

Supplementary Table 1. Activity distribution and model performance for each in vivo toxicity endpoint

In vivo endpoint	Toxic	non-Toxic	AUC-ROC (activity model)	AUC-ROC (structure model)	AUC-ROC (combined model)	Most predictive assay	AUC-ROC (most predictive assay)
acute toxicity LC50 Mouse Inhalation	200	100	0.55±0.05	0.74±0.04	0.84±0.14	DT40 WT	0.62
acute toxicity LC50 Rat Inhalation	571	144	0.55±0.03	0.68±0.04	0.7±0.12	DT40 Rev3	0.62
acute toxicity LC50 Rat Inhalation	82	136	0.56±0.07	0.63±0.06	0.69±0.21	VDR-BLA antagonist viability	0.61
acute toxicity LD50 Bird Oral	197	60	0.56±0.1	0.68±0.07	N/A	FXR-BLA agonist ch2	0.58
acute toxicity LD50 Cat Oral	82	57	0.7±0.13	0.86±0.07	N/A	DT40 WT	0.69
acute toxicity LD50 Chicken Oral	74	106	0.74±0.11	0.83±0.05	0.9±0.14	AR-MDA antagonist viability	0.60
acute toxicity LD50 Dog Injection intravenous	281	85	0.63±0.07	0.93±0.04	0.93±0.05	DT40 Rev3	0.72
acute toxicity LD50 Dog Oral	188	348	0.59±0.05	0.82±0.03	0.95±0.02	TR-beta antagonist viability	0.58
acute toxicity LD50 Duck Oral	63	105	0.65±0.11	0.86±0.05	0.9±0.15	ER-BG1 agonist	0.60
acute toxicity LD50 Guinea pig Intraperitoneal	107	73	0.67±0.13	0.89±0.04	0.94±0.07	DT40 WT	0.70
acute toxicity LD50 Guinea pig Oral	189	405	0.64±0.03	0.8±0.03	0.87±0.06	DT40 Rev3	0.67
acute toxicity LD50 Mammal	76	118	0.59±0.09	0.92±0.03	N/A	DT40 Rev3	0.65
acute toxicity LD50 Mammal Oral	60	186	0.58±0.08	0.84±0.07	N/A	DT40 Rad54/Ku70	0.67
acute toxicity LD50 Mouse Injection intravenous	1576	562	0.64±0.02	0.85±0.01	0.87±0.03	DT40 WT	0.70
acute toxicity LD50 Mouse Injection subcutaneous	687	1070	0.62±0.02	0.75±0.01	0.82±0.03	DT40 WT	0.61
acute toxicity LD50 Mouse Intramuscular	111	144	0.82±0.06	0.86±0.06	0.84±0.1	TR-beta antagonist	0.75
acute toxicity LD50 Mouse Intraperitoneal	1618	1360	0.61±0.01	0.73±0.01	0.8±0.02	DT40 WT	0.64
acute toxicity LD50 Mouse	150	199	0.67±0.05	0.81±0.03	0.89±0.07	DT40 WT	0.67

acute toxicity LD50 Mouse Oral	847	2740	0.59±0.01	0.71±0.01	0.8±0.02	DT40 Rev3	0.61
acute toxicity LD50 Quail Oral	101	137	0.55±0.08	0.82±0.05	0.67±0.22	ER-BLA agonist ch2	0.59
acute toxicity LD50 Rabbit Injection intravenous	362	102	0.61±0.06	0.89±0.03	0.91±0.06	DT40 Rev3	0.74
acute toxicity LD50 Rabbit Oral	201	559	0.61±0.03	0.77±0.03	0.89±0.06	ARE ch2	0.61
acute toxicity LD50 Rabbit Skin	117	992	0.55±0.03	0.72±0.03	0.77±0.15	DT40 WT	0.58
acute toxicity LD50 Rat Injection intravenous	946	420	0.68±0.02	0.88±0.01	0.9±0.03	DT40 Rev3	0.73
acute toxicity LD50 Rat Injection subcutaneous	430	923	0.61±0.02	0.76±0.02	0.81±0.03	DT40 WT	0.60
acute toxicity LD50 Rat Intramuscular	87	127	0.72±0.08	0.86±0.04	0.97±0.04	TR-beta antagonist viability	0.67
acute toxicity LD50 Rat Intraperitoneal	975	1010	0.65±0.02	0.74±0.01	0.82±0.03	TR-beta antagonist viability	0.64
acute toxicity LD50 Rat	129	241	0.58±0.05	0.78±0.04	0.84±0.09	DT40 Rev3	0.62
acute toxicity LD50 Rat Oral	842	3390	0.58±0.01	0.72±0.01	0.76±0.02	TR-beta antagonist viability	0.60
acute toxicity LD50 Rat Skin	95	532	0.6±0.04	0.72±0.05	0.73±0.11	ER-BG1 antagonist	0.56
hepatotoxicity	926	470	0.55±0.02	0.63±0.02	0.69±0.04	TR-beta agonist	0.54
irritation standard Draize test Human Skin	80	151	0.89±0.05	0.84±0.04	0.8±0.09	GR-BLA agonist ratio	0.75
irritation standard Draize test Rabbit Eyes	232	530	0.51±0.03	0.71±0.03	0.74±0.07	Aromatase	0.56
irritation standard Draize test Rabbit Skin	226	535	0.51±0.03	0.72±0.02	0.76±0.07	P53 ch1	0.60
multiple dose TCLo Rat Inhalation micro	184	308	0.55±0.04	0.65±0.04	0.78±0.11	PPAR-gamma antagonist viability	0.56
multiple dose TCLo Rat Inhalation	82	154	0.5±0.05	0.59±0.06	N/A	P53 ch2	0.58
multiple dose TDLo Dog Injection intravenous	54	97	0.9±0.06	0.89±0.05	0.97±0.04	DT40 WT	0.76
multiple dose TDLo Dog Oral	247	449	0.63±0.03	0.72±0.03	0.83±0.04	TR-beta antagonist	0.62
multiple dose TDLo Human Female Oral	70	133	0.64±0.06	0.85±0.06	0.97±0.03	AR-BLA antagonist ch2	0.64

multiple dose TDLo Human Male Oral	73	137	0.76±0.06	0.8±0.05	0.93±0.06	Mitochondria toxicity rhodamine	0.57
multiple dose TDLo Human Oral	114	215	0.72±0.05	0.75±0.04	0.95±0.03	ER-BLA agonist ch2	0.61
multiple dose TDLo Monkey Oral	59	91	0.59±0.13	0.93±0.04	0.99±0.08	FXR-BLA agonist viability	0.62
multiple dose TDLo Mouse Injection subcutaneous	65	132	0.74±0.08	0.78±0.05	0.96±0.05	AR-BLA antagonist ch1	0.59
multiple dose TDLo Mouse Intraperitoneal	161	320	0.73±0.05	0.83±0.03	0.91±0.03	AR-BLA antagonist ratio	0.62
multiple dose TDLo Mouse Oral	411	747	0.63±0.02	0.67±0.02	0.78±0.04	P53 ch1	0.60
multiple dose TDLo Rabbit Oral	97	170	0.64±0.07	0.74±0.06	0.65±0.14	P53 ratio	0.60
multiple dose TDLo Rat Injection intravenous	72	143	0.84±0.06	0.9±0.04	0.94±0.04	FXR-BLA antagonist ratio	0.70
multiple dose TDLo Rat Injection subcutaneous	175	302	0.7±0.04	0.78±0.03	0.79±0.05	DT40 WT	0.63
multiple dose TDLo Rat Intramuscular	56	90	0.9±0.08	0.89±0.05	0.97±0.04	DT40 Rev3	0.72
multiple dose TDLo Rat Intraperitoneal	242	473	0.63±0.03	0.71±0.03	0.81±0.05	DT40 Rev3	0.62
multiple dose TDLo Rat	76	148	0.62±0.09	0.75±0.05	0.89±0.1	P53 ratio	0.63
multiple dose TDLo Rat Oral	917	1701	0.56±0.01	0.64±0.01	0.71±0.03	DT40 WT	0.59
multiple dose TDLo Rat Skin	61	110	0.71±0.08	0.86±0.06	0.89±0.14	ER-BLA agonist ch2	0.65
reproductive TDLo Human Female Oral	56	94	0.74±0.09	0.8±0.06	0.62±0.15	ER-BLA agonist ch2	0.67
reproductive TDLo Mouse Injection subcutaneous	114	216	0.67±0.05	0.87±0.03	0.91±0.04	DT40 Rev3	0.72
reproductive TDLo Mouse Intraperitoneal	124	207	0.62±0.06	0.81±0.04	0.87±0.07	P53 ratio	0.67
reproductive TDLo Mouse Oral	237	453	0.73±0.03	0.77±0.03	0.91±0.04	DT40 Rad54/Ku70	0.65
reproductive TDLo Rabbit Oral	164	294	0.68±0.05	0.79±0.04	0.92±0.04	AR-BLA agonist ratio	0.63
reproductive TDLo Rat Injection intravenous	65	123	0.67±0.1	0.87±0.05	0.89±0.09	PPAR-gamma antagonist viability	0.68
reproductive TDLo Rat Injection subcutaneous	161	294	0.66±0.05	0.81±0.03	0.8±0.05	ER-BLA agonist ch2	0.69
reproductive TDLo Rat Intraperitoneal	154	256	0.66±0.05	0.8±0.04	0.9±0.04	P53 ratio	0.66

reproductive TDLo Rat	66	117	0.85±0.07	0.86±0.06	0.83±0.09	GR-BLA antagonist ch1	0.67
reproductive TDLo Rat Oral	555	1021	0.62±0.02	0.7±0.02	0.82±0.03	DT40 Rev3	0.62
tumorigenic TD Mouse Oral	69	114	0.61±0.09	0.92±0.04	0.95±0.07	FXR-BLA agonist viability	0.60
tumorigenic TD Rat Oral	74	139	0.52±0.09	0.77±0.05	0.59±0.21	PPAR-gamma agonist ch1	0.57
tumorigenic TDLo Mouse Injection subcutaneous	63	121	0.7±0.1	0.72±0.07	0.69±0.12	PPAR-gamma antagonist ch1	0.71
tumorigenic TDLo Mouse Oral	174	304	0.58±0.04	0.75±0.04	0.92±0.05	GR-BLA antagonist viability	0.60
tumorigenic TDLo Mouse Skin	52	99	0.69±0.1	0.86±0.04	0.83±0.19	GR-BLA agonist ch2	0.65
tumorigenic TDLo Rat Oral	186	350	0.55±0.05	0.67±0.03	0.93±0.04	GR-BLA antagonist viability	0.55
acute toxicity	3532	2185	0.57±0.01	0.73±0.01	0.72±0.01	DT40 Rev3	0.59
reproductive	860	1535	0.62±0.01	0.7±0.01	0.78±0.02	DT40 WT	0.63
tumorigenic	367	622	0.56±0.03	0.69±0.02	0.83±0.04	TR-beta antagonist	0.59