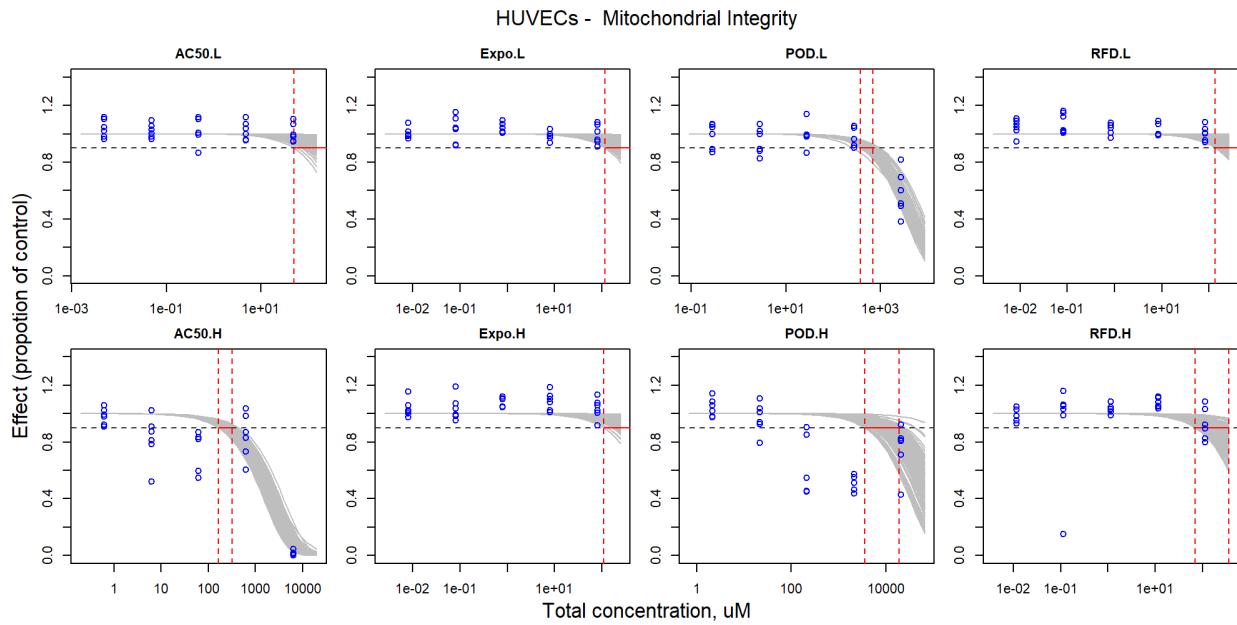


Figure S62. Curve-fitting of mixture concentration and observed response (Mitochondrial Integrity) in HUVECs.

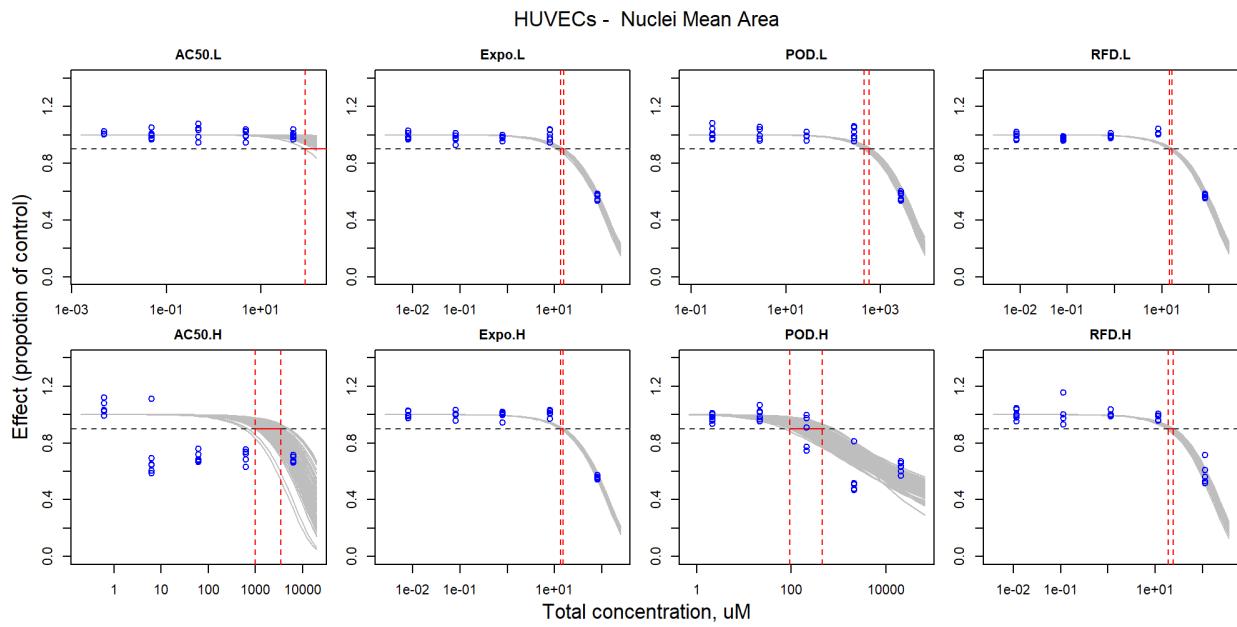


Figure S63. Curve-fitting of mixture concentration and observed response (Nuclei Mean Area) in HUVECs.

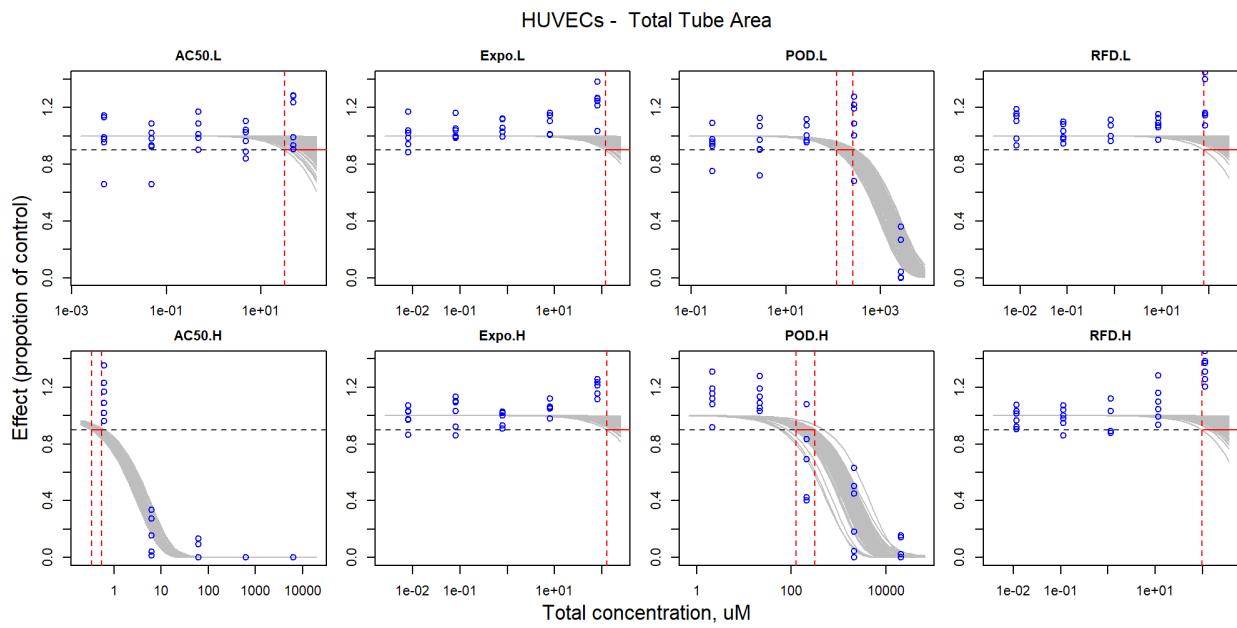


Figure S64. Curve-fitting of mixture concentration and observed response (Total Tube Area) in HUVECs.

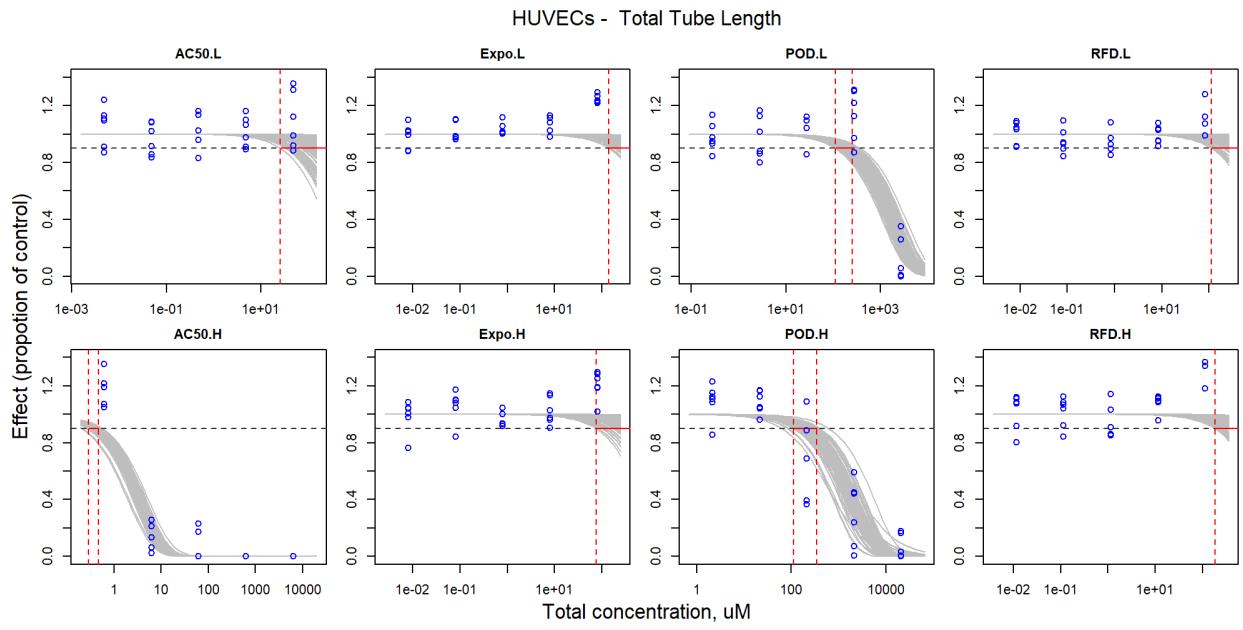


Figure S65. Curve-fitting of mixture concentration and observed response (Total Tube Length) in HUVECs.

3.2.3 iCell Hepatocytes

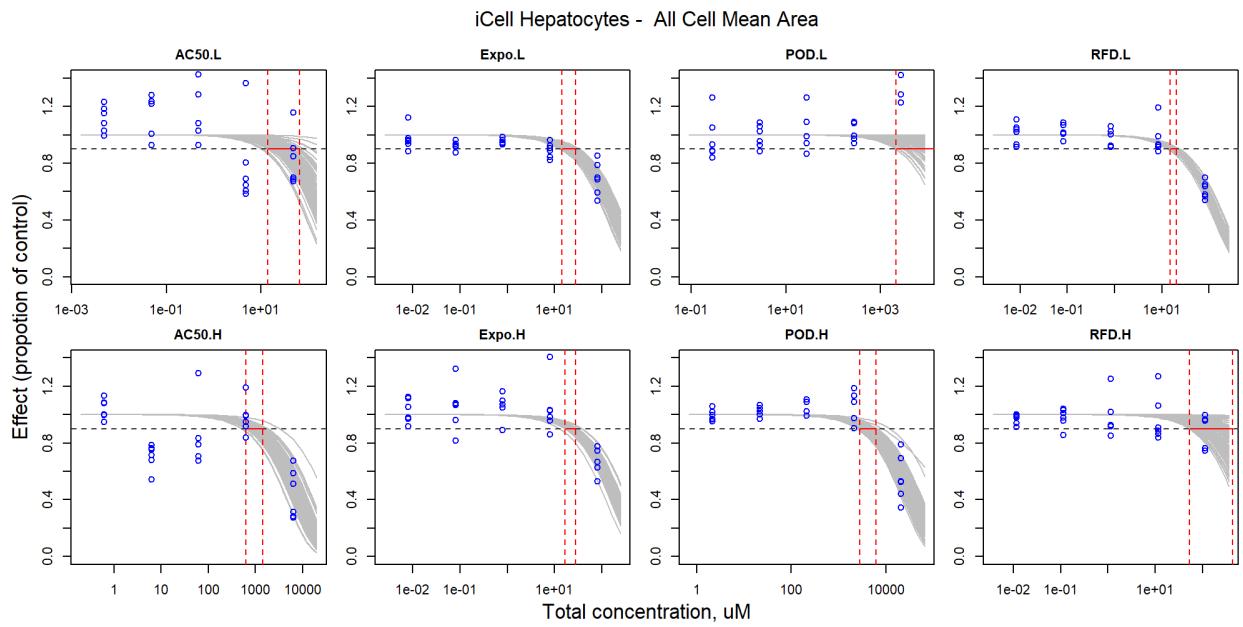


Figure S66. Curve-fitting of mixture concentration and observed response (All Cell Mean Area) in iCell Hepatocytes.

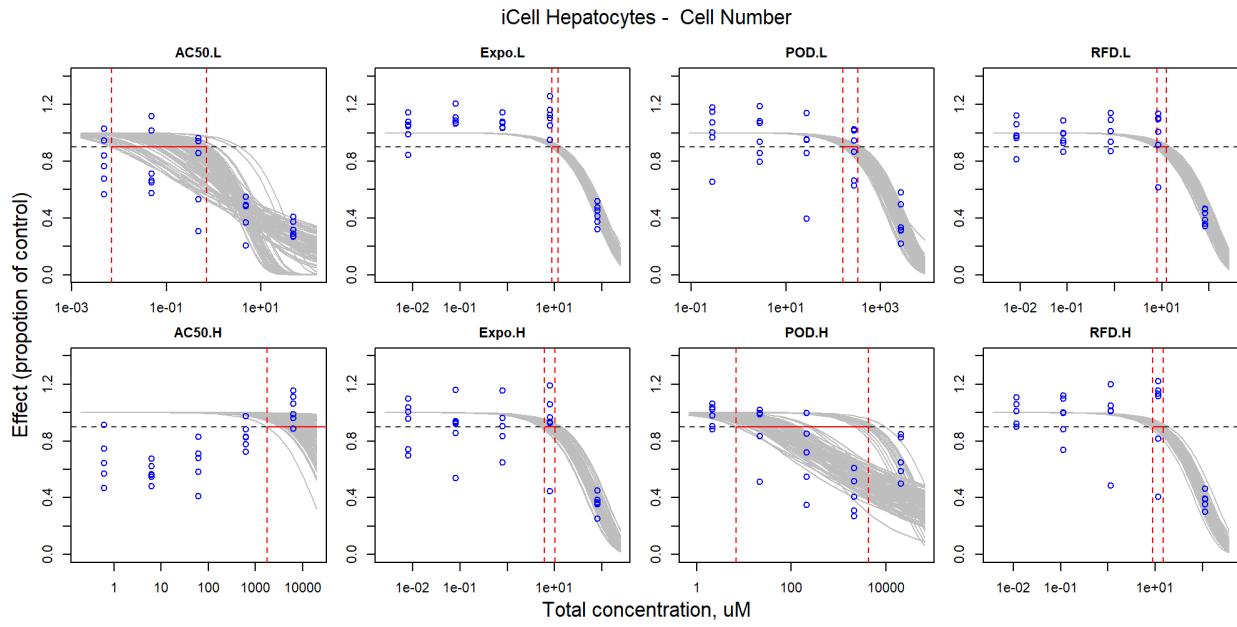


Figure S67. Curve-fitting of mixture concentration and observed response (Cell Number) in iCell Hepatocytes.

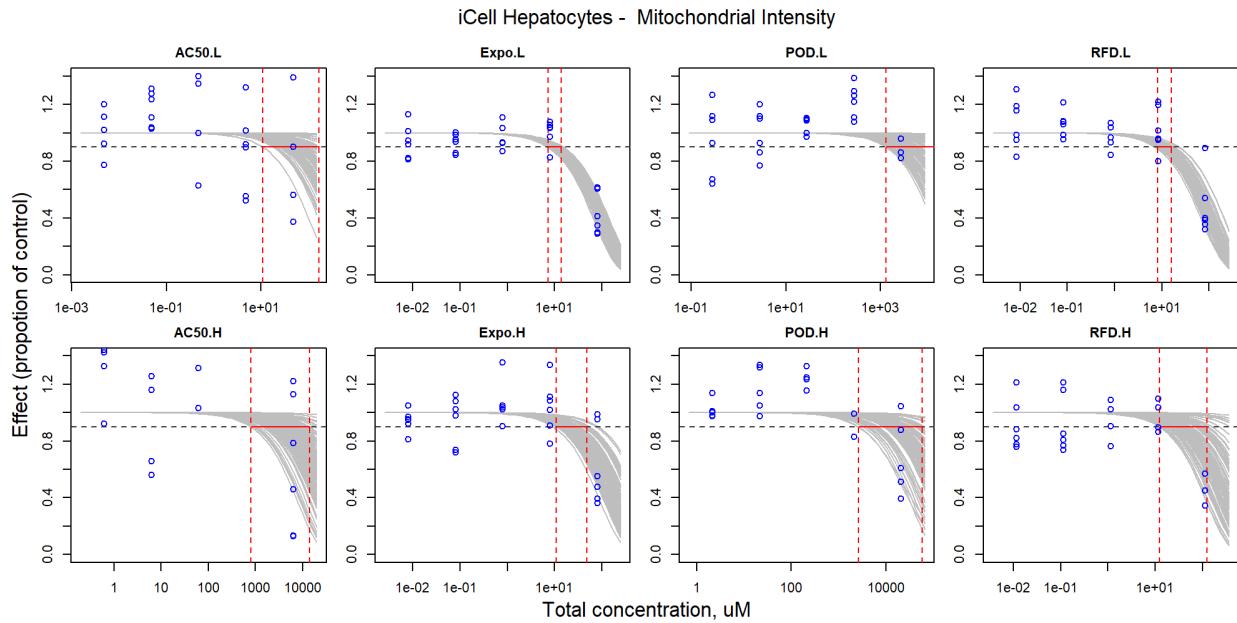


Figure S68. Curve-fitting of mixture concentration and observed response (Mitochondrial Intensity) in iCell Hepatocytes.

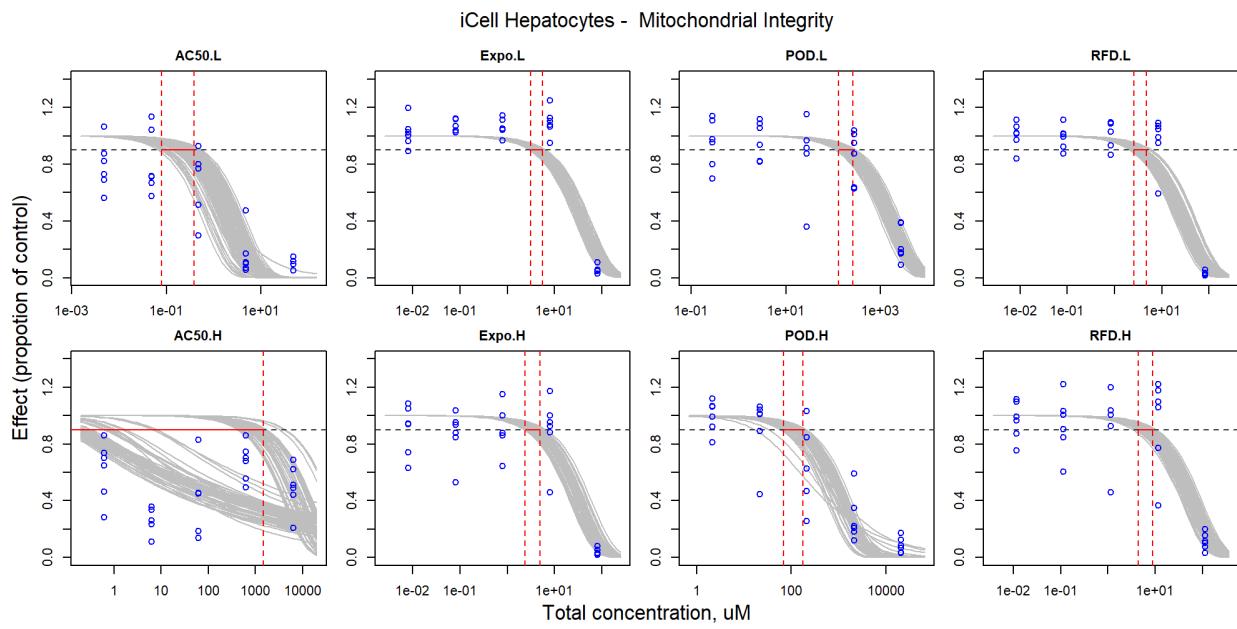


Figure S69. Curve-fitting of mixture concentration and observed response (Mitochondrial Integrity) in iCell Hepatocytes.

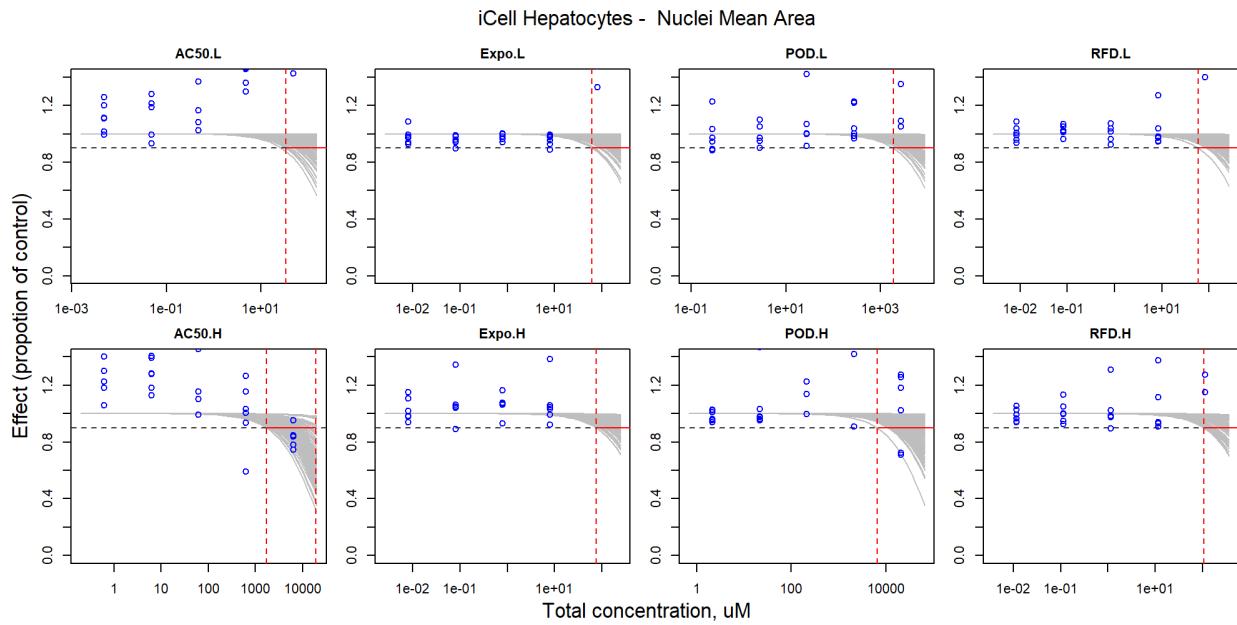


Figure S70. Curve-fitting of mixture concentration and observed response (Nuclei Mean Area) in iCell Hepatocytes.

3.2.4 iCell Endothelial cells

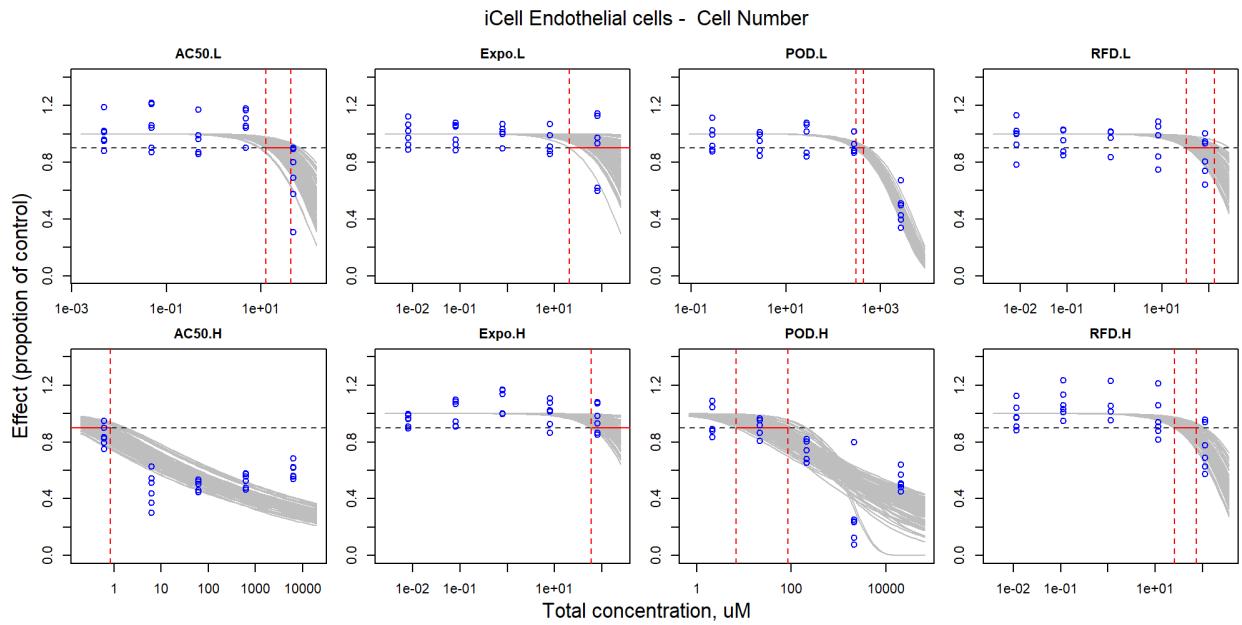


Figure S71. Curve-fitting of mixture concentration and observed response (Cell Number) in iCell Endothelial cells.

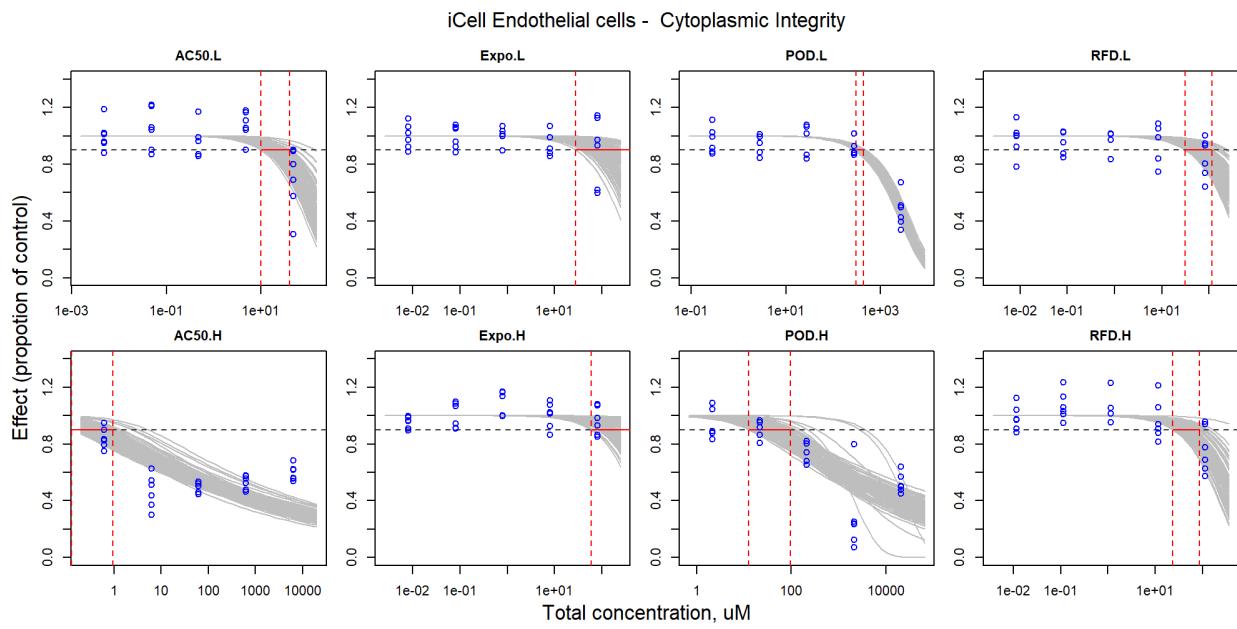


Figure S72. Curve-fitting of mixture concentration and observed response (Cytoplasmic Integrity) in iCell Endothelial cells.

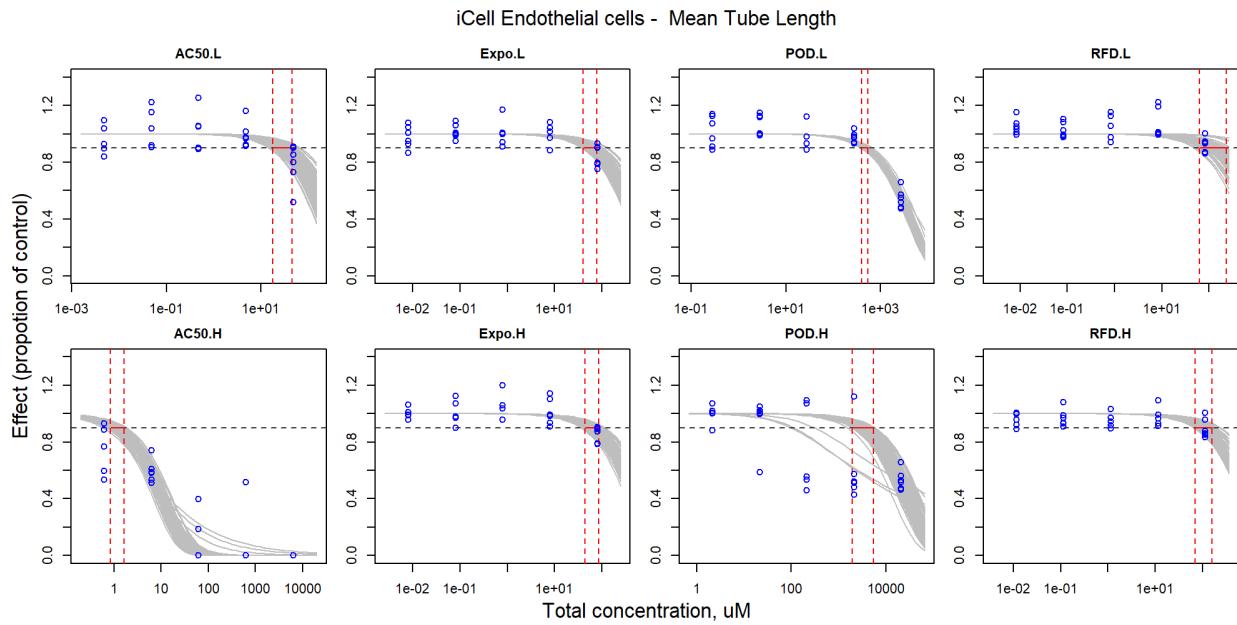


Figure S73. Curve-fitting of mixture concentration and observed response (Mean Tube Length) in iCell Endothelial cells.

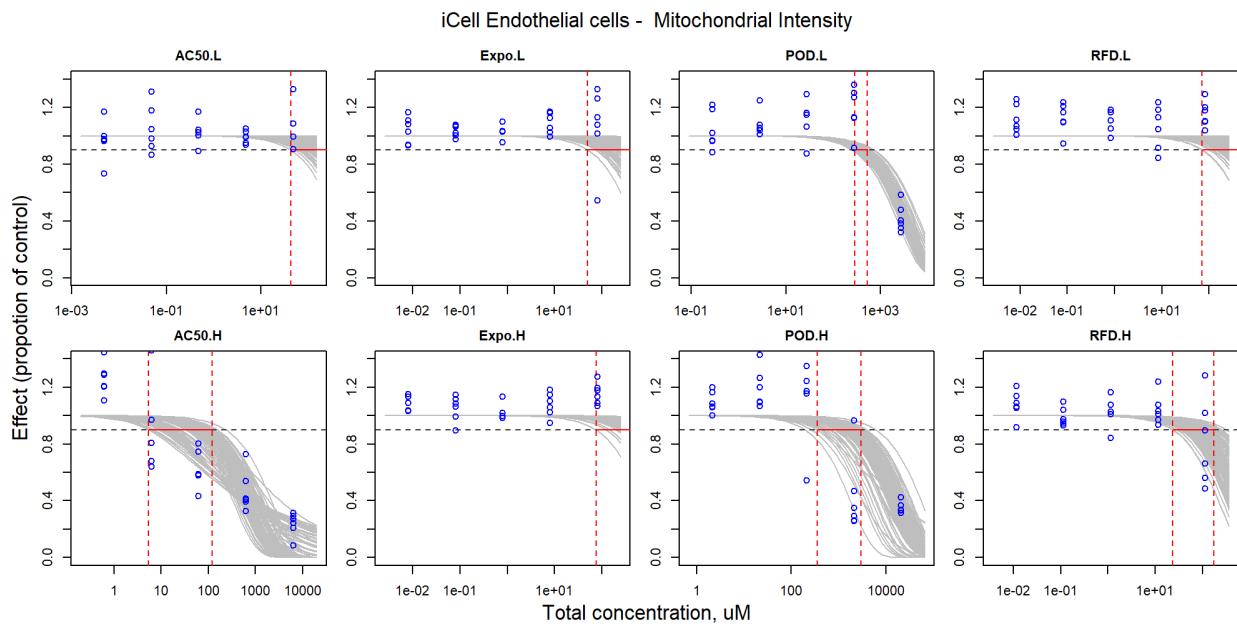


Figure S74. Curve-fitting of mixture concentration and observed response (Mitochondrial Intensity) in iCell Endothelial cells.

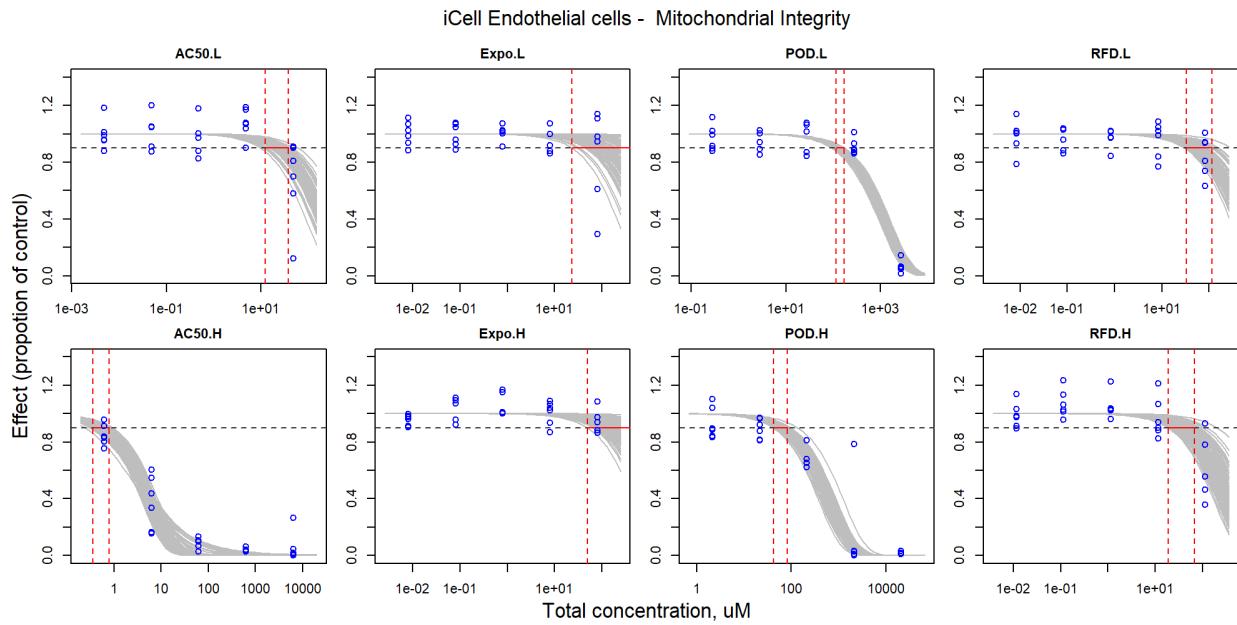


Figure S75. Curve-fitting of mixture concentration and observed response (Mitochondrial Integrity) in iCell Endothelial cells.

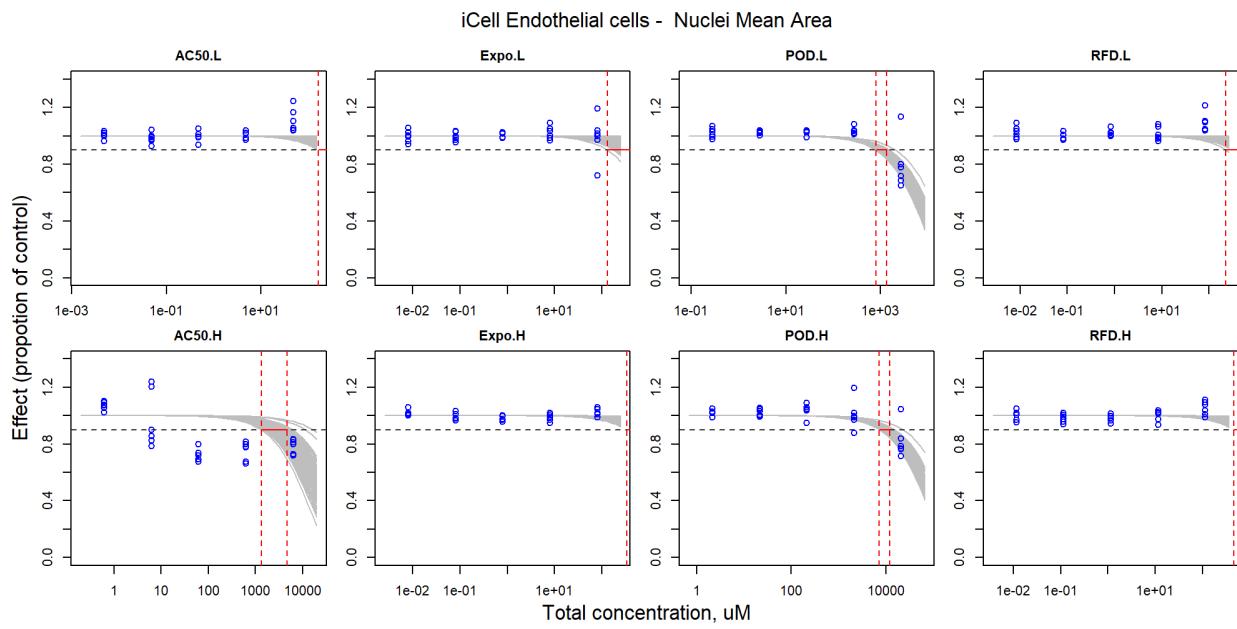


Figure S76. Curve-fitting of mixture concentration and observed response (Nuclei Mean Area) in iCell Endothelial cells.

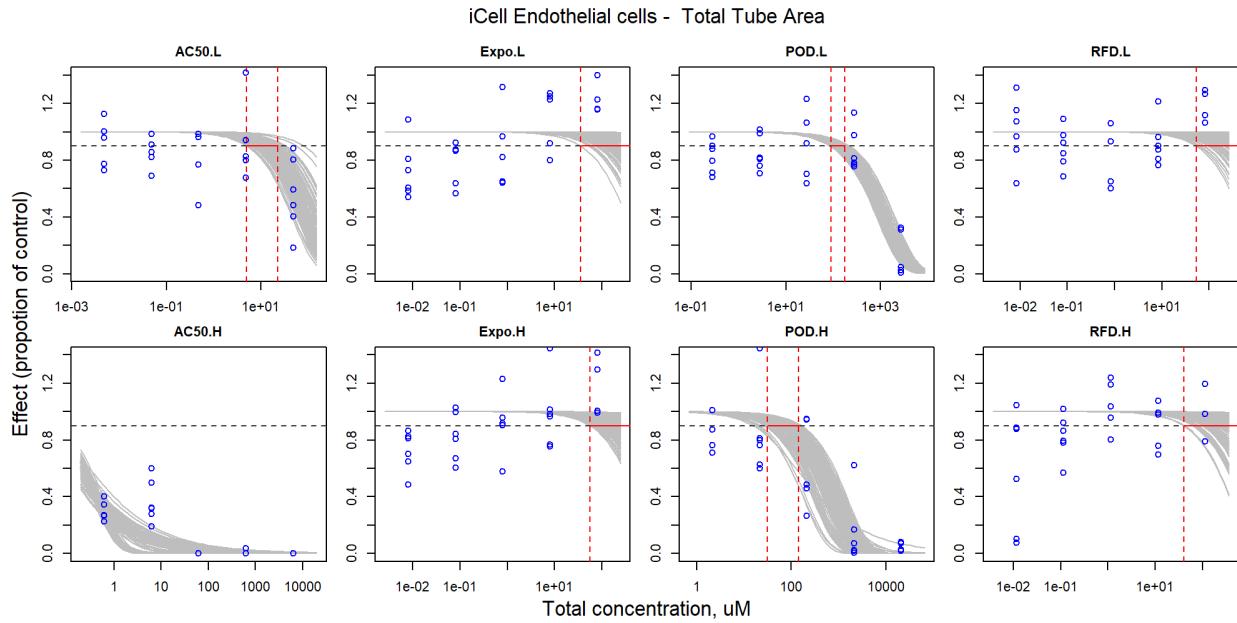


Figure S77. Curve-fitting of mixture concentration and observed response (Total Tube Area) in iCell Endothelial cells.

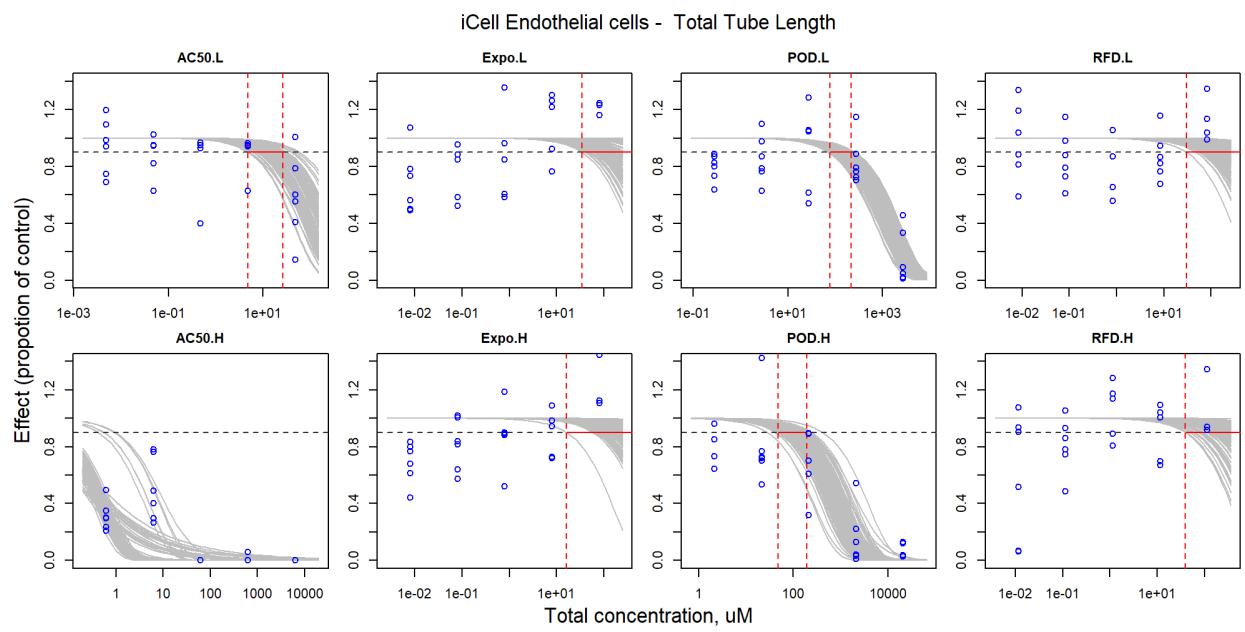


Figure S78. Curve-fitting of mixture concentration and observed response (Total Tube Length) in iCell Endothelial cells.

3.2.5 iCell Cardiomyocytes

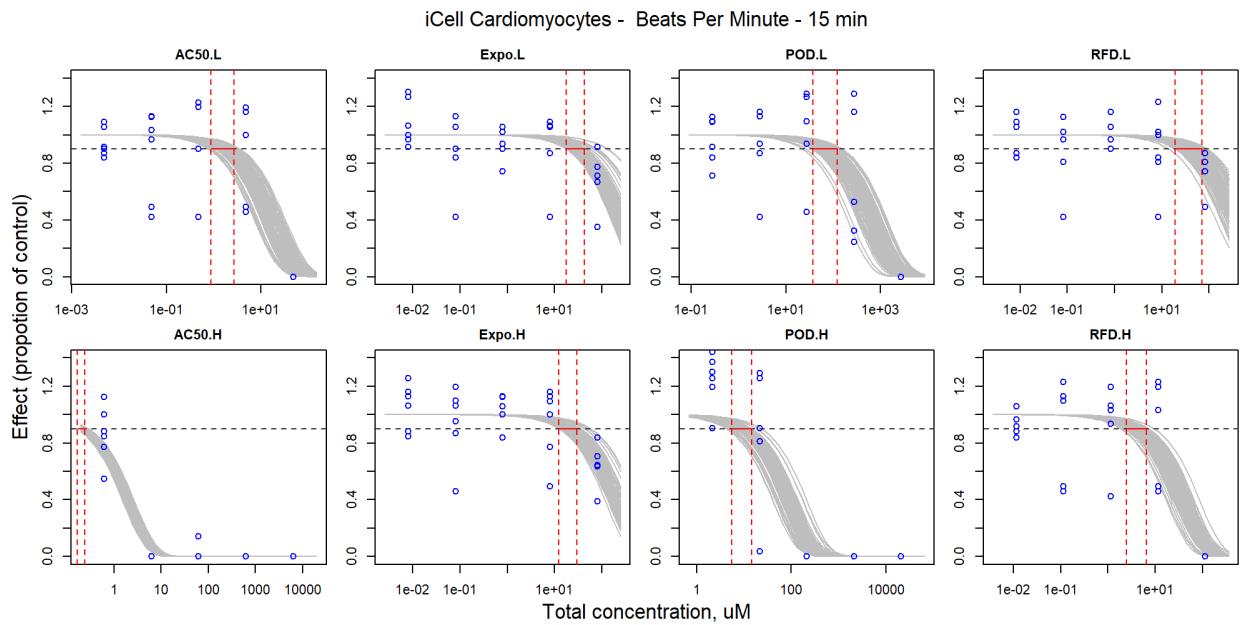


Figure S79. Curve-fitting of mixture concentration and observed response (Beats Per Minute - 15 min) in iCell Cardiomyocytes.

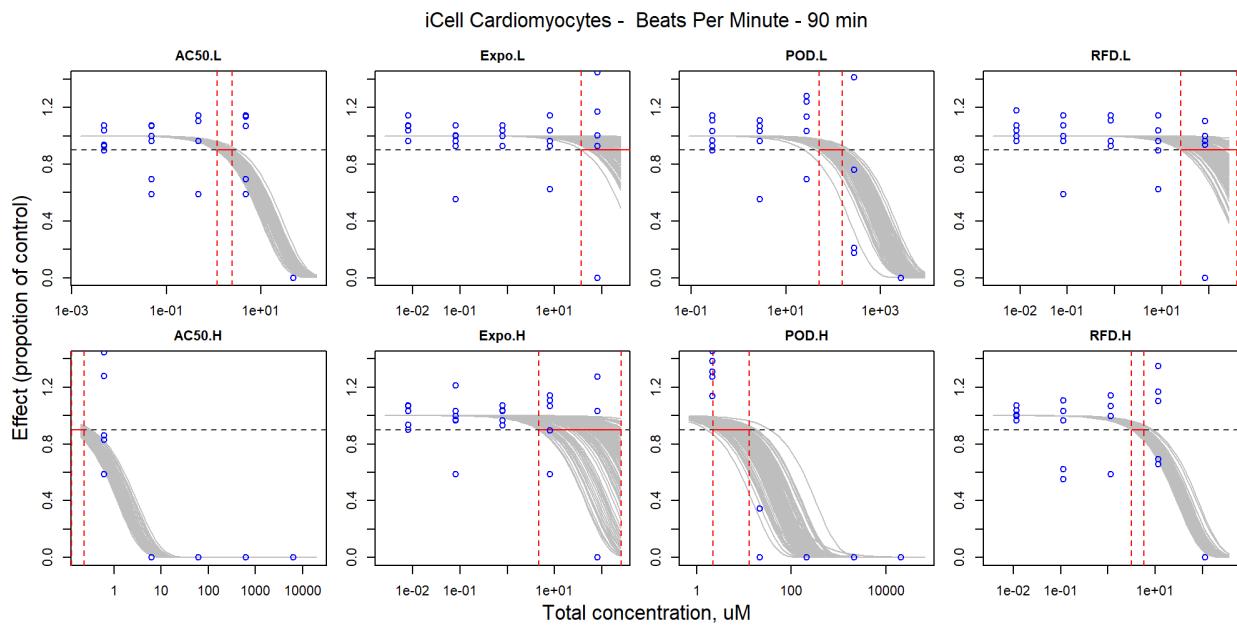


Figure S80. Curve-fitting of mixture concentration and observed response (Beats Per Minute - 90 min) in iCell Cardiomyocytes.

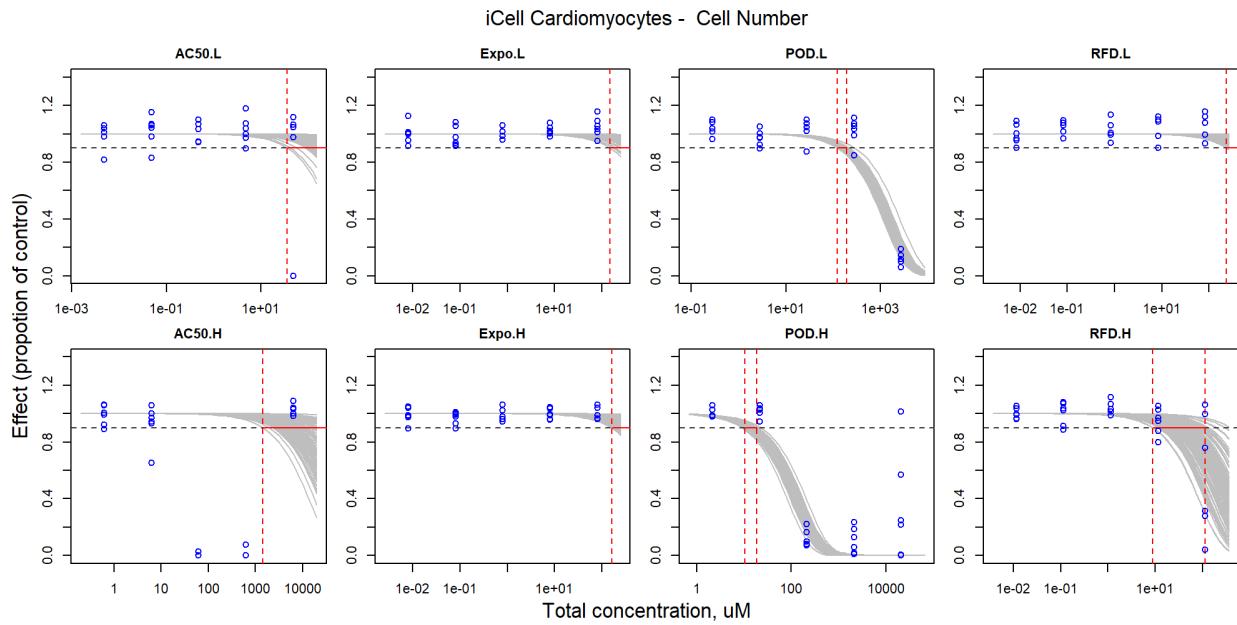


Figure S81. Curve-fitting of mixture concentration and observed response (Cell Number) in iCell Cardiomyocytes.

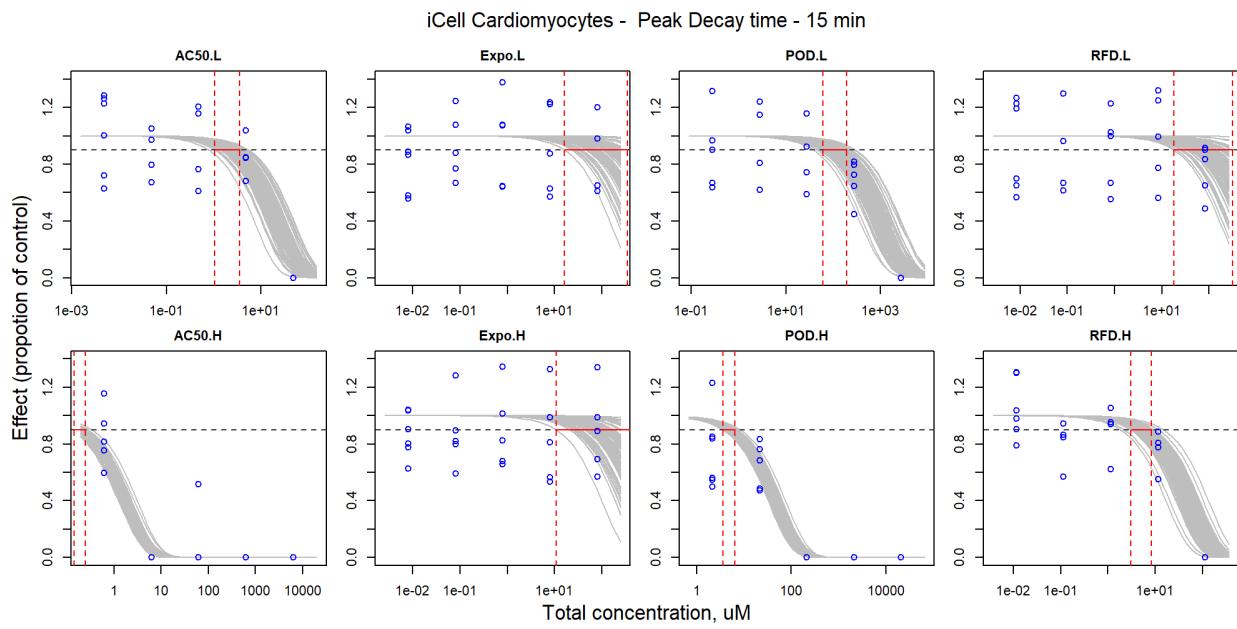


Figure S82. Curve-fitting of mixture concentration and observed response (Peak Decay time - 15 min) in iCell Cardiomyocytes.

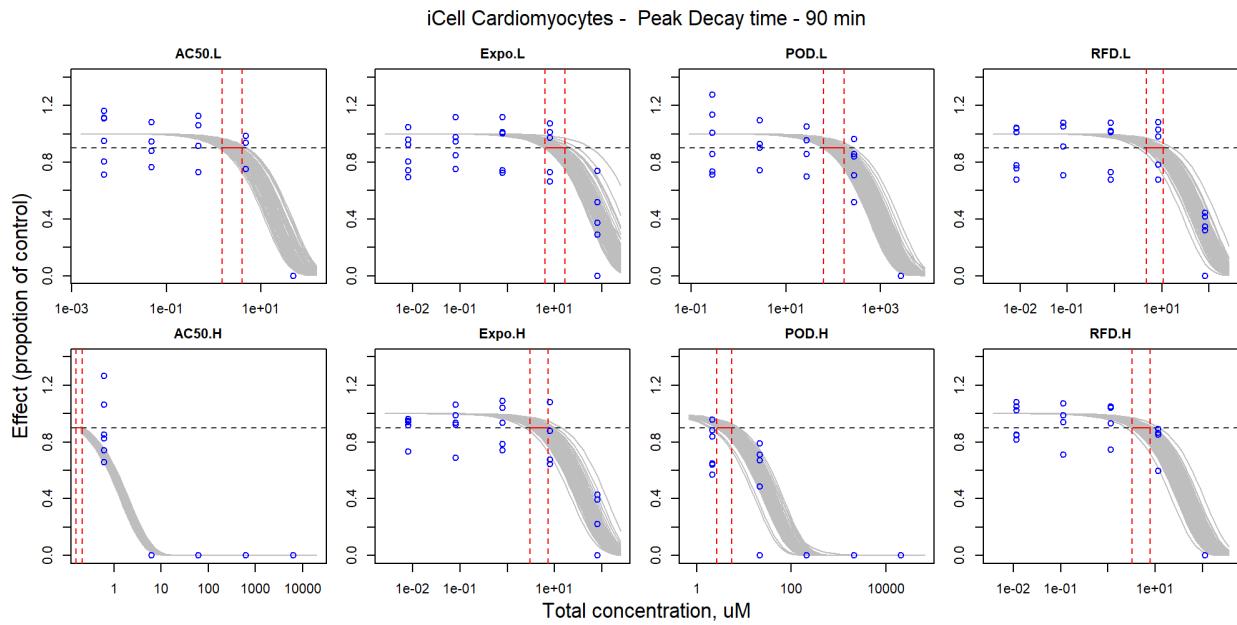


Figure S83. Curve-fitting of mixture concentration and observed response (Peak Decay time - 90 min) in iCell Cardiomyocytes.

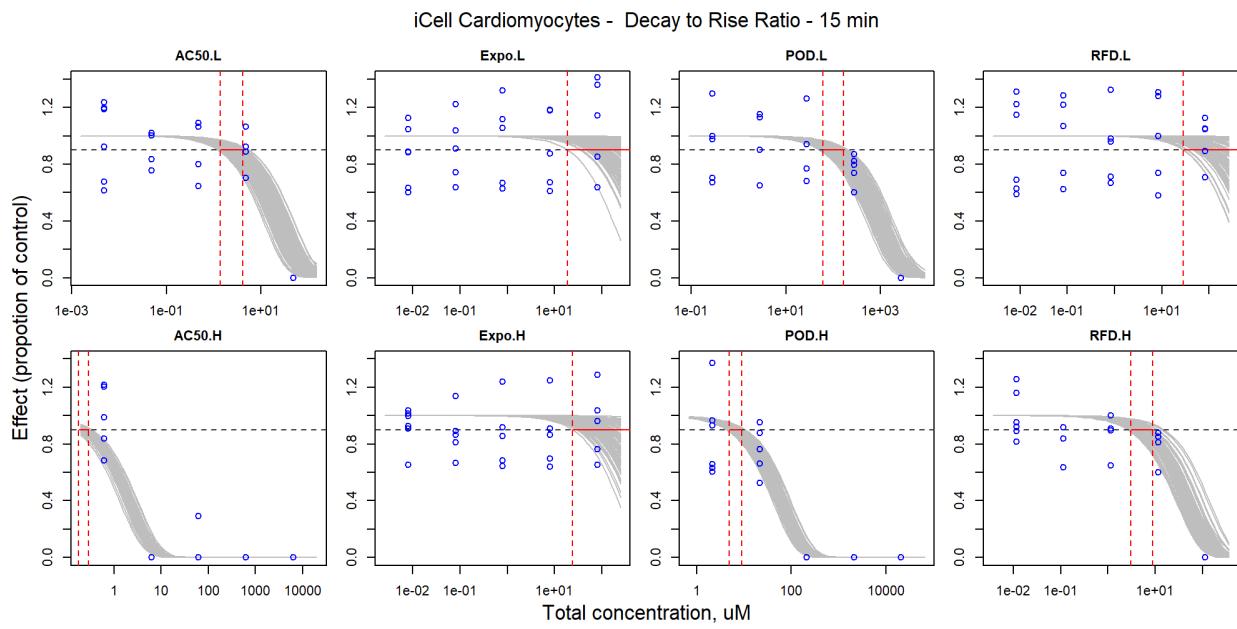


Figure S84. Curve-fitting of mixture concentration and observed response (Decay to Rise Ratio - 15 min) in iCell Cardiomyocytes.

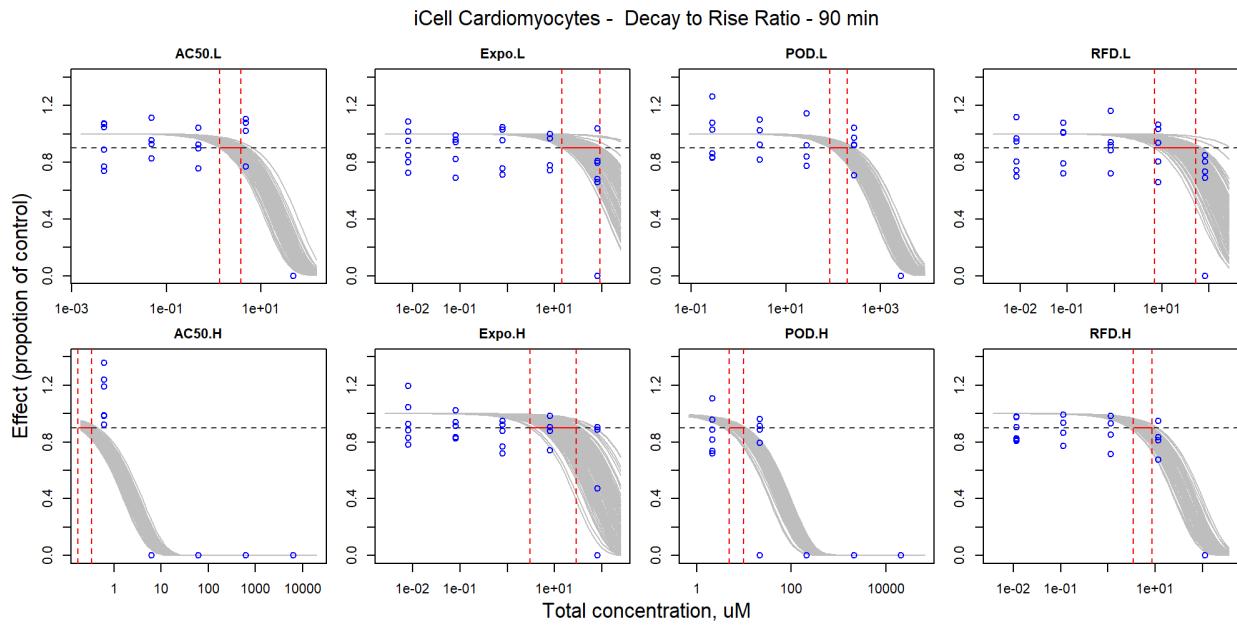


Figure S85. Curve-fitting of mixture concentration and observed response (Decay to Rise Ratio - 90 min) in iCell Cardiomyocytes.

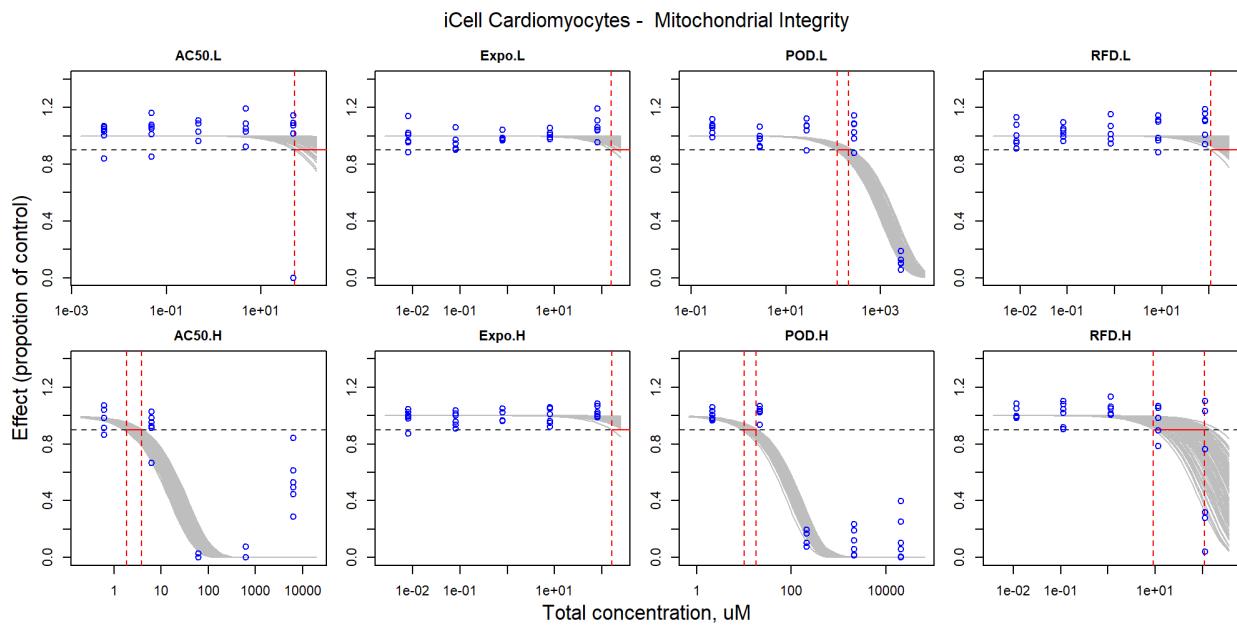


Figure S86. Curve-fitting of mixture concentration and observed response (Mitochondrial Integrity) in iCell Cardiomyocytes.

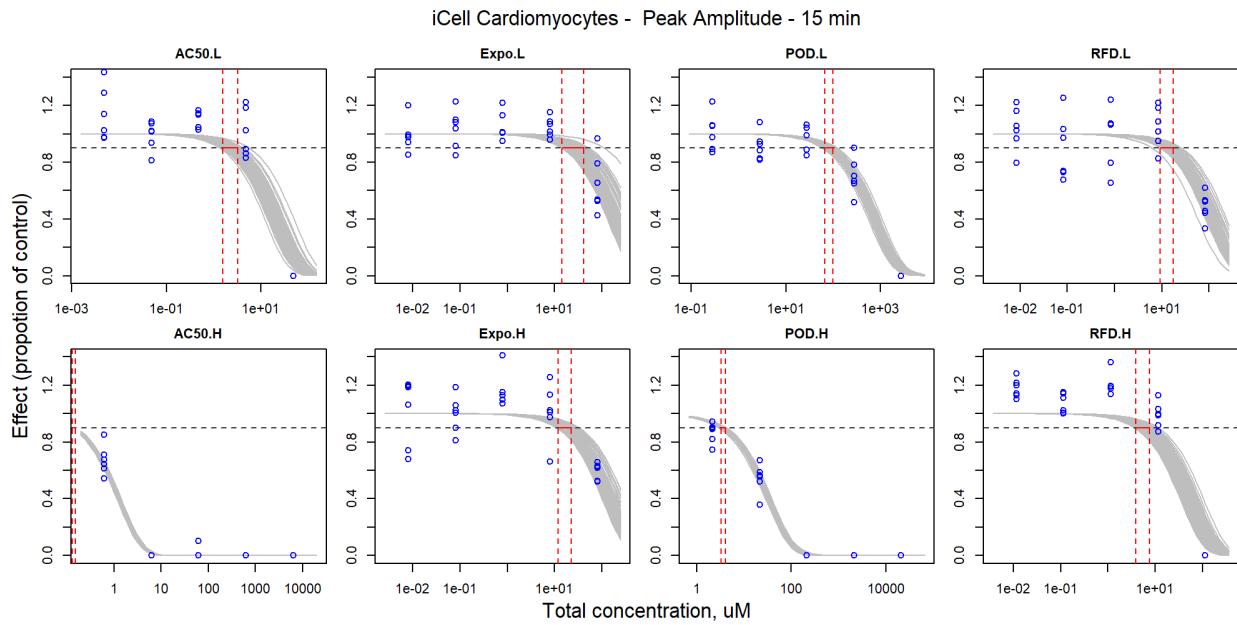


Figure S87. Curve-fitting of mixture concentration and observed response (Peak Amplitude - 15 min) in iCell Cardiomyocytes.

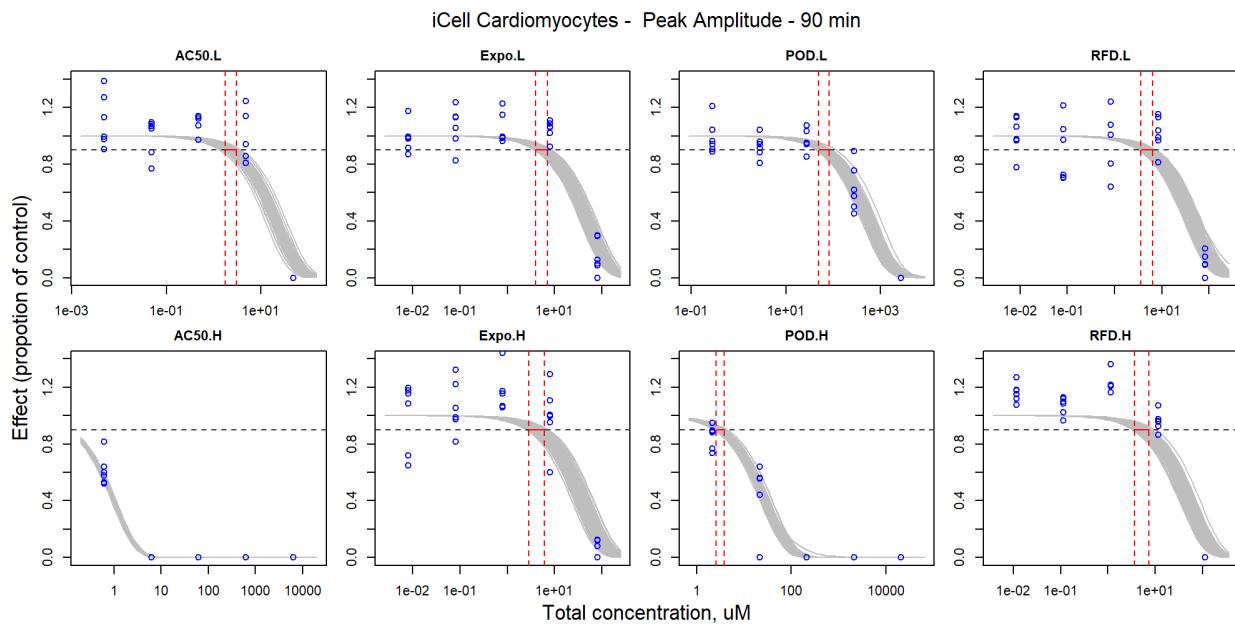


Figure S88. Curve-fitting of mixture concentration and observed response (Peak Amplitude - 90 min) in iCell Cardiomyocytes.

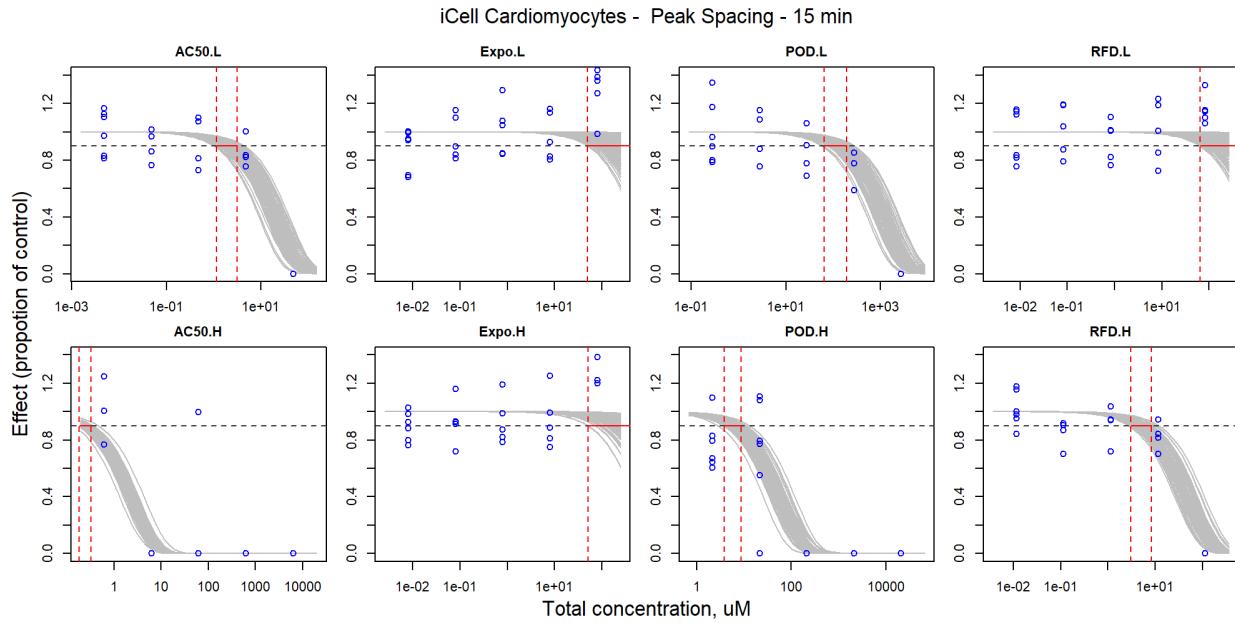


Figure S89. Curve-fitting of mixture concentration and observed response (Peak Spacing - 15 min) in iCell Cardiomyocytes.

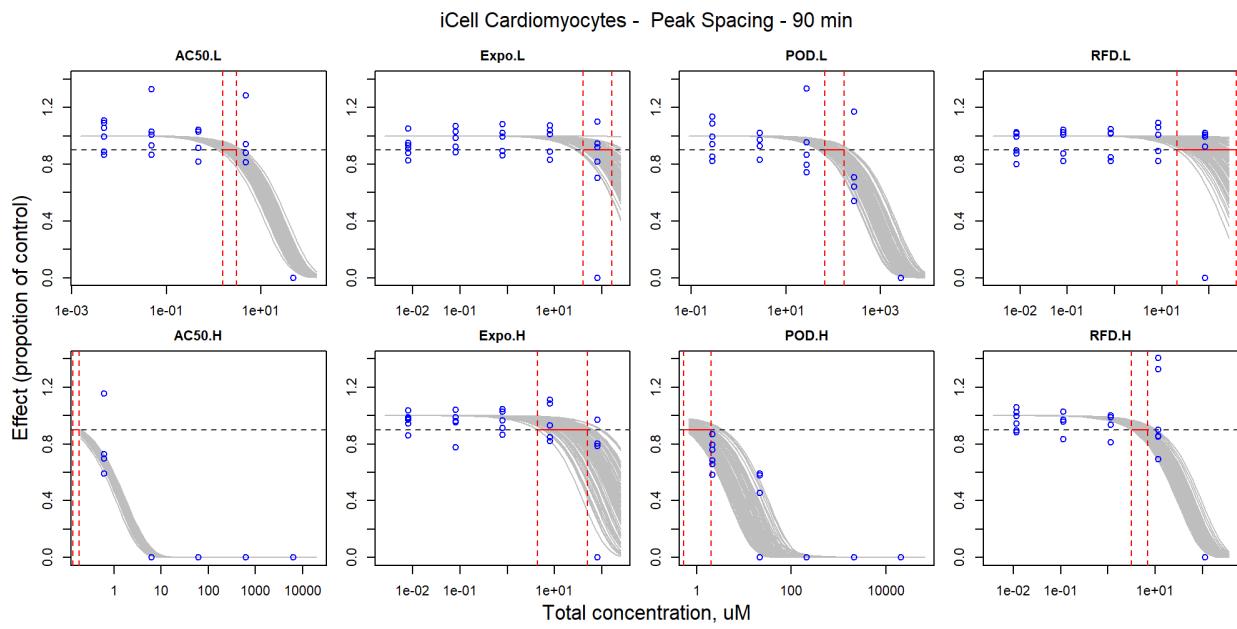


Figure S90. Curve-fitting of mixture concentration and observed response (Peak Spacing - 90 min) in iCell Cardiomyocytes.

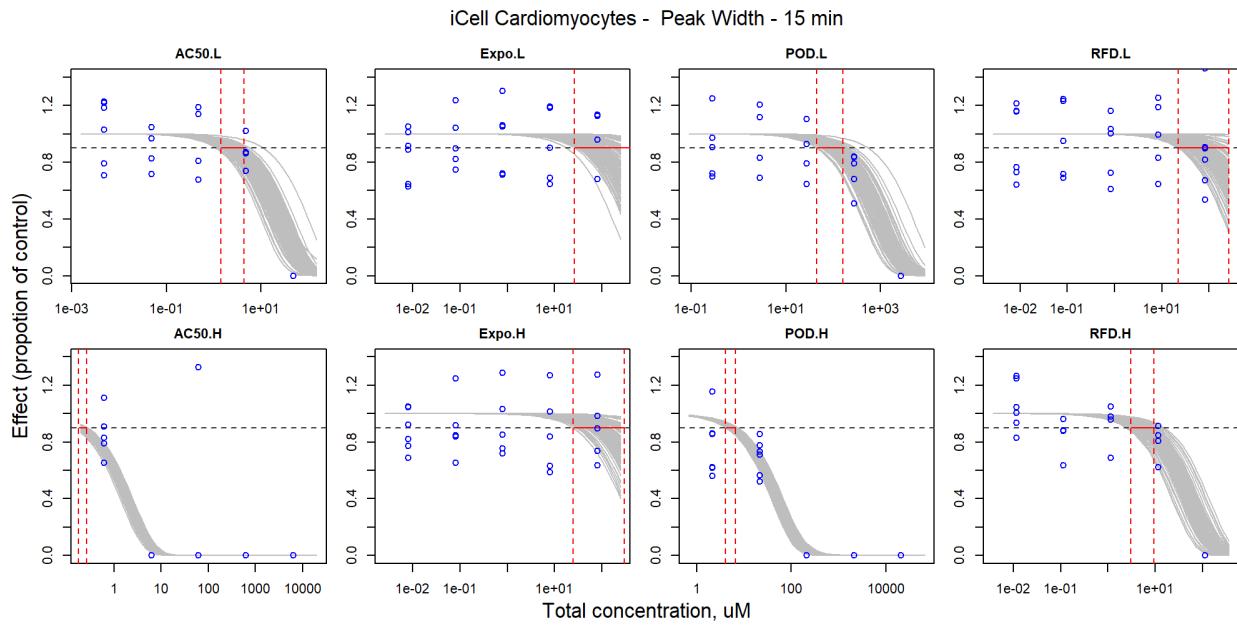


Figure S91. Curve-fitting of mixture concentration and observed response (Peak Width - 15 min) in iCell Cardiomyocytes.

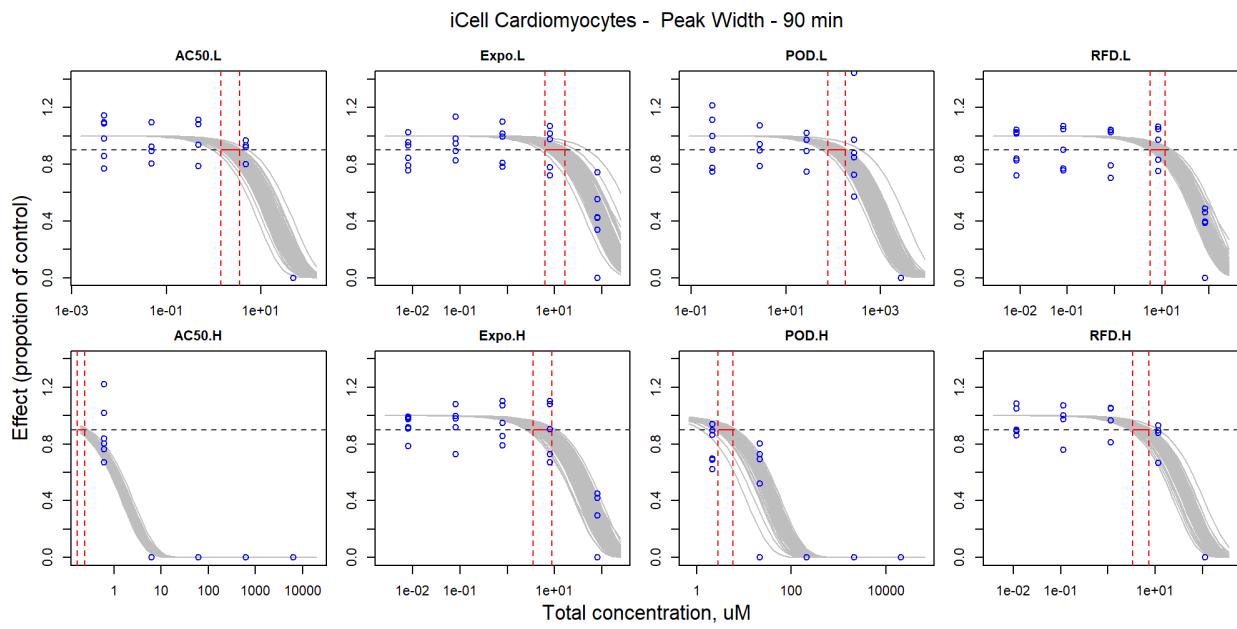


Figure S92. Curve-fitting of mixture concentration and observed response (Peak Width - 90 min) in iCell Cardiomyocytes.

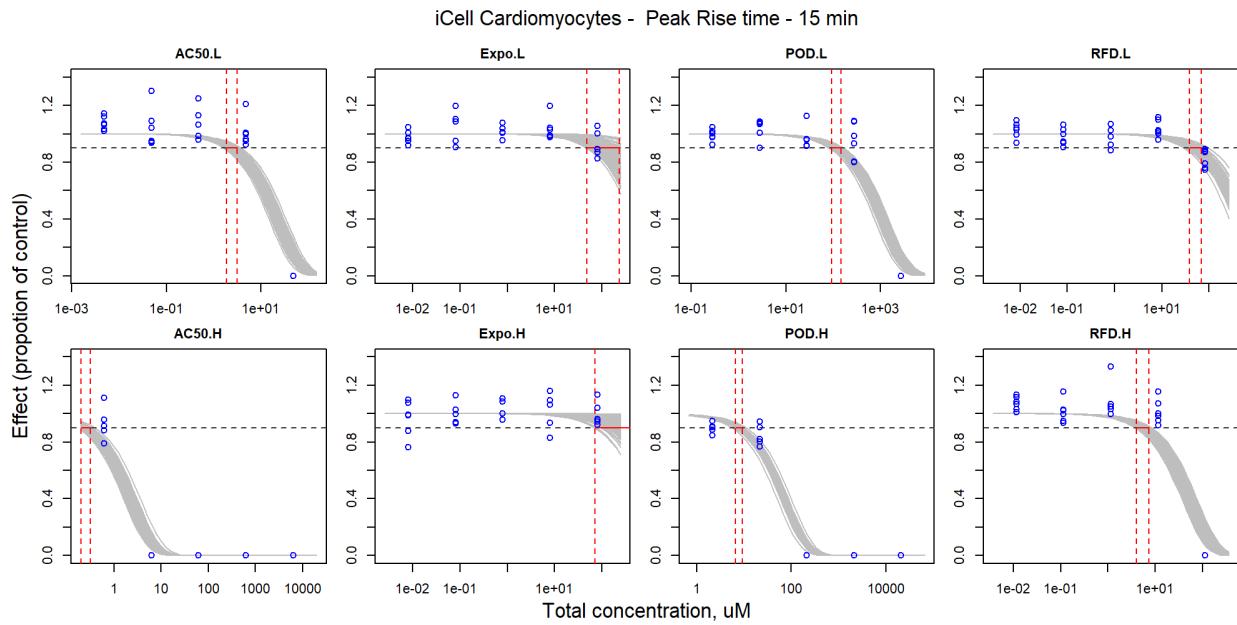


Figure S93. Curve-fitting of mixture concentration and observed response (Peak Rise time - 15 min) in iCell Cardiomyocytes.

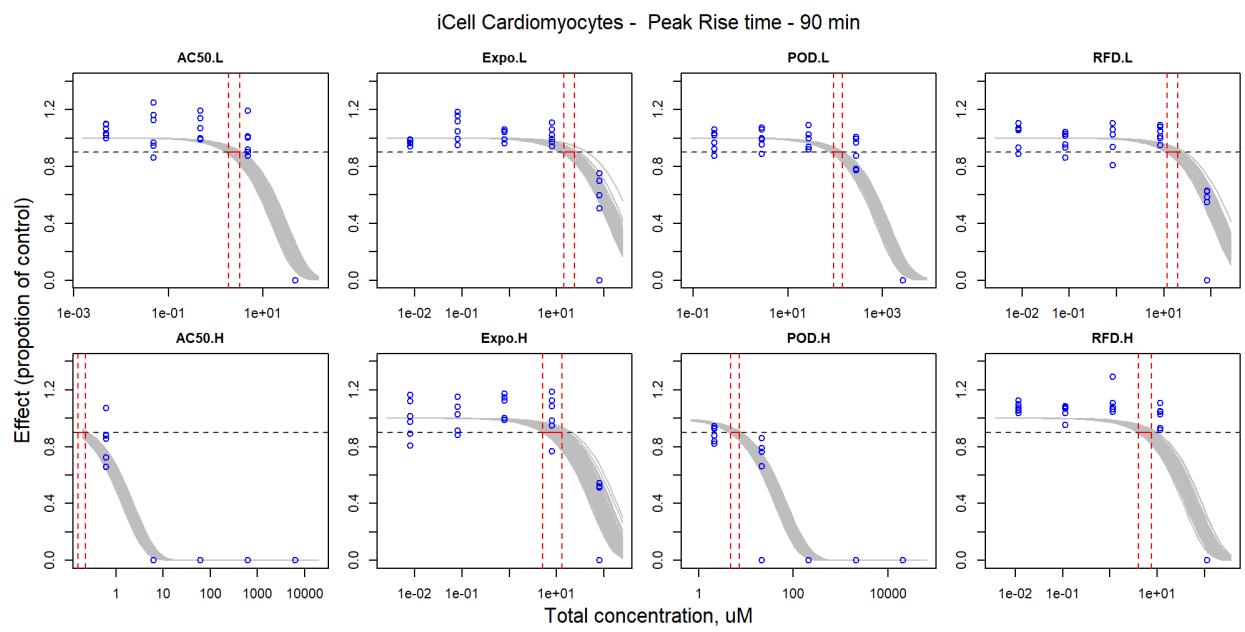


Figure S94. Curve-fitting of mixture concentration and observed response (Peak Rise time - 90 min) in iCell Cardiomyocytes.

3.3 Curve-fitting and prediction of AC50-H concentration-response

3.3.1 iCell Neurons

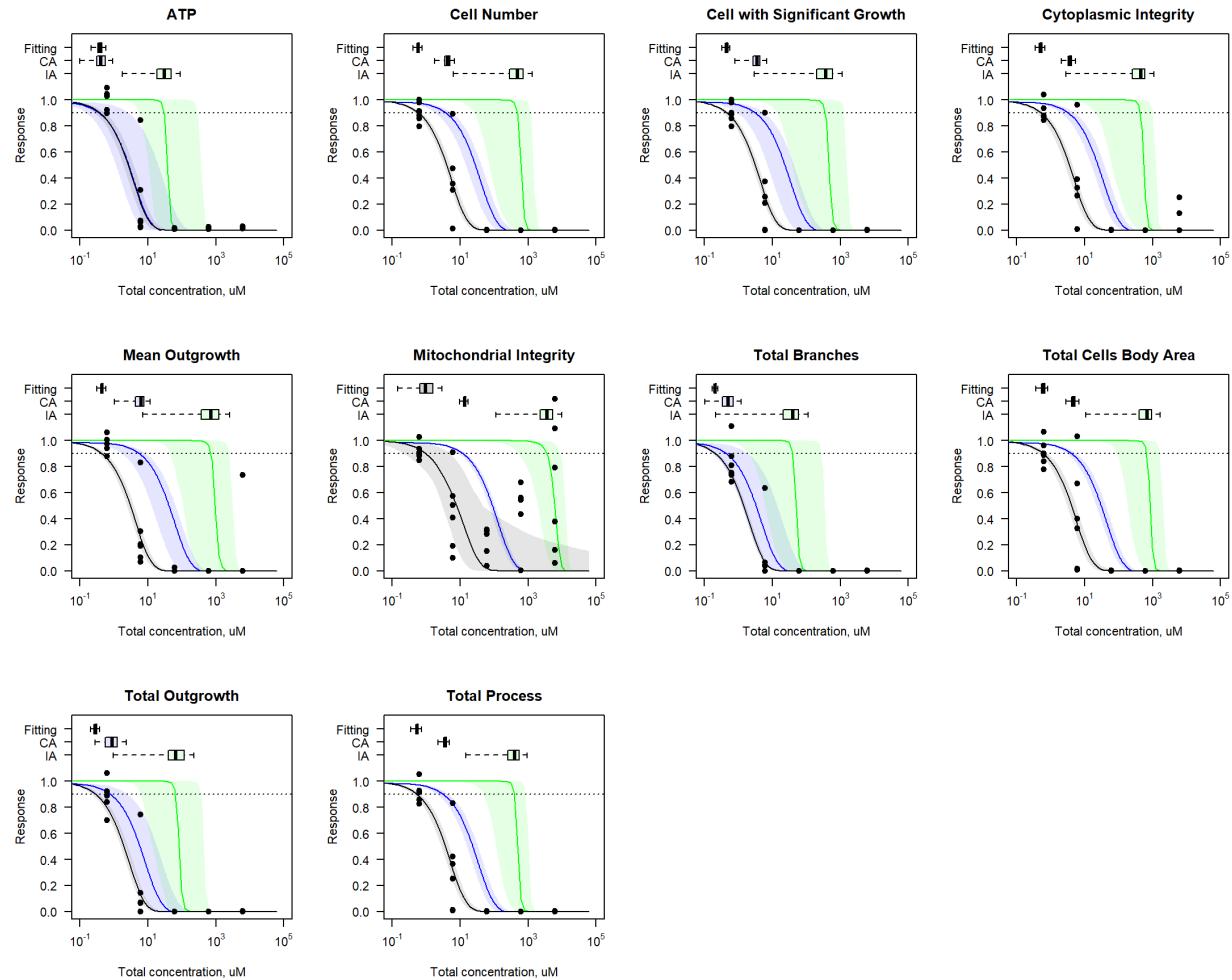


Figure S95. Comparison of curve-fitting and predicted concentration-response profile for iCell Neurons.

3.3.2 HUVECs

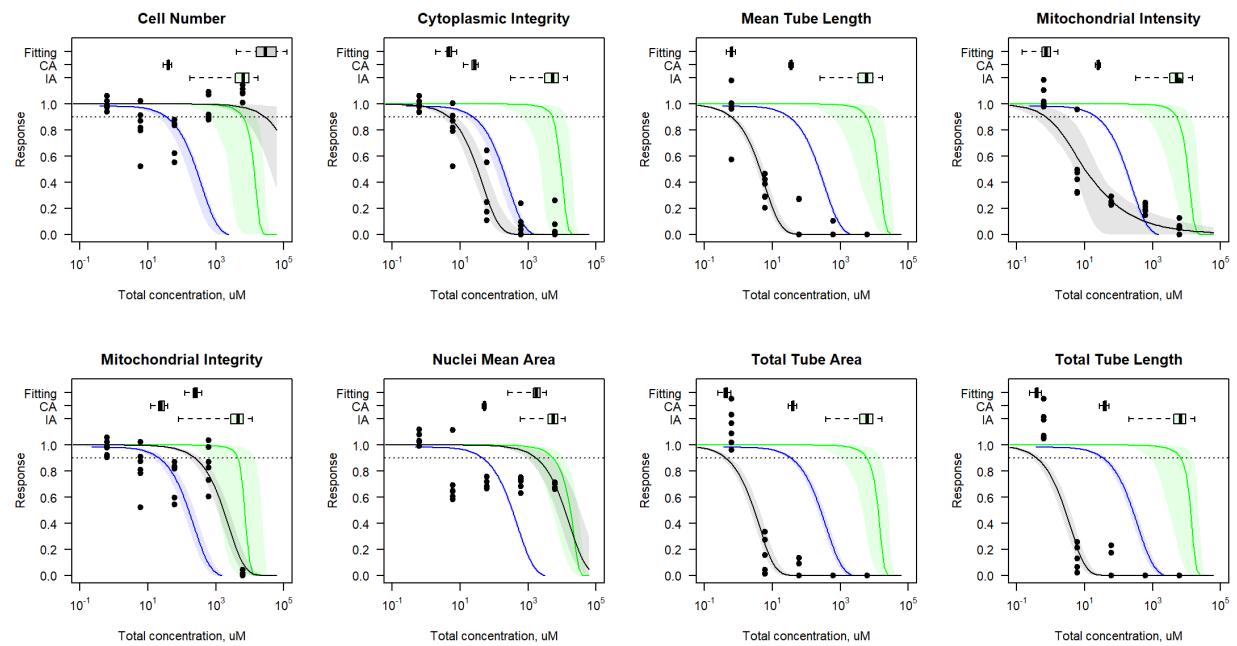


Figure S96. Comparison of curve-fitting and predicted concentration-response profile for HUVECs.

3.3.3 iCell Hepatocytes

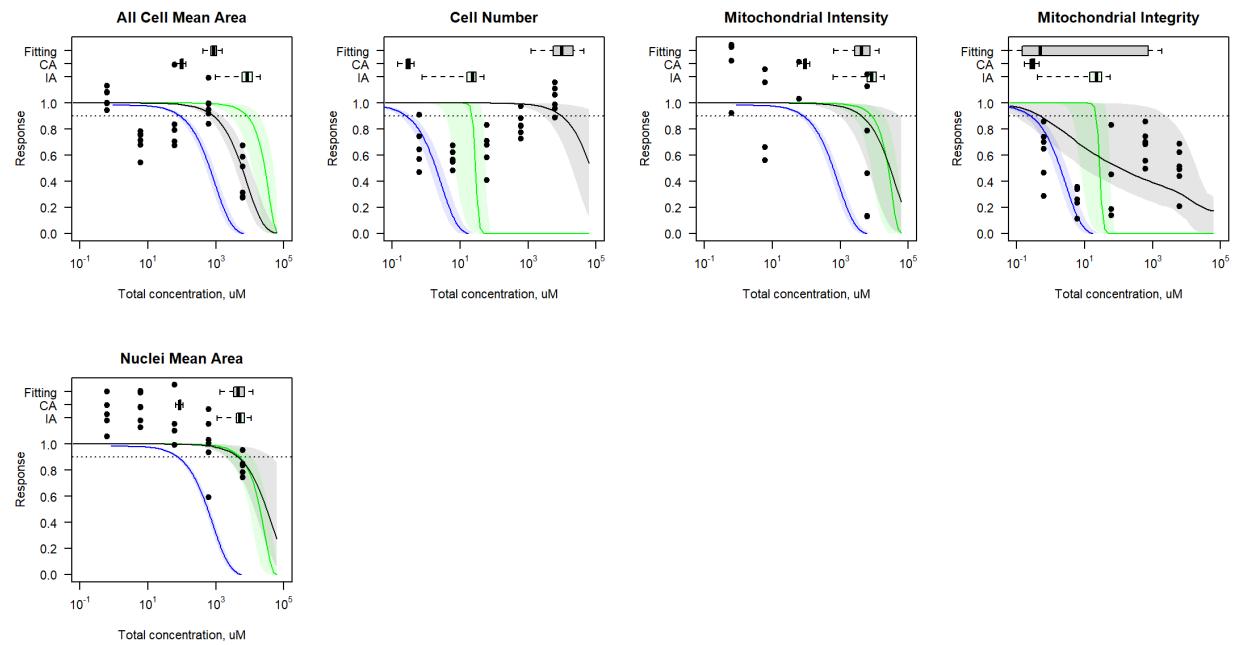


Figure S97. Comparison of curve-fitting and predicted concentration-response profile for iCell Hepatocytes.

3.3.4 iCell Endothelial cells

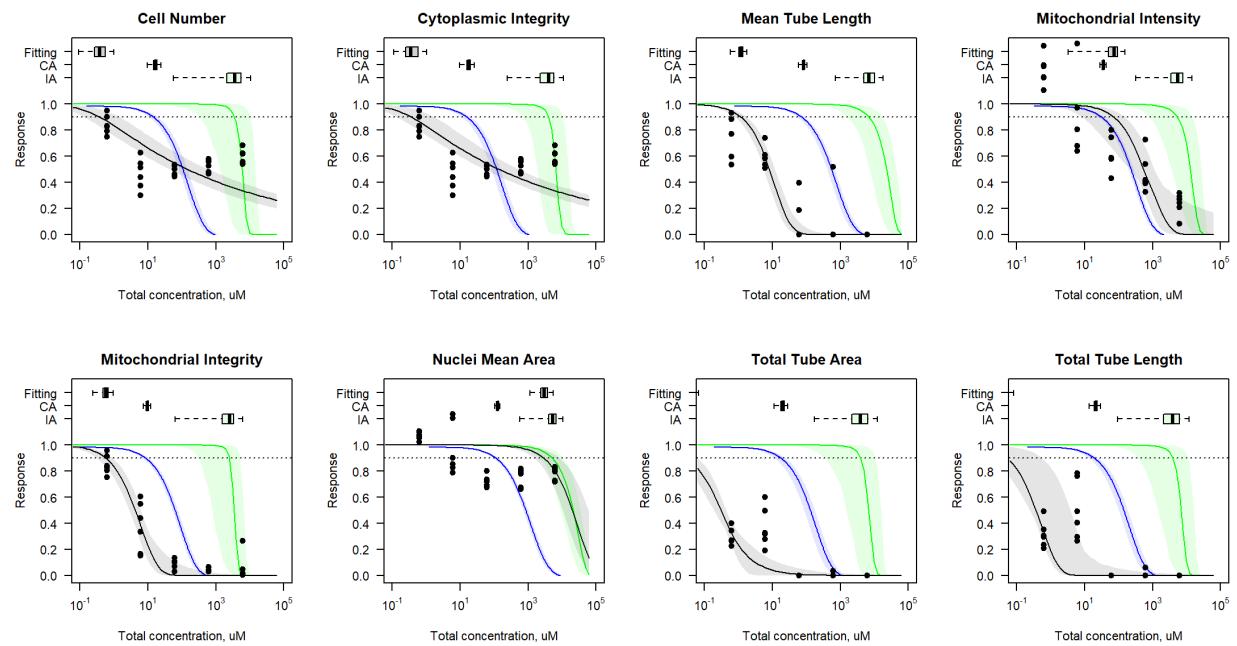


Figure S98. Comparison of curve-fitting and predicted concentration-response profile for iCell Endothelial cells.

3.3.5 iCell Cardiomyocytes

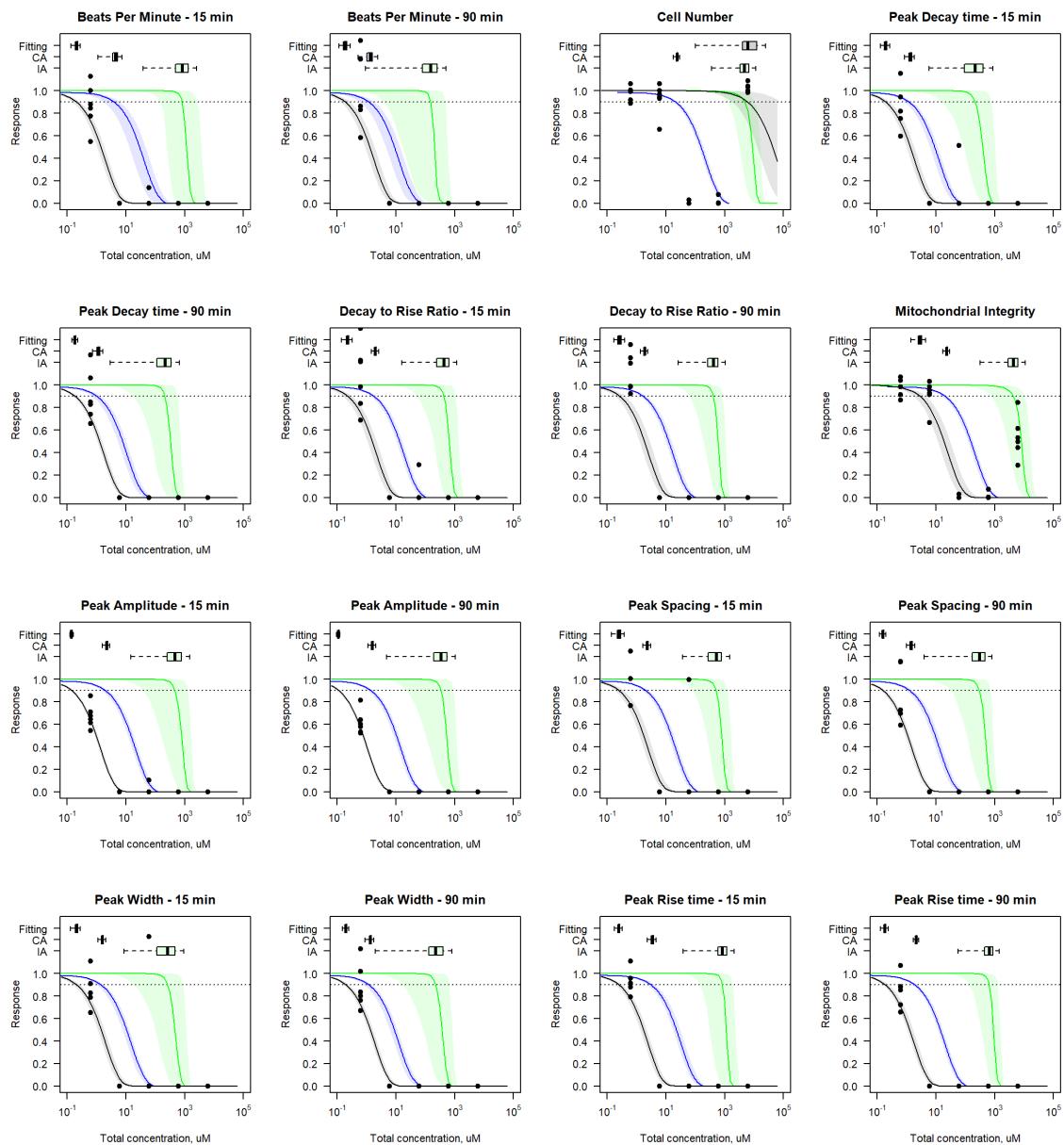


Figure S99. Comparison of curve-fitting and predicted concentration-response profile for iCell Cardiomyocytes.

3.4 Estimation of the margin of exposure under AC50-H exposure

3.4.1 iCell Neurons

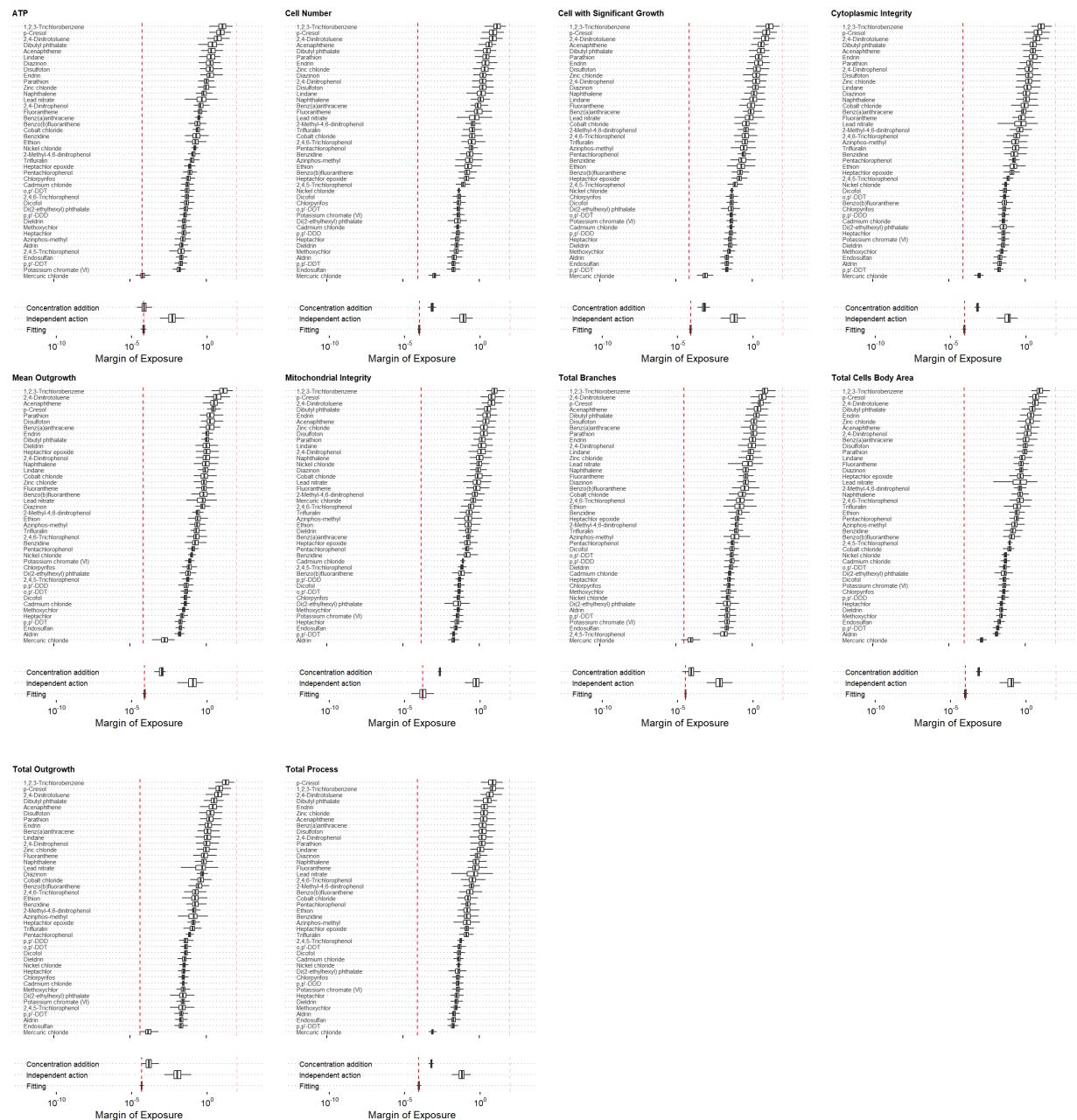


Figure S100. The estimation of the margin of exposure for cytotoxicity phenotypes in the iCell Neurons.

3.4.2 HUVECs

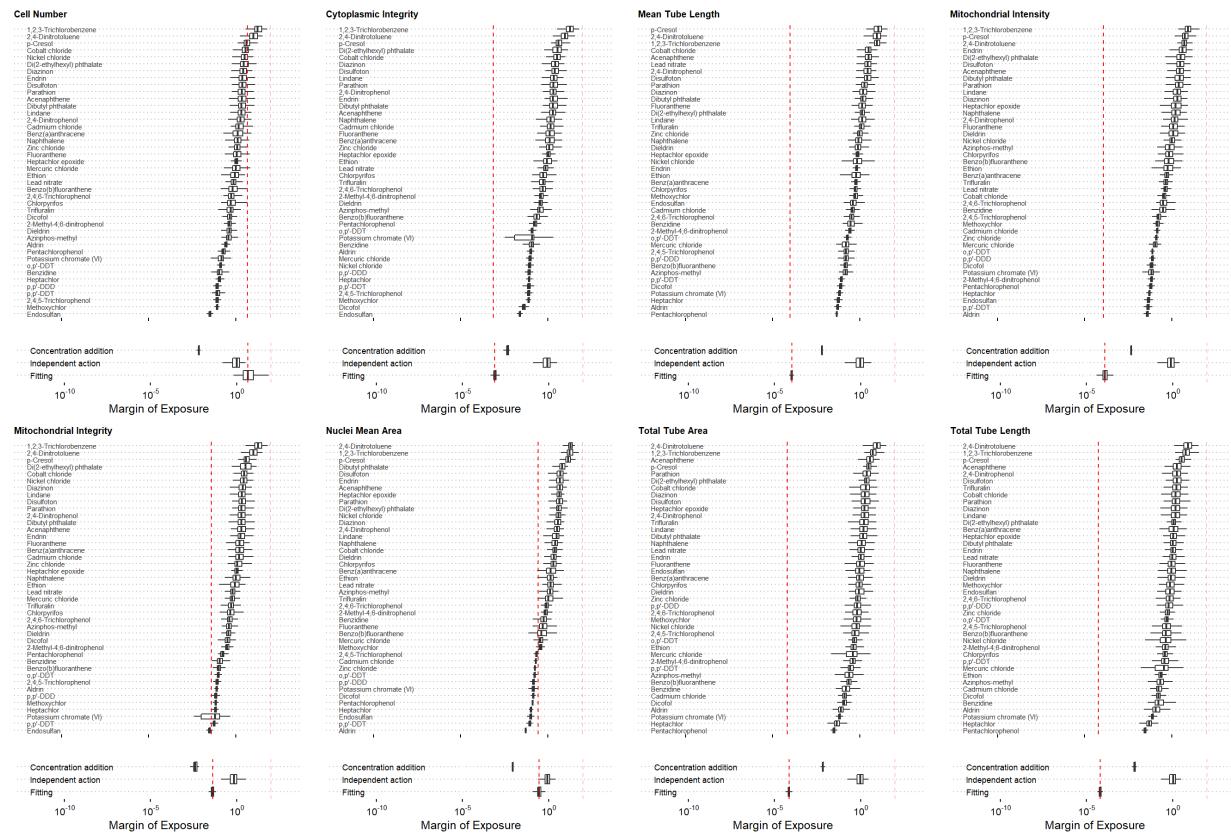


Figure S101. The estimation of the margin of exposure for cytotoxicity phenotypes in the HUVECs.

3.4.3 iCell Hepatocytes

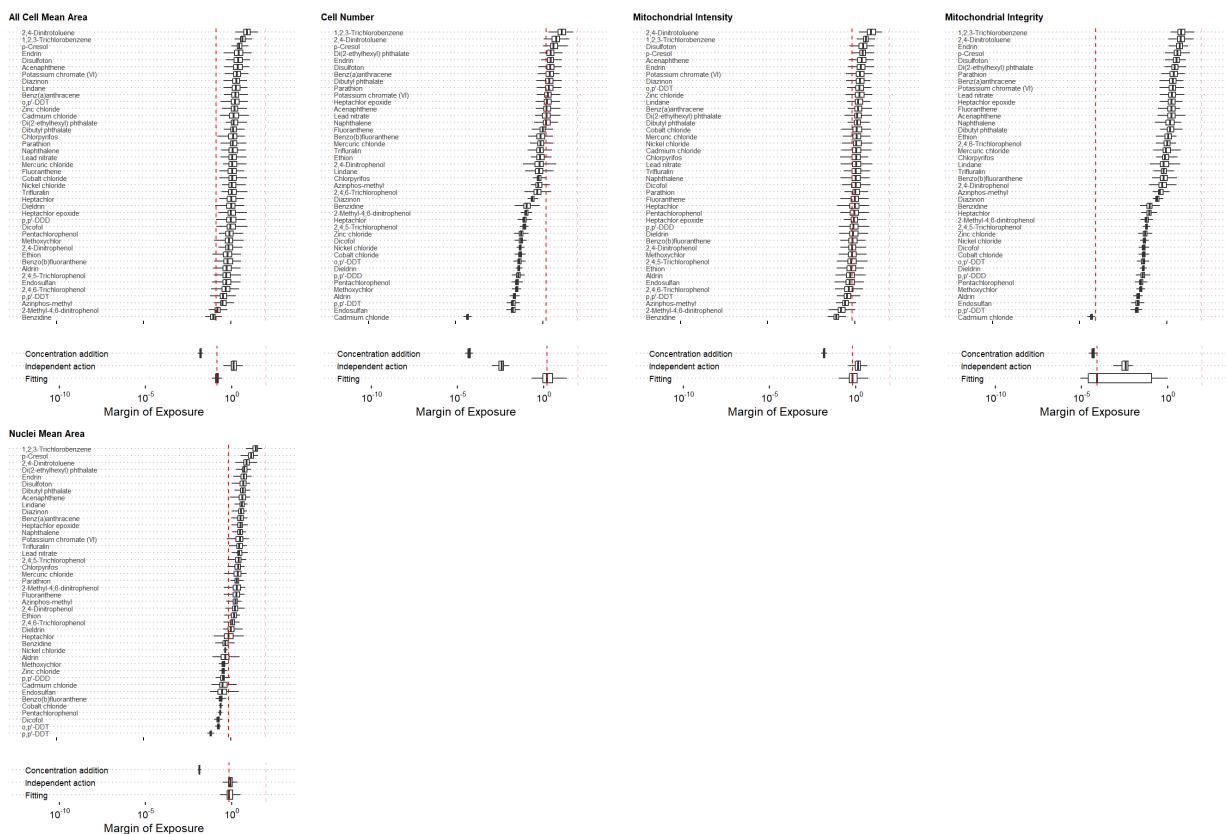


Figure S102. The estimation of the margin of exposure for cytotoxicity phenotypes in the iCell Hepatocytes.

3.4.4 iCell Endothelial cells

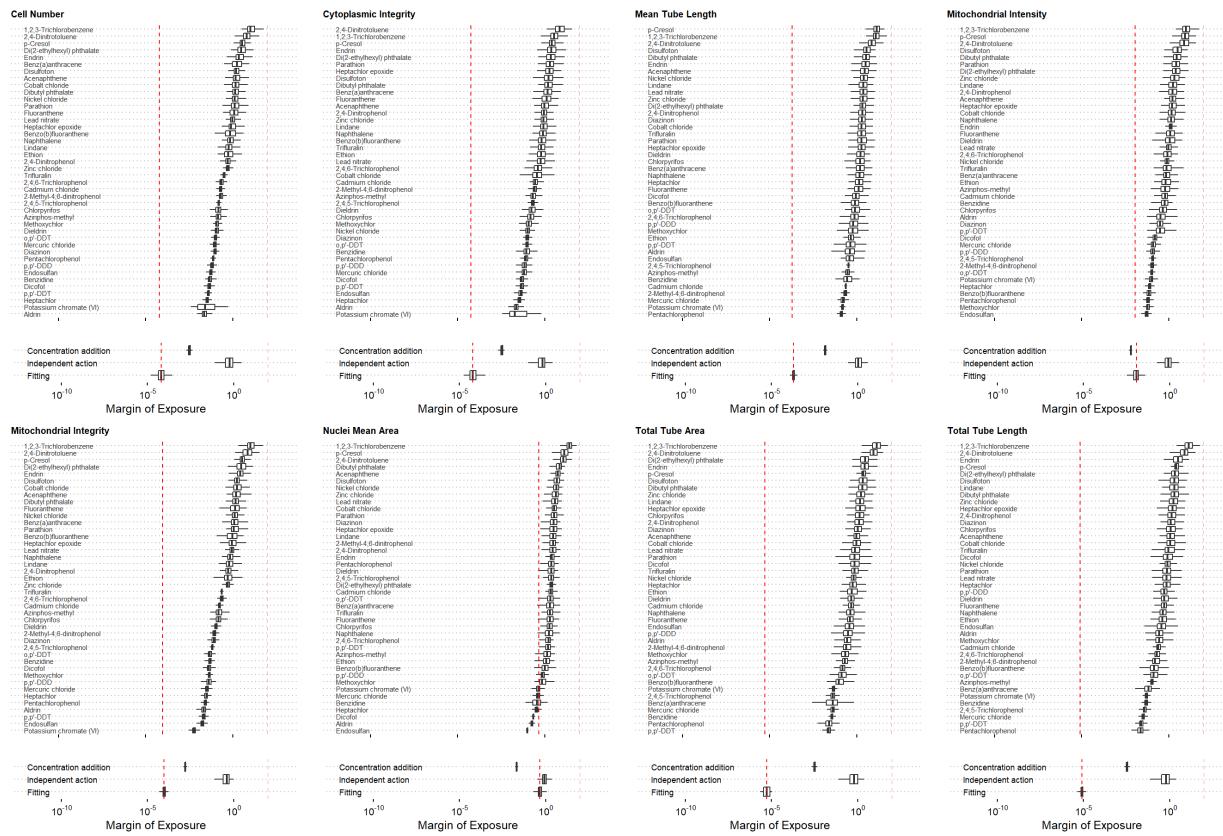


Figure S103. The estimation of the margin of exposure for cytotoxicity phenotypes in the iCell Endothelial cells.

3.4.5 iCell Cardiomyocytes

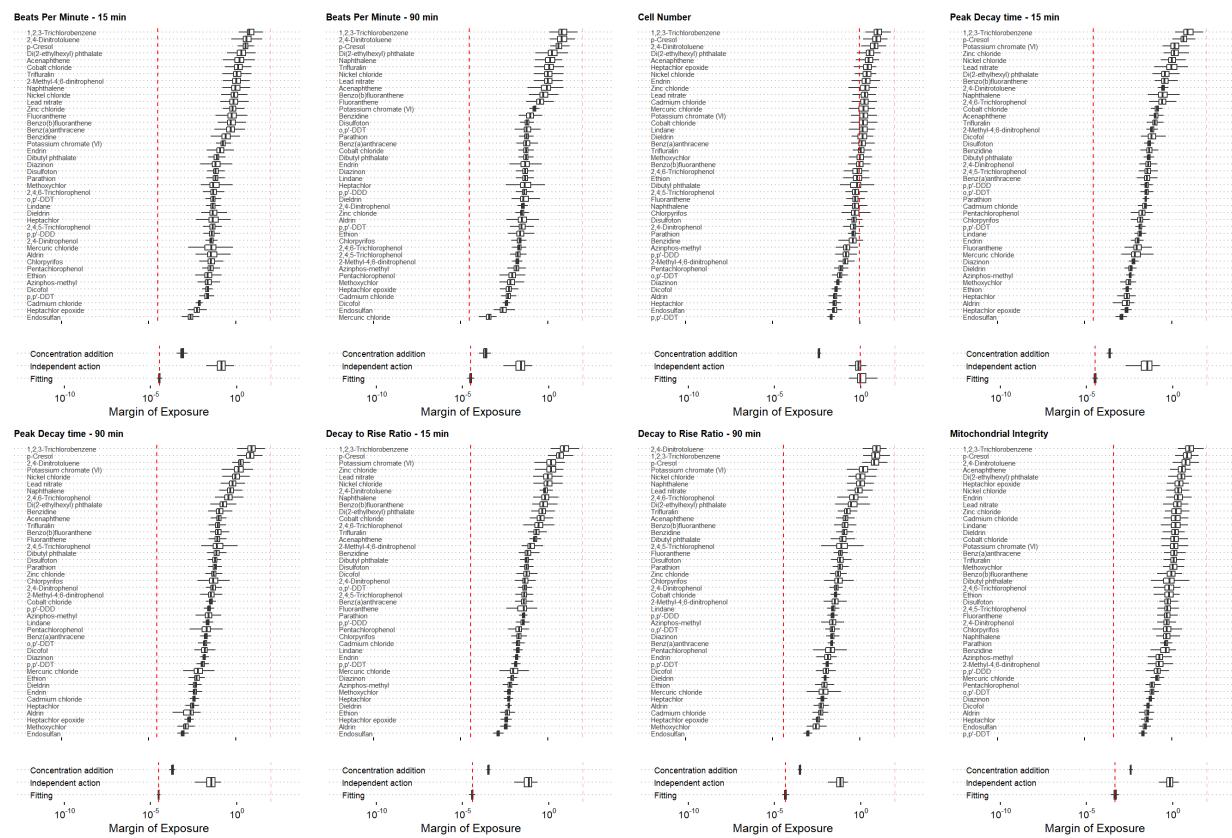


Figure S104. The estimation of the margin of exposure for cytotoxicity phenotypes in the iCell Cardiomyocytes.

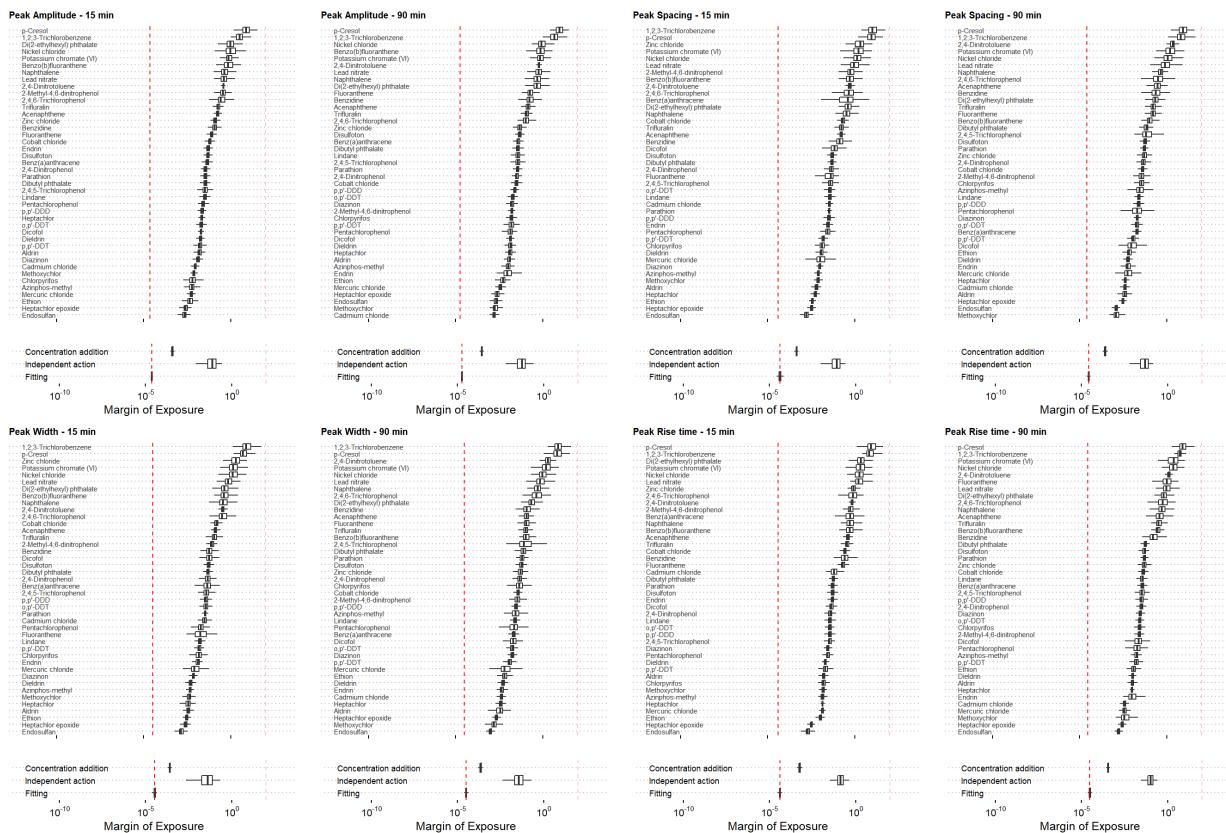


Figure S104. The estimation of the margin of exposure for cytotoxicity phenotypes in the iCell Cardiomyocytes (cont.).

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ggsignif	0.6.0	2019-08-08 [1] CRAN (R 4.0.2)
glue	1.4.1	2020-05-13 [1] CRAN (R 4.0.2)
gridExtra	* 2.3	2017-09-09 [1] CRAN (R 4.0.2)
gttable	0.3.0	2019-03-25 [1] CRAN (R 4.0.2)
haven	2.3.1	2020-06-01 [1] CRAN (R 4.0.2)

highr	0.8	2019-03-20 [1] CRAN (R 4.0.2)
hms	0.5.3	2020-01-08 [1] CRAN (R 4.0.2)
htmltools	0.5.0	2020-06-16 [1] CRAN (R 4.0.2)
httr	1.4.2	2020-07-20 [1] CRAN (R 4.0.2)
inline	0.3.15	2018-05-18 [1] CRAN (R 4.0.2)
insight	0.9.0	2020-07-20 [1] CRAN (R 4.0.2)
jpeg	* 0.1-8.1	2019-10-24 [1] CRAN (R 4.0.0)
jsonlite	1.7.0	2020-06-25 [1] CRAN (R 4.0.2)
knitr	* 1.29	2020-06-23 [1] CRAN (R 4.0.2)
lattice	0.20-41	2020-04-02 [2] CRAN (R 4.0.2)
lifecycle	0.2.0	2020-03-06 [1] CRAN (R 4.0.2)
loo	2.3.1	2020-07-14 [1] CRAN (R 4.0.2)
lubridate	1.7.9	2020-06-08 [1] CRAN (R 4.0.2)
magrittr	1.5	2014-11-22 [1] CRAN (R 4.0.2)
matrixStats	0.56.0	2020-03-13 [1] CRAN (R 4.0.2)
memoise	1.1.0	2017-04-21 [1] CRAN (R 4.0.2)
modelr	0.1.8	2020-05-19 [1] CRAN (R 4.0.2)
munspell	0.5.0	2018-06-12 [1] CRAN (R 4.0.2)
openxlsx	4.1.5	2020-05-06 [1] CRAN (R 4.0.2)
PerformanceAnalytics	* 2.0.4	2020-02-06 [1] CRAN (R 4.0.2)
pillar	1.4.6	2020-07-10 [1] CRAN (R 4.0.2)
pkgbuild	1.1.0	2020-07-13 [1] CRAN (R 4.0.2)
pkgconfig	2.0.3	2019-09-22 [1] CRAN (R 4.0.2)
pkgload	1.1.0	2020-05-29 [1] CRAN (R 4.0.2)
plyr	1.8.6	2020-03-03 [1] CRAN (R 4.0.2)
png	0.1-7	2013-12-03 [1] CRAN (R 4.0.0)
prettyunits	1.1.1	2020-01-24 [1] CRAN (R 4.0.2)

processx	3.4.3	2020-07-05 [1] CRAN (R 4.0.2)
ps	1.3.4	2020-08-11 [1] CRAN (R 4.0.2)
purrr	* 0.3.4	2020-04-17 [1] CRAN (R 4.0.2)
quadprog	1.5-8	2019-11-20 [1] CRAN (R 4.0.0)
R6	2.4.1	2019-11-12 [1] CRAN (R 4.0.2)
Rcpp	1.0.5	2020-07-06 [1] CRAN (R 4.0.2)
D RcppParallel	5.0.2	2020-06-24 [1] CRAN (R 4.0.2)
readr	* 1.3.1	2018-12-21 [1] CRAN (R 4.0.2)
readxl	1.3.1	2019-03-13 [1] CRAN (R 4.0.2)
remotes	2.2.0	2020-07-21 [1] CRAN (R 4.0.2)
reprex	0.3.0	2019-05-16 [1] CRAN (R 4.0.2)
reshape2	* 1.4.4	2020-04-09 [1] CRAN (R 4.0.2)
rio	0.5.16	2018-11-26 [1] CRAN (R 4.0.2)
rlang	0.4.7	2020-07-09 [1] CRAN (R 4.0.2)
rmarkdown	2.3	2020-06-18 [1] CRAN (R 4.0.2)
rprojroot	1.3-2	2018-01-03 [1] CRAN (R 4.0.2)
rstan	* 2.21.2	2020-07-27 [1] CRAN (R 4.0.2)
rstatix	0.6.0	2020-06-18 [1] CRAN (R 4.0.2)
rstudioapi	0.11	2020-02-07 [1] CRAN (R 4.0.2)
rvest	0.3.6	2020-07-25 [1] CRAN (R 4.0.2)
scales	* 1.1.1	2020-05-11 [1] CRAN (R 4.0.2)
sessioninfo	1.1.1	2018-11-05 [1] CRAN (R 4.0.2)
StanHeaders	* 2.21.0-5	2020-06-09 [1] CRAN (R 4.0.2)
stringi	1.4.6	2020-02-17 [1] CRAN (R 4.0.0)
stringr	* 1.4.0	2019-02-10 [1] CRAN (R 4.0.2)
testthat	2.3.2	2020-03-02 [1] CRAN (R 4.0.2)
tibble	* 3.0.3	2020-07-10 [1] CRAN (R 4.0.2)

```
tidyverse      * 1.3.0   2019-11-21 [1] CRAN (R 4.0.2)
tiff          * 0.1-5   2013-09-04 [1] CRAN (R 4.0.0)
treemapify     * 2.5.3   2019-01-30 [1] CRAN (R 4.0.2)
usethis        1.6.1    2020-04-29 [1] CRAN (R 4.0.2)
V8             3.2.0    2020-06-19 [1] CRAN (R 4.0.2)
vctrs           0.3.2    2020-07-15 [1] CRAN (R 4.0.2)
withr           2.2.0    2020-04-20 [1] CRAN (R 4.0.2)
xfun            0.16     2020-07-24 [1] CRAN (R 4.0.2)
xml2            1.3.2    2020-04-23 [1] CRAN (R 4.0.2)
xts             * 0.12-0   2020-01-19 [1] CRAN (R 4.0.2)
yaml            2.2.1    2020-02-01 [1] CRAN (R 4.0.2)
zip              2.1.0    2020-08-10 [1] CRAN (R 4.0.2)
zoo             * 1.8-8    2020-05-02 [1] CRAN (R 4.0.2)
```

```
[1] C:/Users/nan_1/Documents/R/win-library/4.0
```

```
[2] C:/Program Files/R/R-4.0.2/library
```

```
D -- DLL MD5 mismatch, broken installation.
```