United States Environmental Protection Agency

Computational Toxicology : Where is the Data?

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This work was reviewed by EPA and approved for presentation but does not necessarily reflect official Agency policy

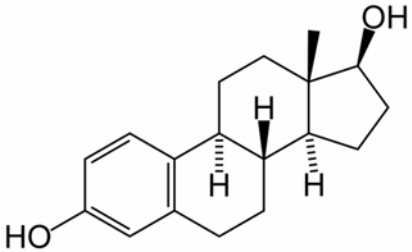
Office of Research and Development
National Center for Computational Toxicology

Goals of Computational Toxicology at the EPA

- Model / Characterize known toxic chemicals
  - Hazard ID
  - Mode of action
  - Mechanism of action
  - Dose response
- Predict potential toxic effects among widely used but uncharacterized chemicals

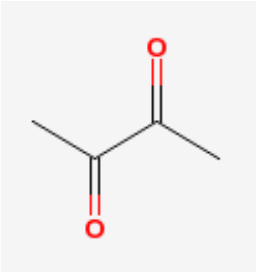
- Working hypothesis:
  - A <u>small</u> number of commonly used chemicals account for a <u>significant</u> amount of human disease / ecological damage

Examples of Disease Burden from Widely Used Chemicals



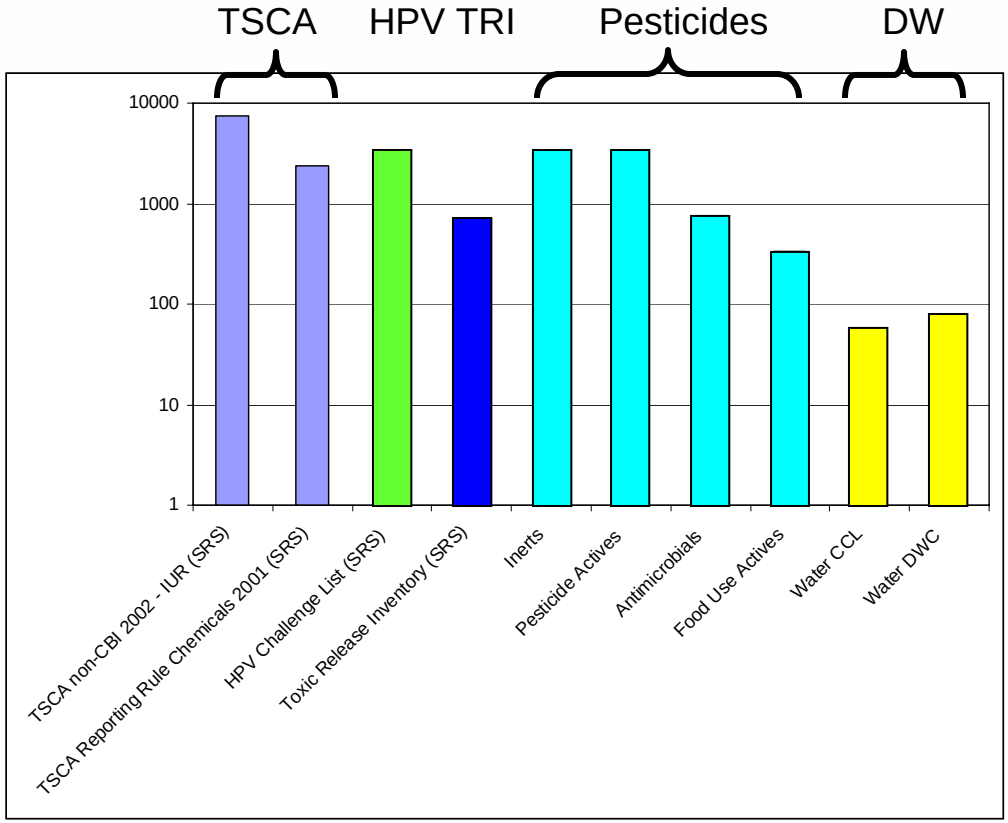
- Estrogen : Hormone Replacement Therapy
  - Identified in 2002 as increasing risk of breast cancer
  - Estrogen use dropped significantly after this report
  - Breast cancer incidence dropped sharply - 6.7% (2003 over 2002)(1)
  - Incidence rate remained down in subsequent years

- Diacetyl
  - Carrier of aroma of butter, vinegar, coffee, and other foods
    - Additive to microwave popcorn
  - Associated with “Popcorn Lung” (bronchiolitis obliterans) in microwave popcorn factory workers
  - First case reports in 2000



(1) NEJM Volume 356:1670-1674

The World of Widely Used Chemicals



~15,000 chemicals are targets for toxicity characterization

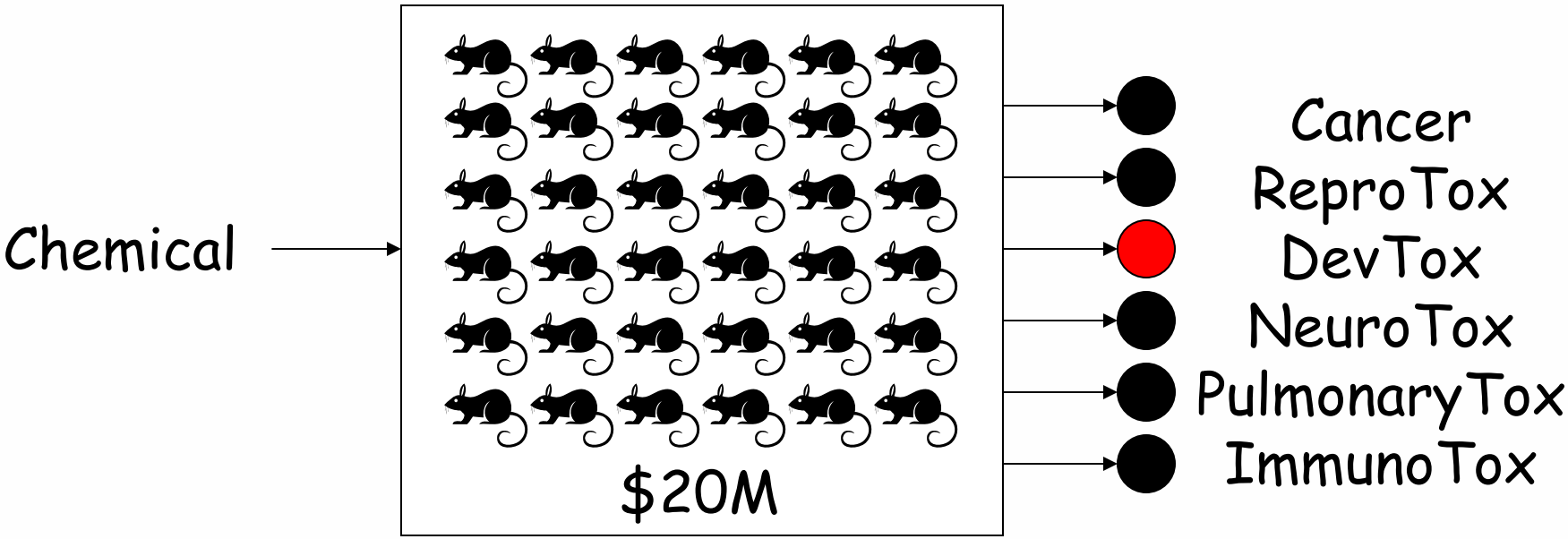
United States Environmental Protection Agency

Many Chemical Lists – Little Overlap

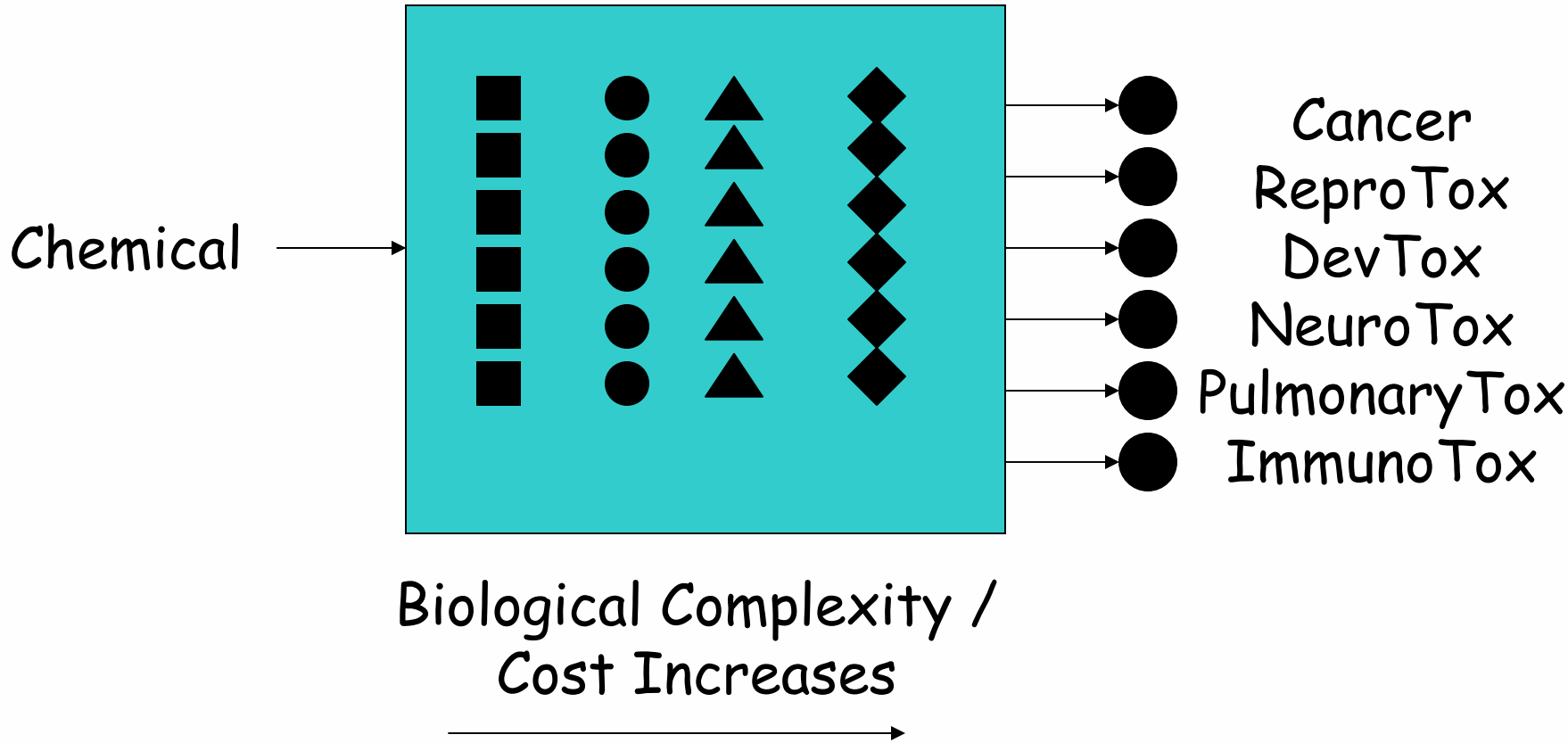
id	124(IUR1)5375	58(SRS_CUS02)7360	59(SRS_CORR)2379	104(SRS_TSCA_4_Tests)296	61(SRS_TSCA_6A_CCCR)10	62(SRS_TSCA_8A_CAIR)47	78(SRS_TSCA_8D_HSDR_a)342	76(SRS_TSCA_8D_HSDR_c)414	77(SRS_TSCA_8D_HSDR_d)414	70(SRS_TSCA_6_Unreasonable_Risk)21	73(SRS_HSDB)2338	121(HPVChallenge2)1973	120(HPV2)2811	110(SRS_HPVC)3358	79(SRS_HPVIS)3581	132(TRI2)579	108(SRS_TRIS)601	105(SRS_TRI)666	80(SRS_FIFRA_Inerts)2166	131(OPPIN_Inerts1)3307	122(INERTSList1)8	123(INERTSList2)96	125(OPPIN_Active1)3448	126(OPPIN_ActiveConventional1)293
124(IUR1)5375	5375	5244	717	194	3	31	198	168	168	5	922	1737	2381	2288	2386	227	243	252	822	1119	8	81	542	8
58(SRS_CUS02)7360	5244	7360	865	202	4	36	224	216	216	8	1069	1944	2743	2719	2834	247	264	277	1009	1389	8	81	661	12
59(SRS_CORR)2379	717	865	2379	288	10	47	338	412	412	21	1114	445	525	619	650	572	596	661	242	355	8	50	465	99
104(SRS_TSCA_4_Tests)296	194	202	288	296	1	6	67	22	22	1	186	151	161	188	189	74	78	80	50	79	6	12	63	1
61(SRS_TSCA_6A_CCCR)10	3	4	10	1	10	0	1	1	1	10	9	2	5	2	2	6	7	9	1	6	0	0	6	0
62(SRS_TSCA_8A_CAIR)47	31	36	47	6	0	47	17	1	1	0	40	22	26	24	28	24	26	26	10	21	0	4	25	0
78(SRS_TSCA_8D_HSDR_a)342	198	224	338	67	1	17	342	2	2	1	236	157	178	196	198	99	103	118	76	108	3	39	71	0
76(SRS_TSCA_8D_HSDR_c)414	168	216	412	22	1	1	2	414	414	1	153	112	127	160	165	30	32	32	59	80	1	4	49	1
77(SRS_TSCA_8D_HSDR_d)414	168	216	412	22	1	1	2	414	414	1	153	112	127	160	165	30	32	32	59	80	1	4	49	1
70(SRS_TSCA_6_Unreasonable_Risk)21	5	8	21	1	10	0	1	1	1	21	16	2	6	2	2	7	8	10	2	9	0	0	10	0
73(SRS_HSDB)2338	922	1069	1114	186	9	40	236	153	153	16	2338	657	766	851	931	504	524	557	455	576	8	44	866	115
121(HPVChallenge2)1973	1737	1944	445	151	2	22	157	112	112	2	657	1973	1954	1973	1973	162	173	181	469	588	8	71	316	6
120(HPV2)2811	2381	2743	525	161	5	26	178	127	127	6	766	1954	2811	2229	2281	179	197	205	587	775	8	75	399	8
110(SRS_HPVC)3358	2288	2719	619	188	2	24	196	160	160	2	851	1973	2229	3358	3284	211	223	231	640	824	8	83	416	15
79(SRS_HPVIS)3581	2386	2834	650	189	2	28	198	165	165	2	931	1973	2281	3284	3581	222	239	248	679	873	8	84	481	19
132(TRI2)579	227	247	572	74	6	24	99	30	30	7	504	162	179	211	222	579	574	575	77	131	6	23	310	92
108(SRS_TRIS)601	243	264	596	78	7	26	103	32	32	8	524	173	197	223	239	574	601	601	93	150	7	25	321	92
105(SRS_TRI)666	252	277	661	80	9	26	118	32	32	10	557	181	205	231	248	575	601	666	96	155	7	25	324	92
80(SRS_FIFRA_Inerts)2166	822	1009	242	50	1	10	76	59	59	2	455	469	587	640	679	77	93	96	2166	2068	6	92	512	2
131(OPPIN_Inerts1)3307	1119	1389	355	79	6	21	108	80	80	9	576	588	775	824	873	131	150	155	2068	3307	8	92	626	5
122(INERTSList1)8	8	8	8	6	0	0	3	1	1	0	8	8	8	8	8	6	7	7	6	8	8	0	4	0
123(INERTSList2)96	81	81	50	12	0	4	39	4	4	0	44	71	75	83	84	23	25	25	92	92	0	96	33	0
125(OPPIN_Active1)3448	542	661	465	63	6	25	71	49	49	10	866	316	399	416	481	310	321	324	512	626	4	33	3448	293
126(OPPIN_ActiveConventional1)293	8	12	99	1	0	0	0	1	1	0	115	6	8	15	19	92	92	92	2	5	0	0	293	293
127(OPPIN_ActiveSupported1)1082	215	249	250	12	1	8	22	12	12	2	404	101	145	150	185	191	194	195	194	242	1	8	1082	265
128(OPPIN_AntiMicrobial1)754	255	301	152	21	2	16	32	16	16	6	285	136	184	181	215	94	97	98	262	306	2	13	754	26
129(OPPIN_AntiMicrobialFoodUse1)26	3	3	13	0	0	0	0	0	0	0	21	1	2	5	5	13	13	13	2	4	0	0	26	26
130(OPPIN_FoodUseActives1)336	8	13	99	3	0	0	0	2	2	0	114	6	9	16	20	91	91	91	2	5	0	0	329	289
90(SRS_OPPIN)3390	518	638	451	61	7	24	69	50	50	10	847	301	383	394	461	306	317	320	508	741	4	31	3192	278
68(SRS_OP_RPT_0798)41	0	1	20	0	0	0	0	0	0	0	32	0	0	1	1	20	20	20	0	1	0	0	41	25
92(SRS_PAI)264	23	28	143	7	1	2	7	2	2	1	203	15	20	35	39	132	134	134	14	26	0	1	261	83
91(SRS_CAA112_b_HON)385	267	287	225	65	2	20	96	47	47	2	320	227	234	270	272	144	150	153	104	151	6	27	128	3
98(SRS_CAA_112R)138	81	88	70	15	0	8	16	9	9	0	132	65	77	80	93	51	52	57	16	30	0	1	32	1
63(SRS_CERCLA)764	251	283	424	82	8	25	114	39	39	13	690	185	216	222	251	293	303	318	113	167	7	20	314	38
56(SRS_CHIPS)397	191	215	188	40	4	24	61	24	24	4	210	138	159	170	182	119	132	133	82	123	4	14	91	1
107(SRS_CWA_307A)39	20	21	31	5	4	6	12	2	2	4	32	19	21	19	19	24	25	27	5	14	2	2	23	0
60(SRS_CWA_311)392	128	145	151	29	3	12	38	23	23	8	339	91	116	103	134	103	106	108	79	110	2	9	189	24
66(SRS_EIMS)408	102	112	184	51	6	14	60	8	8	6	239	76	84	99	101	117	120	142	40	71	4	15	108	9
69(SRS_HAP)169	115	121	166	40	5	19	59	19	19	5	168	96	103	107	109	158	161	163	32	64	6	14	91	6
64(SRS_HDDs_HDFs)89	17	19	73	43	3	1	8	9	9	3	35	12	14	18	18	11	12	27	0	6	1	0	17	0
84(SRS_MTL96)558	405	424	375	194	3	17	111	90	90	3	407	326	352	384	395	122	130	136	141	197	7	22	135	2
87(SRS_NTP_Chemicals)1960	740	866	712	158	5	35	181	97	97	10	1010	484	540	640	665	339	354	381	317	421	8	37	454	42
88(SRS_NTP_Studies)536	230	262	264	55	4	21	75	28	28	6	351	167	185	204	215	169	177	184	115	162	8	26	194	19
93(SRS_PBT)66	2	2	62	3	4	0	1	1	1	4	38	1	2	1	1	16	17	55	0	2	0	0	11	2
97(SRS_PEPS)257	135	157	132	24	1	17	46	19	19	3	154	100	110	130	134	58	66	67	54	75	3	5	43	0
95(SRS_PCB)235	0	0	10	0	1	0	0	0	0	1	9	0	0	0	0	1	1	1	0	2	0	0	2	0
94(SRS_POPs)13	1	1	8	1	1	0	0	0	0	1	10	0	0	0	0	6	6	6	0	2	0	0	11	0
71(SRS_RCRA_Appendix_VIII)449	141	154	307	57	5	14	70	17	17	6	403	103	115	129	134	215	222	244	32	61	4	12	195	23
74(SRS_RCRA_F_Waste)10	9	9	10	6	1	0	3	2	2	1	9	9	10	9	9	5	7	7	8	10	0	4	6	0
96(SRS_SARA_110)426	150	161	253	62	8	19	64	21	21	10	345	118	136	138	149	183	190	208	54	97	5	19	169	22
67(SRS_SARA_302A)406	88	102	148	23	2	10	36	11	11	2	387	62	81	78	92	103	106	112	15	29	2	3	196	21
85(SRS_SDWA_NPDWR)177	64	68	113	25	6	13	41	8	8	6	135	52	57	61	67	88	90	92	19	46	3	7	90	18
72(SRS_RCRA_U_Waste)250	121	125	216	52	2	13	59	11	11	3	239	99	105	115	115	148	154	164	38	65	4	15	110	8
86(SRS_SDWA_NSDWR)10	1	1	6	1	2	0	0	1	1	2	6	0	1	0	0	5	6	6	3	5	0	0	4	0
99(SRS_SDWIS_Enviro)561	151	163	257	63	7	16	69	27	27	7	340	125	131	150	156	190	196	206	66	108	6	19	218	47
100(SRS_SIDS)244	198	210	83	16	0	1	35	25	25	0	167	165	177	187	211	33	37	39	86	106	2	10	69	1
102(SRS_SubHazProf)109	64	65	46	11	5	7	23	4	4	5	69	48	53	50	56	29	32	33	49	60	1	10	36	0
106(SRS_TTO)113	50	54	89	27	3	12	33	6	6	3	110	41	43	49	49	66	70	79	13	35	4	8	58	1

id	127(OPPIN_ActiveSupported1)1082	128(OPPIN_AntiMicrobial1)754	129(OPPIN_AntiMicrobialFoodUse1)26	130(OPPIN_FoodUseActives1)336	90(SRS_OPPIN)3390	68(SRS_OP_RPT_0798)41	92(SRS_PAI)264	91(SRS_CAA112_b_HON)385	98(SRS_CAA_112R)138	63(SRS_CERCLA)764	56(SRS_CHIPS)397	107(SRS_CWA_307A)39	60(SRS_CWA_311)392	66(SRS_EIMS)408	69(SRS_HAP)169	64(SRS_HDDs_HDFs)89	84(SRS_MTL96)558	87(SRS_NTP_Chemicals)1960	88(SRS_NTP_Studies)536	93(SRS_PBT)66	97(SRS_PEPS)257	95(SRS_PCB)235	94(SRS_POPs)13	71(SRS_RCRA_Appendix_VIII)449	74(SRS_RCRA_F_Waste)10	96(SRS_SARA_110)426	67(SRS_SARA_302A)406	85(SRS_SDWA_NPDWR)177	72(SRS_RCRA_U_Waste)250	86(SRS_SDWA_NSDWR)10	99(SRS_SDWIS_Enviro)561	100(SRS_SIDS)244	102(SRS_SubHazProf)109	106(SRS_TTO)113
124(IUR1)5375	215	255	3	8	518	0	23	267	81	251	191	20	128	102	115	17	405	740	230	2	135	0	1	141	9	150	88	64	121	1	151	198	64	50
58(SRS_CUS02)7360	249	301	3	13	638	1	28	287	88	283	215	21	145	112	121	19	424	866	262	2	157	0	1	154	9	161	102	68	125	1	163	210	65	54
59(SRS_CORR)2379	250	152	13	99	451	20	143	225	70	424	188	31	151	184	166	73	375	712	264	62	132	10	8	307	10	253	148	113	216	6	257	83	46	89
104(SRS_TSCA_4_Tests)296	12	21	0	3	61	0	7	65	15	82	40	5	29	51	40	43	194	158	55	3	24	0	1	57	6	62	23	25	52	1	63	16	11	27
61(SRS_TSCA_6A_CCCR)10	1	2	0	0	7	0	1	2	0	8	4	4	3	6	5	3	3	5	4	4	1	1	1	5	1	8	2	6	2	2	7	0	5	3
62(SRS_TSCA_8A_CAIR)47	8	16	0	0	24	0	2	20	8	25	24	6	12	14	19	1	17	35	21	0	17	0	0	14	0	19	10	13	13	0	16	1	7	12
78(SRS_TSCA_8D_HSDR_a)342	22	32	0	0	69	0	7	96	16	114	61	12	38	60	59	8	111	181	75	1	46	0	0	70	3	64	36	41	59	0	69	35	23	33
76(SRS_TSCA_8D_HSDR_c)414	12	16	0	2	50	0	2	47	9	39	24	2	23	8	19	9	90	97	28	1	19	0	0	17	2	21	11	8	11	1	27	25	4	6
77(SRS_TSCA_8D_HSDR_d)414	12	16	0	2	50	0	2	47	9	39	24	2	23	8	19	9	90	97	28	1	19	0	0	17	2	21	11	8	11	1	27	25	4	6
70(SRS_TSCA_6_Unreasonable_Risk)21	2	6	0	0	10	0	1	2	0	13	4	4	8	6	5	3	3	10	6	4	3	1	1	6	1	10	2	6	3	2	7	0	5	3
73(SRS_HSDB)2338	404	285	21	114	847	32	203	320	132	690	210	32	339	239	168	35	407	1010	351	38	154	9	10	403	9	345	387	135	239	6	340	167	69	110
121(HPVChallenge2)1973	101	136	1	6	301	0	15	227	65	185	138	19	91	76	96	12	326	484	167	1	100	0	0	103	9	118	62	52	99	0	125	165	48	41
120(HPV2)2811	145	184	2	9	383	0	20	234	77	216	159	21	116	84	103	14	352	540	185	2	110	0	0	115	10	136	81	57	105	1	131	177	53	43
110(SRS_HPVC)3358	150	181	5	16	394	1	35	270	80	222	170	19	103	99	107	18	384	640	204	1	130	0	0	129	9	138	78	61	115	0	150	187	50	49
79(SRS_HPVIS)3581	185	215	5	20	461	1	39	272	93	251	182	19	134	101	109	18	395	665	215	1	134	0	0	134	9	149	92	67	115	0	156	211	56	49
132(TRI2)579	191	94	13	91	306	20	132	144	51	293	119	24	103	117	158	11	122	339	169	16	58	1	6	215	5	183	103	88	148	5	190	33	29	66
108(SRS_TRIS)601	194	97	13	91	317	20	134	150	52	303	132	25	106	120	161	12	130	354	177	17	66	1	6	222	7	190	106	90	154	6	196	37	32	70
105(SRS_TRI)666	195	98	13	91	320	20	134	153	57	318	133	27	108	142	163	27	136	381	184	55	67	1	6	244	7	208	112	92	164	6	206	39	33	79
80(SRS_FIFRA_Inerts)2166	194	262	2	2	508	0	14	104	16	113	82	5	79	40	32	0	141	317	115	0	54	0	0	32	8	54	15	19	38	3	66	86	49	13
131(OPPIN_Inerts1)3307	242	306	4	5	741	1	26	151	30	167	123	14	110	71	64	6	197	421	162	2	75	2	2	61	10	97	29	46	65	5	108	106	60	35
122(INERTSList1)8	1	2	0	0	4	0	0	6	0	7	4	2	2	4	6	1	7	8	8	0	3	0	0	4	0	5	2	3	4	0	6	2	1	4
123(INERTSList2)96	8	13	0	0	31	0	1	27	1	20	14	2	9	15	14	0	22	37	26	0	5	0	0	12	4	19	3	7	15	0	19	10	10	8
125(OPPIN_Active1)3448	1082	754	26	329	3192	41	261	128	32	314	91	23	189	108	91	17	135	454	194	11	43	2	11	195	6	169	196	90	110	4	218	69	36	58
126(OPPIN_ActiveConventional1)293	265	26	26	289	278	25	83	3	1	38	1	0	24	9	6	0	2	42	19	2	0	0	0	23	0	22	21	18	8	0	47	1	0	1
127(OPPIN_ActiveSupported1)1082	1082	347	26	265	993	37	185	29	13	123	26	5	83	32	23	4	39	184	79	4	11	0	3	79	0	70	76	36	33	3	100	30	15	12
128(OPPIN_AntiMicrobial1)754	347	754	26	25	708	3	64	60	17	100	50	10	77	40	34	9	59	171	79	0	18	0	1	54	3	71	33	25	34	4	58	35	26	23
129(OPPIN_AntiMicrobialFoodUse1)26	26	26	26	25	26	3	13	1	0	11	1	0	7	3	1	0	0	12	5	0	0	0	0	4	0	6	2	2	1	0	8	1	0	0
130(OPPIN_FoodUseActives1)336	265	25	25	336	312	25	80	5	1	41	1	0	26	10	6	0	2	42	19	2	0	0	0	24	0	23	21	18	8	0	50	1	0	1
90(SRS_OPPIN)3390	993	708	26	312	3390	40	258	126	32	313	89	24	190	108	90	15	132	449	193	12	41	2	11	195	7	168	192	91	109	5	219	66	37	59
68(SRS_OP_RPT_0798)41	37	3	3	25	40	41	34	0	0	15	0	0	12	4	2	0	0	15	11	0	0	0	0	6	0	14	20	0	0	0	13	0	0	0
92(SRS_PAI)264	185	64	13	80	258	34	264	10	0	73	6	4	42	22	20	5	4	94	53	7	2	0	4	68	1	46	53	33	24	1	85	1	1	10
91(SRS_CAA112_b_HON)385	29	60	1	5	126	0	10	385	37	173	89	21	78	82	113	11	141	265	119	4	50	0	1	102	7	109	46	50	96	1	106	67	29	53
98(SRS_CAA_112R)138	13	17	0	1	32	0	0	37	138	64	29	4	31	8	31	0	32	64	18	0	13	0	0	36	1	33	71	12	22	0	23	11	2	7
63(SRS_CERCLA)764	123	100	11	41	313	15	73	173	64	764	109	38	384	164	168	12	135	421	158	25	52	9	9	374	10	252	160	102	248	4	220	36	24	112
56(SRS_CHIPS)397	26	50	1	1	89	0	6	89	29	109	397	14	39	50	67	5	100	178	84	2	125	0	0	64	7	82	38	34	60	5	68	33	26	26
107(SRS_CWA_307A)39	5	10	0	0	24	0	4	21	4	38	14	39	19	27	24	4	14	27	17	5	8	1	2	27	2	33	9	17	20	1	31	3	6	28
60(SRS_CWA_311)392	83	77	7	26	190	12	42	78	31	384	39	19	392	59	62	6	67	162	75	7	17	2	8	92	3	112	71	46	56	1	88	19	7	37
66(SRS_EIMS)408	32	40	3	10	108	4	22	82	8	164	50	27	59	408	71	27	58	212	84	41	16	44	10	119	5	218	32	96	82	10	214	19	28	108
69(SRS_HAP)169	23	34	1	6	90	2	20	113	31	168	67	24	62	71	169	6	81	148	87	9	27	1	5	107	5	103	49	51	90	1	95	25	13	54
64(SRS_HDDs_HDFs)89	4	9	0	0	15	0	5	11	0	12	5	4	6	27	6	89	36	37	10	17	1	0	0	12	1	17	1	8	10	1	15	2	2	8
84(SRS_MTL96)558	39	59	0	2	132	0	4	141	32	135	100	14	67	58	81	36	558	290	110	2	67	0	0	70	8	90	39	43	67	2	87	159	21	34
87(SRS_NTP_Chemicals)1960	184	171	12	42	449	15	94	265	64	421	178	27	162	212	148	37	290	1960	508	30	126	12	10	284	9	251	151	105	200	2	246	121	46	111
88(SRS_NTP_Studies)536	79	79	5	19	193	11	53	119	18	158	84	17	75	84	87	10	110	508	536	13	46	1	8	109	4	118	56	62	85	1	112	47	23	54
93(SRS_PBT)66	4	0	0	2	12	0	7	4	0	25	2	5	7	41	9	17	2	30	13	66	0	12	6	31	1	30	5	11	15	1	22	0	2	16
97(SRS_PEPS)257	11	18	0	0	41	0	2	50	13	52	125	8	17	16	27	1	67	126	46	0	257	0	0	31	1	34	18	6	28	0	25	13	7	13
95(SRS_PCB)235	0	0	0	0	2	0	0	0	0	9	0	1	2	44	1	0	0	12	1	12	0	235	1	1	0	11	0	10	0	0	10	0	0	8
94(SRS_POPs)13	3	1	0	0	11	0	4	1	0	9	0	2	8	10	5	0	0	10	8	6	0	1	13	10	0	12	4	8	3	0	11	0	0	8
71(SRS_RCRA_Appendix_VIII)449	79	54	4	24	195	6	68	102	36	374	64	27	92	119	107	12	70	284	109	31	31	1	10	449	1	174	127	76	226	2	150	15	16	83
74(SRS_RCRA_F_Waste)10	0	3	0	0	7	0	1	7	1	10	7	2	3	5	5	1	8	9	4	1	1	0	0	1	10	10	1	3	9	1	9	3	4	2
96(SRS_SARA_110)426	70	71	6	23	168	14	46	109	33	252	82	33	112	218	103	17	90	251	118	30	34	11	12	174	10	426	76	101	113	7	253	28	29	111
67(SRS_SARA_302A)406	76	33	2	21	192	20	53	46	71	160	38	9	71	32	49	1	39	151	56	5	18	0	4	127	1	76	406	25	41	1	58	13	7	20
85(SRS_SDWA_NPDWR)177	36	25	2	18	91	0	33	50	12	102	34	17	46	96	51	8	43	105	62	11	6	10	8	76	3	101	25	177	50	4	170	13	17	53
72(SRS_RCRA_U_Waste)250	33	34	1	8	109	0	24	96	22	248	60	20	56	82	90	10	67	200	85	15	28	0	3	226	9	113	41	50	250	1	104	14	12	66
86(SRS_SDWA_NSDWR)10	3	4	0	0	5	0	1	1	0	4	5	1	1	10	1	1	2	2	1	1	0	0	0	2	1	7	1	4	1	10	10	0	5	1
99(SRS_SDWIS_Enviro)561	100	58	8	50	219	13	85	106	23	220	68	31	88	214	95	15	87	246	112	22	25	10	11	150	9	253	58	170	104	10	561	27	32	112
100(SRS_SIDS)244	30	35	1	1	66	0	1	67	11	36	33	3	19	19	25	2	159	121	47	0	13	0	0	15	3	28	13	13	14	0	27	244	8	10
102(SRS_SubHazProf)109	15	26	0	0	37	0	1	29	2	24	26	6	7	28	13	2	21	46	23	2	7	0	0	16	4	29	7	17	12	5	32	8	109	7
106(SRS_TTO)113	12	23	0	1	59	0	10	53	7	112	26	28	37	108	54	8	34	111	54	16	13	8	8	83	2	111	20	53	66	1	112	10	7	113

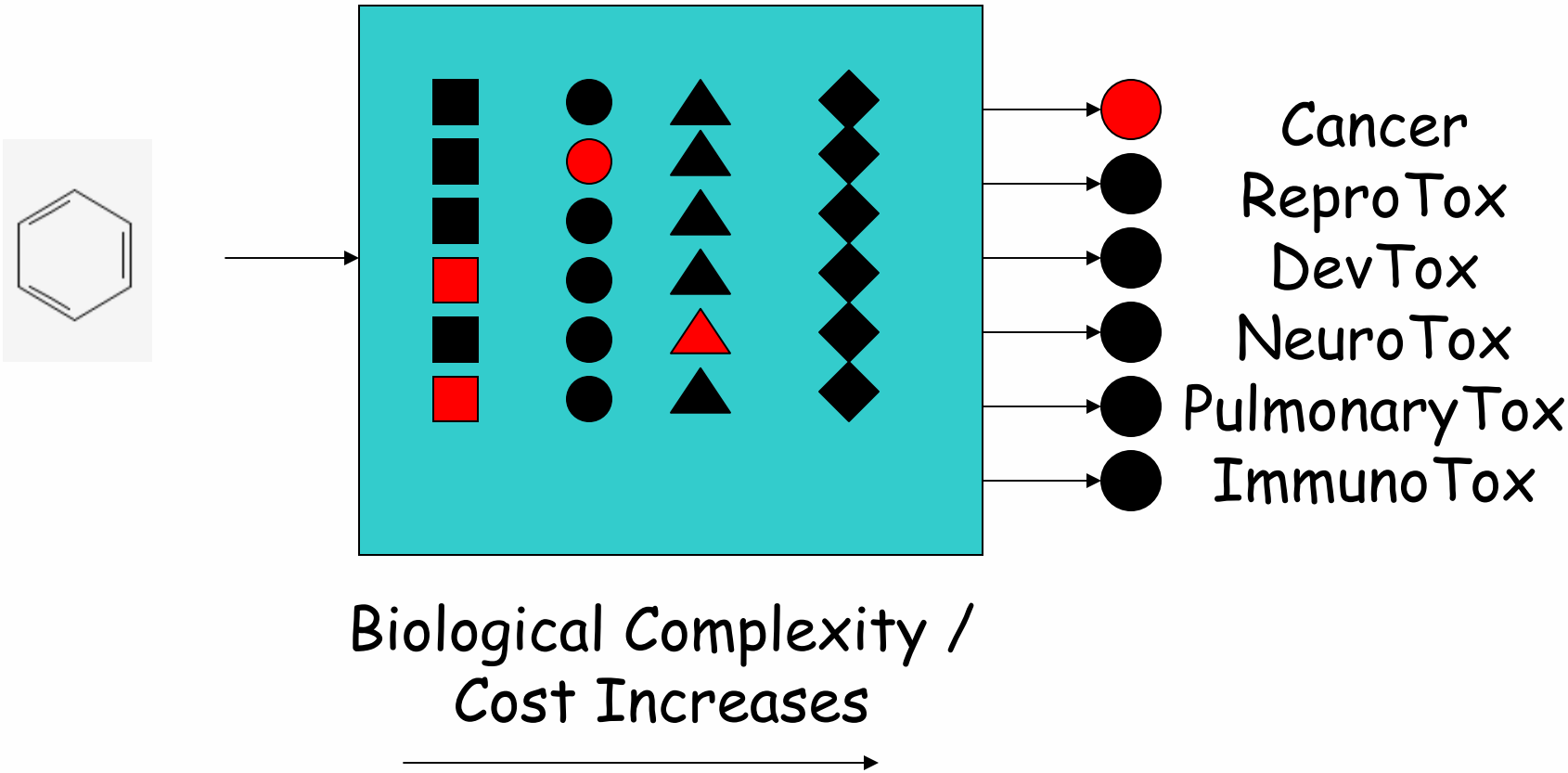
Toxicity Prediction Today



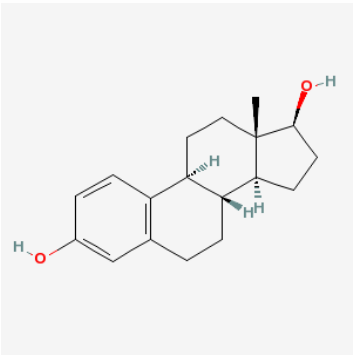
Toxicity Prediction Tomorrow: Find Pattern that Predicts Toxicity using Inexpensive Assays

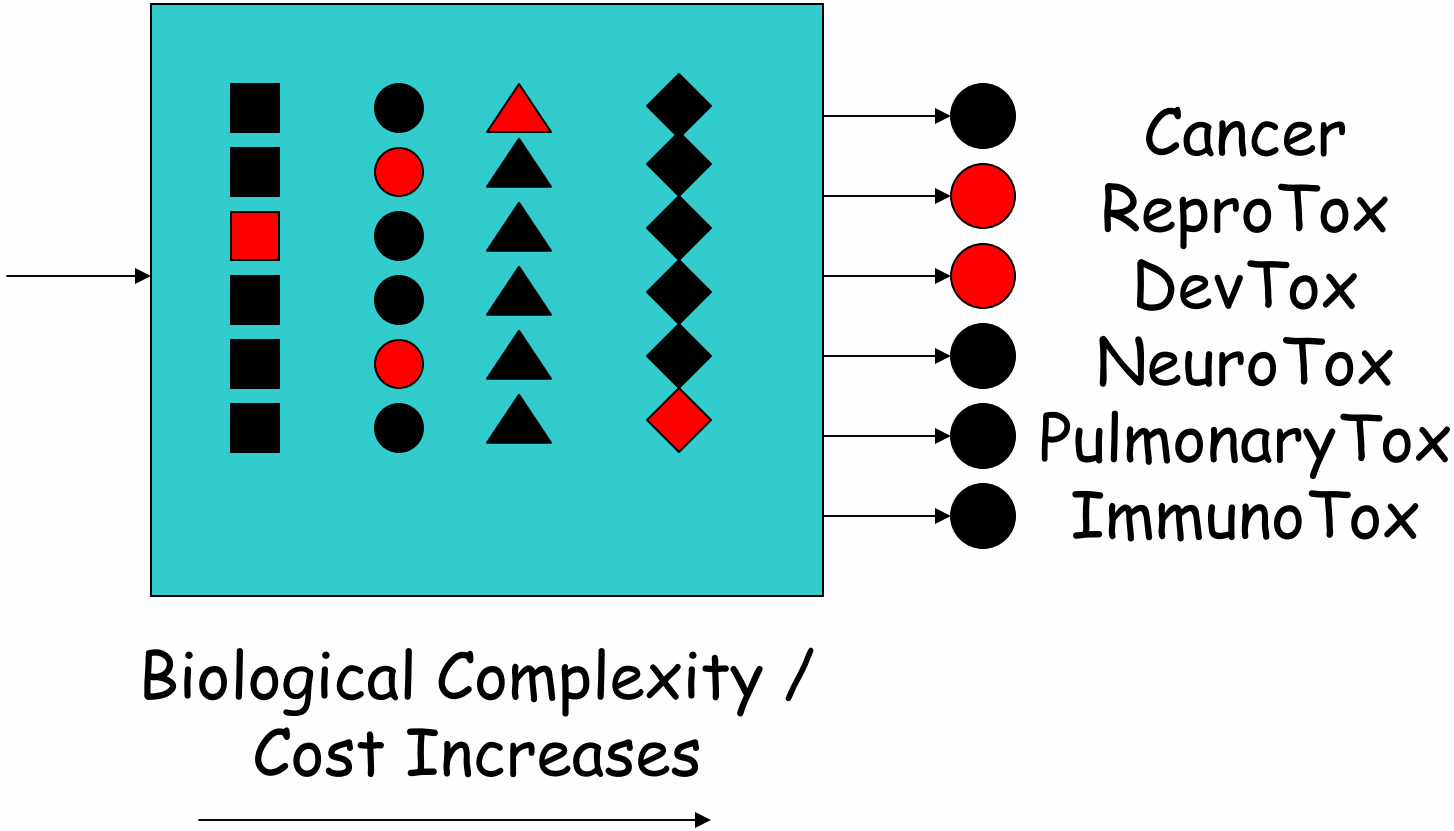


Toxicity Prediction Tomorrow: Find Pattern of Assays that Predicts Tox

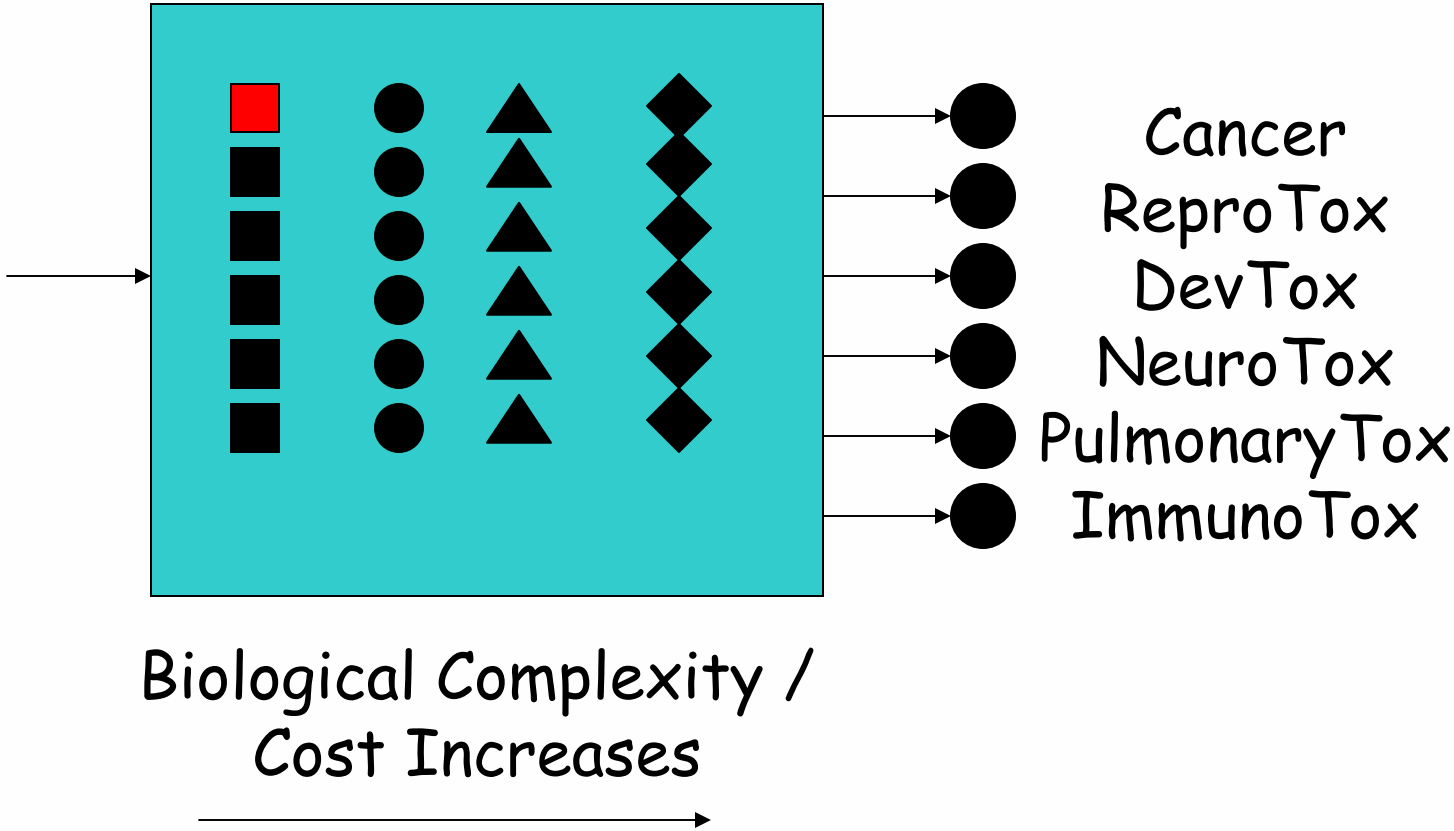


Toxicity Prediction Tomorrow: Find Pattern of Assays that Predicts Tox





Toxicity Prediction Tomorrow: Find Pattern of Assays that Predicts Tox



Data Required for Pattern Mining Approach

- Chemical and Biological Descriptors
  - Bioactivity
  - Structure
- Endpoint – many are of interest
  - More complex bioactivity
  - Pathway
  - Cell
  - Tissue
  - Organ
  - Animal

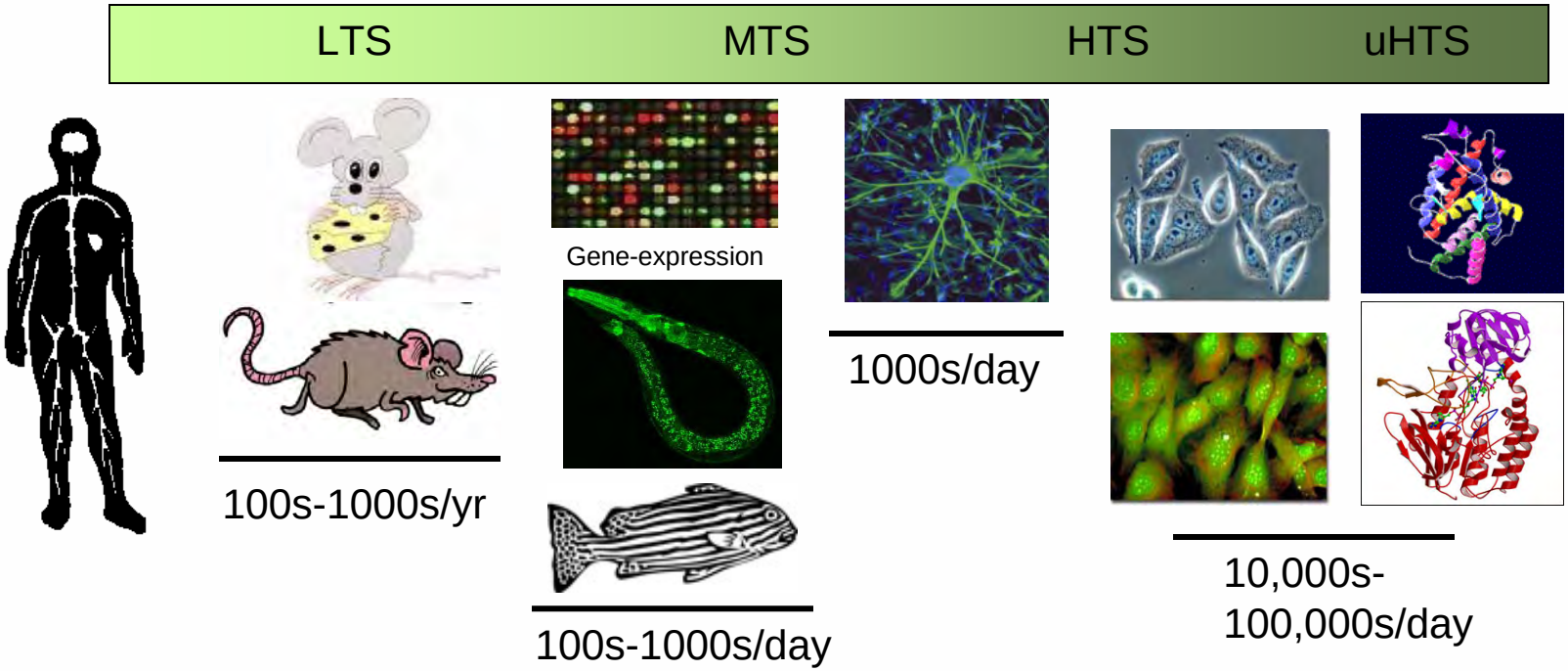
Chemical Toxicity Prioritization Approach

- Tox-Score=f(bioactivity, structure, …)
  - If(Tox-Score > Threshold) prioritize for further testing

- “Fast Biology predicts Slow Biology”

- Approach requires high quality training data
  - Bioactivity, chemical structure
  - Toxicity data
  - Both negative and positive examples

Bioactivity and Toxicity Data Types



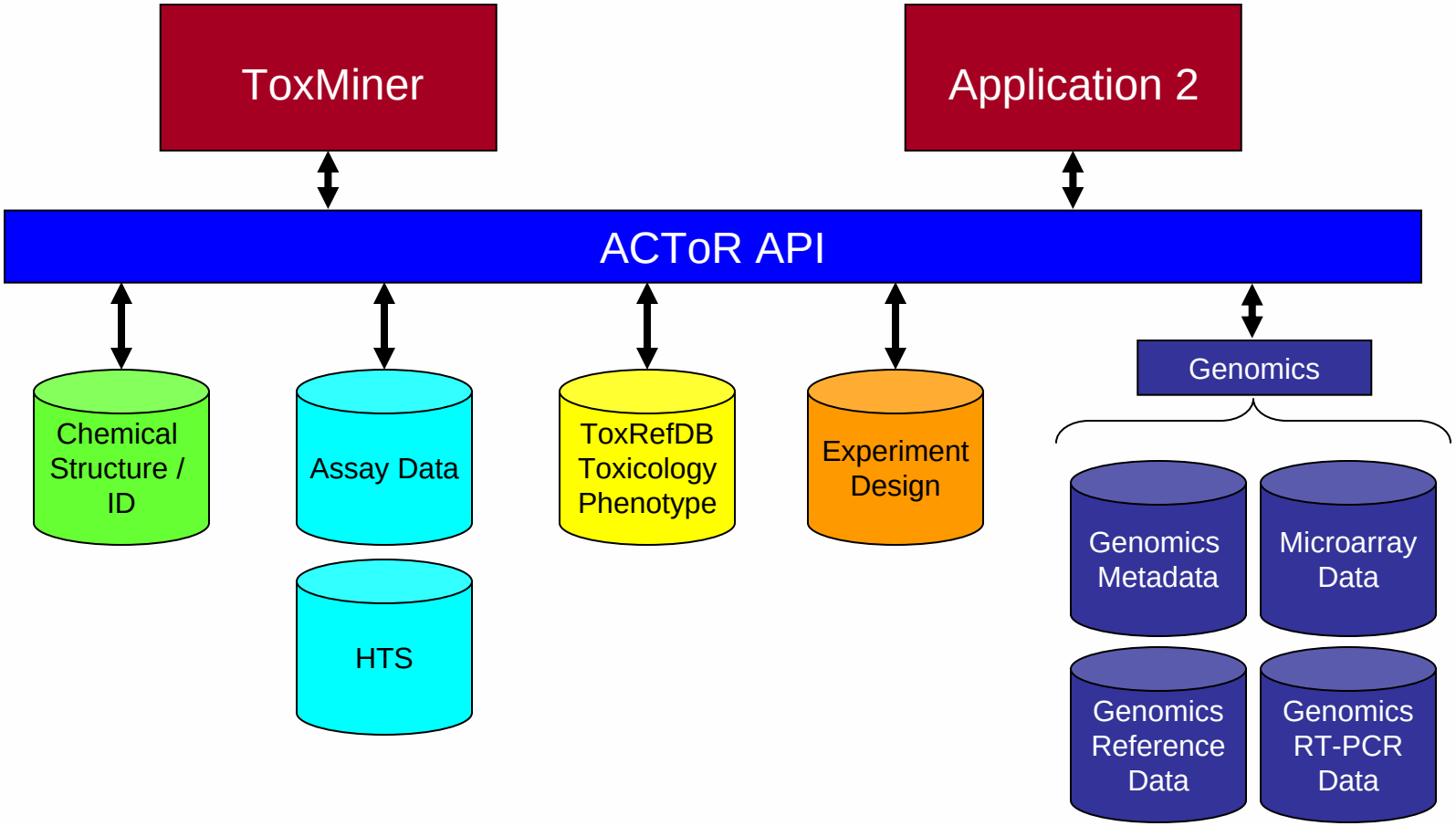
Human Relevance/
Cost/Complexity

Major Data Sources

Source	Chemicals	Data
NCBI PubChem	>17M	Chemical Structure, HTS assays
NLM Toxnet	>5,000	Databases covering toxicology, hazardous chemicals, environmental health and related areas
FDA	>1,000	Data on toxicology of drugs (genetox, repro- and developmental)
NTP	>2,000	National Toxicology Program – animal testing data
EPA ToxCast	320, 1408	Program to identify bioassay / toxicity links
EPA OPP	~800	Animal toxicology data summaries for pesticides
EPA SRS	>70,000	Links to EPA and external data sources, especially useful for regulatory categories and lists of chemicals of interest to EPA
EPA DSSTox	>10,000	Curated compilation of structure and function
Scorecard	>3,000	Compilation of toxicity data on environmental chemicals – originated by EDF

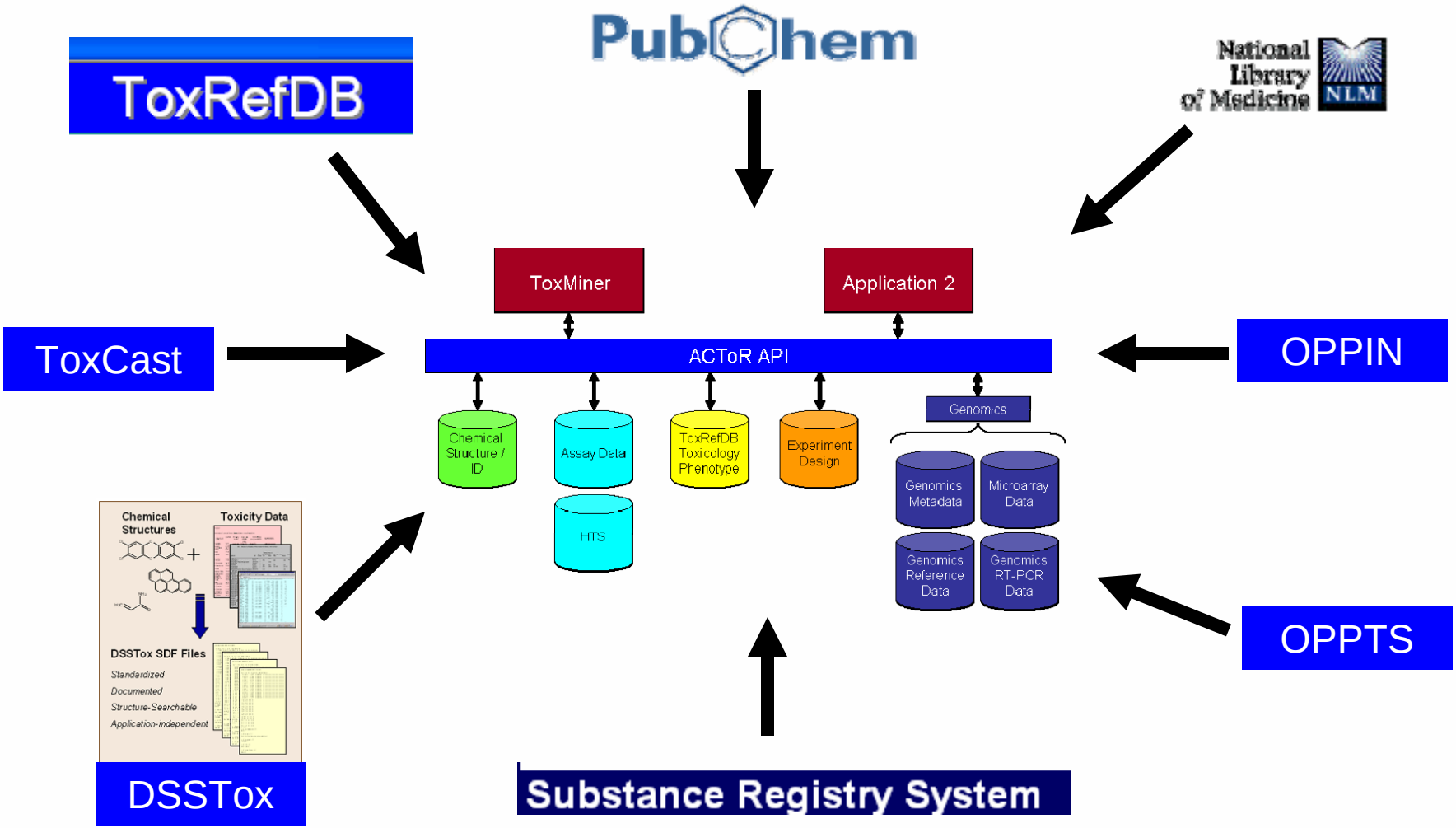
ACToR

Aggregated Computational Toxicology Resource



Addresses data needs of ToxCast and other EPA programs

ACToR Draws from Diverse Data Sources

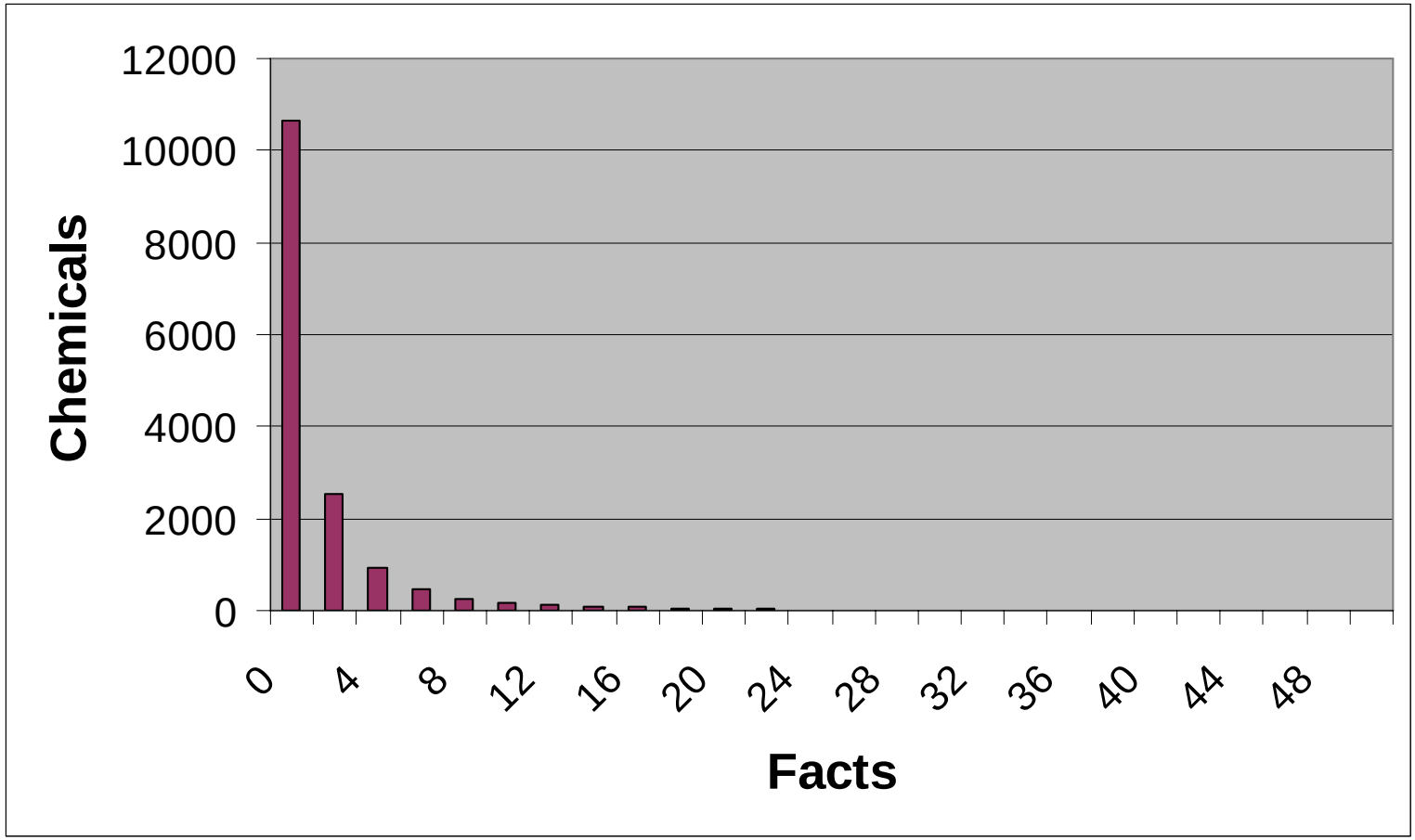


ACToR is Compiling Chemical Facts for Computational Toxicology

- Chemical Structure
- Physico-chemical properties
- Direct molecular interactions
- Pathway induction
- Cellular processes / outcomes
- Tissue / Organ effects
- Whole animal effects
- Toxicology Summaries

Tabular Data (quantitative and qualitative) (facts) on target chemicals

How Much Do We Know About the ~15,000 Target Chemicals?



Computational Toxicology Challenges

- Compile more data
  - Aggregate existing databases
  - Mine the literature
  - Get research groups to compile and submit (i.e. PubChem route)
- Generate targeted data
  - ToxCast
- Extrapolate computationally from know to unknown
  - QSAR – structure-based extrapolation
  - QBAR – bioactivity-based extrapolation
  - Modeling – PBPK to multi-scale cell and organism models
  - Understand limits to extrapolation (domain of applicability)