Tox21 Toxicology in the 21st Century

Tox21 General Meeting, October 8th, 2021

Cross-Partner Project 8:

Automation of Reference Chemical Generation

CPP8 Team

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EPA | NIH National Center for Advancing Translational Sciences | FDA U.S. FOOD & DRUG ADMINISTRATION | NTP National Toxicology Program U.S. Department of Health and Human Services

Purpose

Develop an automated process to develop lists of positive and negative *in vitro* reference chemicals for target genes and/or cell processes

Use case study targets for which to generate reference chemicals

Use only ToxCast/Tox21 data [initially no new experiments or literature review included]

A reference chemical is one that gives consistent results (active vs inactive) across multiple different assays that measure activity against a target or molecular mechanism (Judson et al, 2019)

The views expressed are those of the authors and do not necessarily represent the policies of the US EPA

Candidate Targets for Case Studies

For a candidate target to be included for generating reference chemicals, it needs to have at least 3 orthogonal assays (ideally from different source groups and using different technologies)

Gene Targets List	Gene Symbol(s)	Assay Sources
Androgen Receptor	AR	ACEA, ATG, NVS, OT, TOX21, UPITT
Estrogen Receptors	ESR1/2	ACEA, ATG, NVS, OT, TOX21
Glucocorticoid Receptor	NR3C1	ATG, NVS, TOX21
Peroxisome Proliferator Activated Receptor Gamma	PPARG	ATG, NVS, OT, TOX21
Progesterone Receptor	PGR	ATG, NVS, TOX21
Retinoic Acid Receptors	RARA/B/G	ATG, NVS, TOX21
Thyroid Hormone Receptor	TRA/B	ATG, NVS, TOX21
Tumor Protein P53	TP53	APR, ATG, TOX21

Cell Processes List	Assay Sources
Mitochondria Toxicity	APR, NCCT, NVS, TOX21
Stress Pathways	APR, ATG, TOX21

Assay Abbreviations ACEA: ACEA Biosciences, ATG: Attagene, NVS: NovaScreen, OT: Oddessy Theta, TOX21: Tox21, UPITT: University of Pittsburg, NCCT: National Center for Computational Toxicology (now CCTE)

Other Gene Targets that were considered

Excluded because there are only two assay source groups
[minimum of three sources were necessary to be included in our list]

Candidate Target List	Gene Symbol(s)	Assay Sources
Acetylcholinesterase	AChE	NVS, TOX21
Cytochrome P450 Enzymes	CYP19A1 + CYP3A4	NVS, TOX21
G-Protein Coupled Receptor	GPCR	ERF, NVS
Transforming Growth Factor Beta 1	TGFB1	ATG, BSK

Assay Abbreviations ATG: Attagene, BSK: BSK Associates, ERF: Eurofins, NVS: NovaScreen, TOX21: Tox21

Proposed Methods and Goals

Quality Control: Will start by filtering the assay data to remove cytotoxic doses

Positive reference chemicals: will need to be consistently positive in the target assays at concentrations below the burst

Negative reference chemicals: will need to be consistently negative for the target assays, but will be checked that they have positive activity in off-target assays

Results Goal: Generate at least 2+ reference chemicals per target, but 10+ reference chemicals per target would be best, with a range of potencies

Assessment of method performance:

Compare to expert-panel selected reference chemicals (ER/AR)

Conduct literature search to identify supporting or contradictory information

Proposed Methods, Continued

Two workflows to compare:

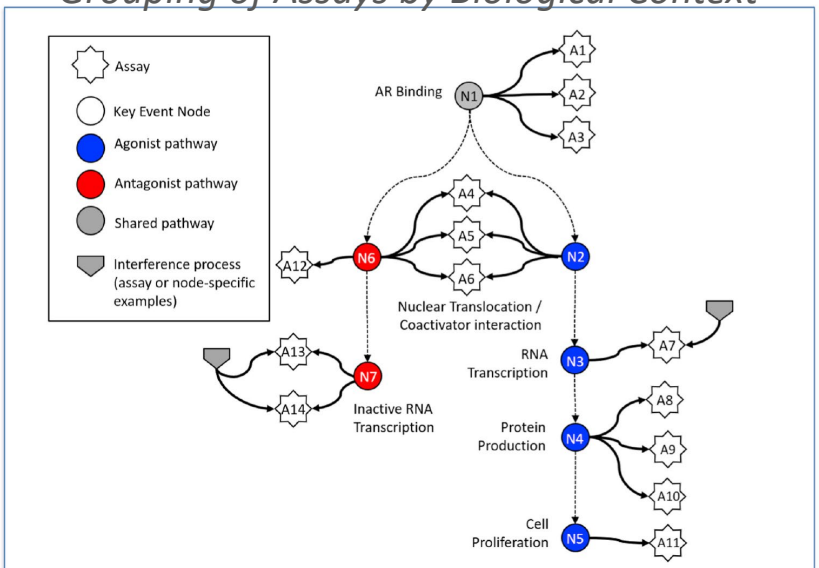
- <u>Majority rule</u>
  If the majority of assays are positive (around a similar concentration), then the chemical is deemed a reference chemical

- <u>Biological context</u>
  Use assays for different parts of the biological pathways and ensure that a chemical is activating the pathway (around a similar concentration) for it to be deemed a reference chemical

Majority rule testing workflow

Some sources have multiple assays for the target

Grouping of Assays by Biological Context



Judson, Richard, et al. "Selecting a minimal set of androgen receptor assays for screening chemicals." *Regulatory Toxicology and Pharmacology* 117 (2020): 104764.

**Similar concentration refers to concentrations within 10-fold*

Candidate Targets for Case Studies

Proposal: we will compare results when restricting the process to the most common assay sources to the findings when all assay sources are included

Gene Targets List	Gene Symbol(s)	Assay Sources
Androgen Receptor	AR	ATG, NVS, TOX21, ACEA, OT, UPITT
Estrogen Receptors	ESR1/2	ATG, NVS, TOX21, ACEA, OT
Glucocorticoid Receptor	NR3C1	ATG, NVS, TOX21
Peroxisome Proliferator Activated Receptor Gamma	PPARG	ATG, NVS, TOX21, OT
Progesterone Receptor	PGR	ATG, NVS, TOX21
Retinoic Acid Receptors	RARA/B/G	ATG, NVS, TOX21
Thyroid Hormone Receptor	TRA/B	ATG, NVS, TOX21
Tumor Protein P53	TP53	APR, ATG, TOX21

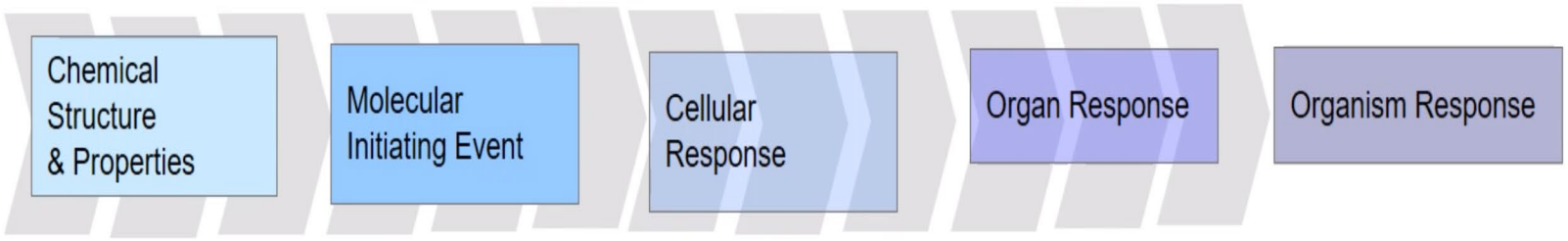
Cell Processes List	Assay Sources
Mitochondria Toxicity	APR, NVS, TOX21, NCCT
Stress Pathways	APR, ATG, TOX21

Assay Abbreviations ACEA: ACEA Biosciences, ATG: Attagene, NVS: NovaScreen, OT: Oddessy Theta, TOX21: Tox21, UPITT: University of Pittsburg, NCCT: National Center for Computational Toxicology (now CCTE)

Potential Application: Adverse Outcome Pathways (AOPs) Validation

- Screen chemicals that disrupt any part of AOP pathways to generate reference chemicals for particular adverse outcomes
- Compare list of reference chemicals with zebrafish toxicity screen results and other curated findings, such as from CPP13 for RAR AOPs

Adverse Outcome Pathway (AOP) Framework (OECD 2014)



Example AOPs for developmental defects from RAR pathway perturbation

REGION	MIE	KE1	KE2	KE3	KE4	KE5	AO
Headfold	Inhibition of CYP26A1 enzymatic activity	Local increase in endogenous ATRA levels	Hyperactivation of the RAR/RXR heterodimer	Repression of *Fgf8* limits FGF8 signaling	Mis-specification of CNC cell fate and behavior	Maxillary arch dysplasia alters palatal outgrowth	Cleft palate
Paraxial Mesoderm	Reduction in RDH/RALDH2 activity	Local decrease in endogenous ATRA levels	Hypoactivation of the RAR/RXR heterodimer	Overextension of FGF8 signaling	Disruption of the periodic somitic wavefront	Altered somite number, shape, and alignment	Hemivertebra
Limb-bud	Hyperactivation of the RAR/RXR heterodimer	Underextension FGF8 signaling from the AER	Dysregulation of *Meis1/2* and *Hox* gene expression	Proximalization of the limb-bud mesenchyme	Mis-specification of precartilage blastema	Delayed or aberrant differentiation	Phocomelia

Knudsen, Thomas B., Jocylin D. Pierro, and Nancy C. Baker. "Retinoid signaling in skeletal development: Scoping the system for predictive toxicology." *Reproductive Toxicology* 99 (2021): 109-130.

Timeline and Deliverables

Timeframe	Project progress goal
May 2021 – Dec 2021	**Selection of targets** (genes/cell processes) Determine methods and start **data analysis**
Jan 2022 – June 2022	**Data analysis**
July 2022 – Dec 2022	Write manuscript on gene/cell processes targets **Apply methods to AOPs of interest** with comparisons to zebrafish data
Jan 2023 – June 2023	**Submit manuscript for gene/cell processes targets** Write manuscript for AOP target
June 2023 – Dec 2023	**Submit manuscript for AOP application** Conclude CPP
TBD	Present work to APRCA and/or OECD

Big Picture – Benefits

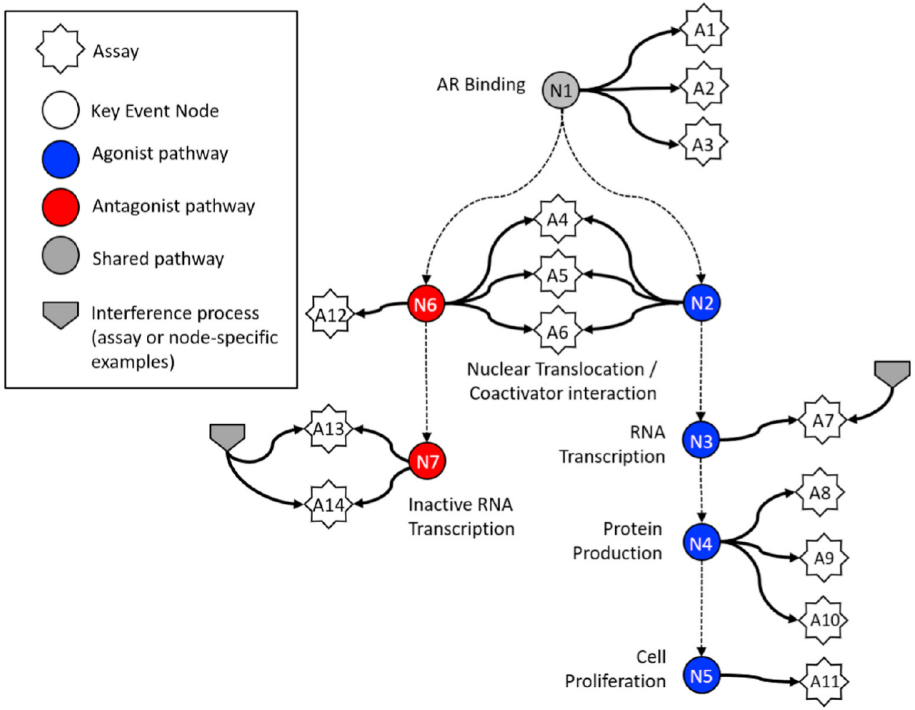
Increase speed of generating new reference chemical lists by automating the process and removing the need for upfront literature review

The list of assays and reference chemicals could be used to **validate new assays or AOPs**

Improve chemical screening abilities when assessing chemical toxicity

Comments?

Extra slides for Q&A



Judson, Richard, et al. "Selecting a minimal set of androgen receptor assays for screening chemicals." *Regulatory Toxicology and Pharmacology* 117 (2020): 104764.

Fig. 1. Diagram indicating the nodes in the AR signaling pathway associated with the assays. White stars indicate assays and correspond to the rows of Table 1. N1–N7 nodes correspond to processes in the underlying biological pathway, where blue is agonism, red is antagonism, and grey is common to both agonism and antagonism. Two representative assay interference processes are indicated, one affecting a single assay (A7) and another affecting a pair of related assays (A13 and A14). All single assays and groups of assays have their corresponding assay interference processes represented in the underlying mathematical model. See Kleinstreuer et al., 2017 for further details (Kleinstreuer et al., 2017). The strengths of these interference processes are indicated by the corresponding AUC values in Supplemental File S2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Androgen Receptor Reference Chemicals

Expert Curated List

in vitro *left image*
Kleinstreuer et al 2017

https://doi.org/10.1021/acs.chemrestox.6b00347

in vivo *right image*
Kleinstreuer et al 2018

https://doi.org/10.1016/j.reprotox.2018.08.017

Table 2. AR Pathway In Vitro Reference Chemicals

CASRN	chemical name	agonist potency category	antagonist potency category	in ToxCast 10/2015 release
52806-53-8	hydroxyflutamide	NA	strong	yes
90357-06-5	bicalutamide	NA	strong	yes
122-14-5	fenitrothion	NA	strong	yes
84371-65-3	mifepristone	NA	strong/moderate	yes
52-01-7	spironolactone	NA	strong/moderate	yes
63612-50-0	nilutamide	negative	moderate	yes
427-51-0	cyproterone acetate	weak	moderate	yes
80-05-7	bisphenol A	NA	moderate/weak	yes
330-55-2	linuron	NA	moderate/weak	yes
50471-44-8	vinclozolin	NA	moderate/weak	yes
13311-84-7	flutamide	negative	moderate/weak	yes
67747-09-5	prochloraz	negative	moderate/weak	yes
140-66-9	4-*tert*-octylphenol	NA	weak	yes
72-43-5	methoxychlor	NA	weak	yes
72-55-9	*p,p'*-DDE	NA	weak	yes
60207-90-1	propiconazole	NA	weak	yes
17924-92-4	zearalenone	NA	weak	yes
789-02-6	*o,p'*-DDT	negative	weak	yes
32809-16-8	procymidone	NA	very weak	yes
60168-88-9	fenarimol	negative	very weak	yes
58-18-4	methyl testosterone	strong	negative	yes
58-22-0	testosterone	strong	negative	propionate form
63-05-8	4-androstenedione	moderate	negative	yes
1912-24-9	atrazine	negative	negative	yes
52918-63-5	deltamethrin	negative	negative	yes
486-66-8	daidzein	NA	negative	yes
16752-77-5	methomyl	NA	negative	yes
122-34-9	simazine	NA	negative	yes
10161-33-8	17b-trenbolone	strong	NA	yes
797-63-7	levonorgestrel	strong	NA	yes
965-93-5	methyltrienolone (R1881)	strong	NA	no
68-22-4	norethindrone	strong	NA	yes
51-98-9	norethindrone acetate	strong	NA	no
76-43-7	fluoxymestrone	strong/moderate	NA	no
434-22-0	19-nortestosterone	moderate	NA	no
521-18-6	5a-dihydrotestosterone	moderate	NA	yes
10418-03-8	stanozolol	moderate	NA	no
71-58-9	medroxyprogesterone acetate	moderate/weak	NA	no
68-23-5	norethynodrel	moderate/weak	NA	no
57-91-0	17a-estradiol	negative	NA	yes
68359-37-5	b-cyfluthrin	negative	NA	yes
52315-07-8	b-cypermethrin	negative	NA	yes
17804-35-2	benomyl	negative	NA	yes
85-68-7	butylbenzyl phthalate	negative	NA	yes
10605-21-7	carbendazim	negative	NA	yes
51630-58-1	fenvalerate	negative	NA	yes
98319-26-7	finasteride	negative	NA	yes
129453-61-8	ICI 182,780	negative	NA	yes
36734-19-7	iprodione	negative	NA	yes
50-29-3	*p,p'*-DDT	negative	NA	yes
52645-53-1	permethrin	negative	NA	yes
501-36-0	resveratrol	negative	NA	no
10540-29-1	tamoxifen	negative	NA	yes
7696-12-0	tetramethrin	negative	NA	yes

Table 1

Summary of comparison between 39 chemicals with reproducible in vivo effects (green = androgenic, red = anti-androgenic, grey = negative) and results of ToxCast AR pathway model (green = agonist, red = antagonist, yellow = inconclusive, grey = negative). Abbreviations: *p,p'*-DDE = *p,p'*-dichlorodipheny chloroethylene, AUC = area under the curve (AR pathway model score), CI = confidence intervals, NA = no activity (in antagonist confirmation assa LOEL = lowest observed effect level, NOEL = no observed effect level, EAD = equivalent administered dose, ACC = activity concentration at cutoff, HCT = higl concentration tested.

Chemicals	CAS	In Vivo Reference Classification	AUC Agonist	AUC Antagonist	Antagonist Confidence Score	Confirmation Assay Flag	Overall AR Model Call	Concordance with In Vivo	HB LOEL range or NOEL (mg/kg/day)	EAD from range of in vitro ACC or HCT (mg/kg/day)
testosterone propionate	57-85-2	Androgenic	1.53	0	1	NA	Agonist	1	0.0125 – 0.25	1.6E-03 – 2
17-methyl testosterone	58-18-4	Androgenic	1.55	0	1	NA	Agonist	1	0.5 – 100	1.8E-06 – 0.4
trenbolone	10161-33-8	Androgenic	1.59	0	1	NA	Agonist	1	8 – 200	1.4E-07 – 0.8
flutamide	13311-84-7	Anti-androgenic	0	0.547	5	True antagonist shift (Hit/Hit)	Antagonist	1	0.1 – 100	0.06 – 26.1
linuron	330-55-2	Anti-androgenic	0	0.3	5	True antagonist shift (No hit/Hit)	Antagonist	1	10 – 100	0.9 – 41.3
vinclozolin	50471-44-8	Anti-androgenic	0	0.416	6	True antagonist shift (Hit/Hit)	Antagonist	1	10 – 100	1.5 – 129.8
procymidone	32809-16-8	Anti-androgenic	0	0.316	6	True antagonist shift (Hit/Hit)	Antagonist	1	3 – 100	0.7 – 57.2
p,p'-DDE	72-55-9	Anti-androgenic	0	0.251	4	True antagonist shift (No hit/Hit)	Antagonist	1	5 – 200	2.6 – 5
prochloraz	67747-09-5	Anti-androgenic	0	0.295	5	True antagonist shift (Hit/Hit)	Antagonist	1	50 – 250	0.6 – 12
finasteride	98319-26-7	Anti-androgenic	0	0	3	True antagonist shift (No hit/Hit)	Inconclusive	NA	0.008 – 25	43.6 – 787.9
propargite	2312-35-8	Anti-androgenic	0	0.187	1	FLAG: Wrong direction shift (Hit/Hit)	Inconclusive	NA	15 – 15	1.8 – 71
fenarimol	60168-88-9	Anti-androgenic	0	0.0446	4	True antagonist shift (Hit/Hit)	Inconclusive	NA	200 – 200	1.4 – 5.6
benfluralin	1861-40-1	Anti-androgenic	0	0.00012	0	NA	Inconclusive	NA	750 – 750	4.6 – 9
permethrin	52645-53-1	Anti-androgenic	0	0	0	NA	Negative	0	10 – 50	*13.2*
bis(2-ethylhexyl) phthalate (DEHP)	117-81-7	Anti-androgenic	0	0	0	NA	Negative	0	100 – 200	142.7 – 142.7
noflurazon	27314-13-2	Anti-androgenic	0	0	0	NA	Negative	0	1000 – 1000	*26.4*
ethoprop	13194-48-4	Anti-androgenic	0	0	0	NA	Negative	0	16 – 16	*333.3*
cyfluthrin	68359-37-5	Anti-androgenic	0	0	0	NA	Negative	0	18 – 50	*30.4*
iprodione	36734-19-7	Anti-androgenic	0	0	0	NA	Negative	0	200 – 200	*0.8*
pronamide	23950-58-5	Anti-androgenic	0	0	0	NA	Negative	0	200 – 200	7.7 – 7.7
trifluralin	1582-09-8	Anti-androgenic	0	0	0	NA	Negative	0	450 – 450	*10.3*
dibutyl phthalate (DBP)	84-74-2	Anti-androgenic	0	0	0	NA	Negative	0	500 – 1000	*67.4*
metolachlor	51218-45-2	Anti-androgenic	0	0	0	NA	Negative	0	500 – 500	238.6 – 427
carbofuran	1563-66-2	Negative	0	0	0	NA	Negative	1	*0.3*	*441*
oxamyl	23135-22-0	Negative	0	0	0	NA	Negative	1	*0.5*	*410.1*
esfenvalerate	66230-04-4	Negative	0	0	0	NA	Negative	1	*9*	*26.2*
2,4 -dinitrophenol	51-28-5	Negative	0	0	1	FLAG: Antagonist shift, but CI overlap	Negative	1	*10*	1.2 – 1.3
chlorpyrifos	2921-88-2	Negative	0	0	0	NA	Negative	1	*12*	10.4 – 12.1
metribuzin	21087-64-9	Negative	0	0	0	NA	Negative	1	*120*	*418.5*
metalayl	57837-19-1	Negative	0	0	1	NA	Negative	1	*375*	0.05 – 0.05
3-amino-1,2,4-triazole	61-82-5	Negative	0	0	0	NA	Negative	1	*1000*	641.9
flutolanil	66332-96-5	Negative	0	0	0	NA	Negative	1	*1000*	21.8 – 21.8
pentachloronitrobenzene (PCNB)	82-68-8	Negative	0	0	1	FLAG: Antagonist shift, but CI overlap	Negative	1	*1000*	0.3 – 4.1
methomyl	16752-77-5	Negative	0	0	3	True antagonist shift (No hit/Hit)	Inconclusive	NA	*1*	4.9E-04 – 0.7
abamectin	71751-41-2	Negative	0	0.388	1	FLAG: Wrong direction shift (Hit/Hit)	Inconclusive	NA	*5*	2.4 – 18.7
tetrachlorvinfos	22248-79-9	Negative	0	0.0315	3	FLAG: Antagonist shift, but CI overlap	Inconclusive	NA	*350*	17.9 – 70.2
folpet	133-07-3	Negative	0	0.141	1	FLAG: Wrong direction shift (Hit/Hit)	Inconclusive	NA	*800*	7.8 – 65.2
mgk-264	113-48-4	Negative	0	0.0935	2	FLAG: Antagonist shift, but CI overlap	Inconclusive	NA	*850*	2 – 7.6
chlorothalonil	1897-45-6	Negative	0	0.481	1	FLAG: Wrong direction shift (Hit/Hit)	Inconclusive	NA	*1000*	3.4 – 311.9

Estrogen Receptor Reference Chemicals

Expert Curated List

Browne et al 2015

https://doi.org/10.1021/acs.est.5b02641

Table 2. In Vitro Estrogen Receptor (ER) Agonist Reference Chemicals

CASRN	chemical name	agonist potency[a]	ToxCast ER model score
57−63−6	17α-Ethinyl estradiol	strong	1
84−16−2	*meso*-Hexestrol	strong	0.99
56−53−1	Diethylstilbestrol (DES)	strong	0.94
50−28−2	17β-Estradiol	strong	0.94
57−91−0	17α-Estradiol	moderate	1.06
53−16−7	Estrone	moderate	0.81
140−66−9	4-*tert*-Octylphenol	moderate	0.39
446−72−0	Genistein	weak	0.54
77−40−7	Bisphenol B	weak	0.49
80−05−7	Bisphenol A	weak	0.45
486−66−8	Daidzein	weak	0.44
521−18−6	5α-Dihydrotestosterone	weak	0.40
789−02−6	*o,p'*-DDT	weak	0.39
599−64−4	4-Cumylphenol	weak	0.38
143−50−0	Kepone	weak	0.17
58−18−4	17α-Methyltestosterone	very weak	0.50
520−36−5	Apigenin	very weak	0.31
72−43−5	Methoxychlor	very weak	0.25
520−18−3	Kaempferol	very weak	0.25
85−68−7	Butylbenzyl phthalate	very weak	0.18
480−40−0	Chrysin	very weak	0.13
60168−88−9	Fenarimol	very weak	0.11
104−40−5	*p-n*-Nonylphenol	very weak	0.1
120−47−8	Ethylparaben	very weak	0.1
72−55−9	*p,p'*-DDE	very weak	0.1
84−74−2	Di-*n*-butyl phthalate	very weak	0.03
115−32−2	Dicofol	very weak	0
117−81−7	Diethylhexyl phthalate	very weak	0
52−86−8	Haloperidol	inactive	0.01
52−01−7	Spironolactone	inactive	0
50−22−6	Corticosterone	inactive	0
13311−84−7	Flutamide	inactive	0
1912−24−9	Atrazine	inactive	0
32809−16−8	Procymidone	inactive	0
330−55−2	Linuron	inactive	0
50−55−5	Reserpine	inactive	0
52806−53−8	Hydroxyflutamide	inactive	0
57−30−7	Phenobarbital Sodium	inactive	0
65277−42−1	Ketoconazole	inactive	0
66−81−9	Cycloheximide	inactive	0

[a]Reference chemical potency, determined by concentration required to elicit 50% of the maximal response (AC_{50}), in low throughput in vitro ER assays.[28,29] Strong = AC_{50} < 0.0001 μM, moderate = AC_{50} < 0.1 μM, weak = AC_{50} < 1 μM, very weak = all other activities, and inactive = no detected activity.[29]

Table 3. In Vivo Estrogen Receptor (ER) Agonist Reference Chemicals with at Least Two Independent Active or Inactive Guideline-Like Uterotrophic Studies[a,14]

CASRN	name	active	inactive	bioactivity	ToxCast ER model score
57−91−0	17α-Estradiol	2	0	active	1.06
57−63−6	Ethinyl Estradiol	59	0	active	1
56−53−1	Diethylstilbestrol (DES)	8	1	active	0.94
50−28−2	Estradiol	25	0	active	0.94
474−86−2	Equilin	2	0	active	0.82
53−16−7	Estrone	9	0	active	0.81
50−27−1	Estriol	4	0	active	0.79
72−33−3	Mestranol	3	0	active	0.74
17924−92−4	Zearalenone	4	0	active	0.71
1478−61−1	Bisphenol AF	4	0	active	0.55
446−72−0	Genistein	27	1	active	0.54
68−22−4	Norethindrone	2	0	active	0.52
58−18−4	Methyltestosterone	3	0	active	0.50
77−40−7	Bisphenol B	2	0	active	0.49
80−05−7	Bisphenol A	37	6	active	0.45
104−43−8	4-Dodecylphenol	3	0	active	0.41
521−18−6	Dihydrotestosterone	3	0	active	0.4
131−55−5	Benzophenone-2	6	0	active	0.40
140−66−9	4-(1,1,3,3-Tetramethylbutyl)phenol	3	1	active	0.39
789−02−6	*o,p'*-DDT	15	1	active	0.39
599−64−4	*p*-Cumylphenol	2	0	active	0.38
5153−25−3	Benzoic acid, 4-hydroxy-, 2-ethylhexyl ester	2	0	active	0.37
80−46−6	4-(1,1-Dimethylpropyl)phenol	4	0	active	0.28
131−56−6	2,4-Dihydroxybenzophenone	3	0	active	0.27
80−09−1	Bisphenol S	2	0	active	0.26
72−43−5	Methoxychlor	18	1	active	0.25
94−26−8	Butylparaben	8	2	active	0.25
98−54−4	*p-tert*-Butylphenol	2	0	active	0.16
104−40−5	Nonylphenol	5	4	active	0.10
556−67−2	Octamethylcyclotetrasiloxane	3	0	active	0
520−18−3	Kaempferol	0	3	inactive	0.25
84−74−2	Dibutyl phthalate	0	2	inactive	0.03
84−61−7	Dicyclohexyl phthalate	0	2	inactive	0.02
84−75−3	Dihexyl phthalate	0	2	inactive	0.01
51630−58−1	Fenvalerate	0	2	inactive	0.01
103−23−1	Bis(2-ethylhexyl)hexanedioate	0	2	inactive	0
117−81−7	Bis(2-ethylhexyl)phthalate	0	2	inactive	0
1461−22−9	Tributylchlorostannane	0	2	inactive	0
1912−24−9	Atrazine	0	2	inactive	0
61−82−5	Amitrole	0	2	inactive	0
84−66−2	Diethyl phthalate	0	2	inactive	0
87−86−5	Pentachlorophenol	0	2	inactive	0
99−96−7	4-Hydroxybenzoic acid	0	2	inactive	0

[a]The numbers of guideline-like active and inactive study results are reported for each chemical.

Androgen Receptor, Example of Assays

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
ACEA_AR_agonist_AUC	ACEA	AR	androgen receptor					old
ACEA_AR_antagonist_AUC	ACEA	AR	androgen receptor					old
ACEA_AR_agonist_80hr	ACEA	AR			human	prostate	22Rv1	new
ACEA_AR_antagonist_80hr	ACEA	AR			human	prostate	22Rv1	new
ATG_AR_TRANS_up	ATG_TRANS	AR	androgen receptor	nuclear receptor ATG	human	liver	HepG2	old
NVS_NR_cAR	NVS_NR	AR	androgen receptor	nuclear receptor NVS	chimpanzee			old
NVS_NR_hAR	NVS_NR	AR	androgen receptor	nuclear receptor NVS	human			old
NVS_NR_rAR	NVS_NR	AR	androgen receptor	nuclear receptor NVS	rat	prostate		old
OT_AR_ARELUC_AG_1440	OT	AR	androgen receptor	nuclear receptor OT	chinese hamster	ovary	CHO-K1	old
OT_AR_ARSRC1_0480	OT	AR	androgen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_AR_ARSRC1_0960	OT	AR	androgen receptor	nuclear receptor OT	human	kidney	HEK293T	old
TOX21_AR_BLA_Agonist_ratio	Tox21_BLA_Agonist	AR	androgen receptor	nuclear receptor Tox21	human	kidney	HEK293T	old
TOX21_AR_BLA_Antagonist_ratio	Tox21_BLA_Antagonist	AR	androgen receptor	nuclear receptor Tox21 ant	human	kidney	HEK293T	old
TOX21_AR_LUC_MDAKB2_Agonist	Tox21_LUC_Agonist	AR	androgen receptor	nuclear receptor Tox21	human	breast	MDA-kb2	old
TOX21_AR_LUC_MDAKB2_Agonist2	Tox21_LUC_Agonist	AR	regulation of transcription factor activity	regulation of transcription factor activity				new
TOX21_AR_LUC_MDAKB2_Antagonist	Tox21_LUC_Antagonist	AR	androgen receptor	nuclear receptor Tox21 ant	human	breast	MDA-kb2	old
TOX21_AR_LUC_MDAKB2_Antagonist2	Tox21_LUC_Antagonist	AR	androgen receptor	nuclear receptor Tox21 ant	human	breast	MDA-kb2	old

ESR1/ESR2, Example of Assays

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
ACEA_ER_80hr	ACEA	ESR1	estrogen receptor	cell proliferation	human	breast	T47D	new
ACEA_T47D_80hr_Positive	ACEA	ESR1	estrogen receptor	nuclear receptor ACEA	human	breast	T47D	old
ACEA_T47D_AUC_ER_agonist	ACEA	ESR1	estrogen receptor					old
ATG_ERE_CIS_up	ATG_CIS	ESR1	estrogen receptor	nuclear receptor ATG	human	liver	HepG2	old
ATG_ERa_TRANS_up	ATG_TRANS	ESR1	estrogen receptor	nuclear receptor ATG	human	liver	HepG2	old
NVS_NR_bER	NVS_NR	ESR1	estrogen receptor	nuclear receptor NVS	bovine	uterus		old
NVS_NR_hER	NVS_NR	ESR1	estrogen receptor	nuclear receptor NVS	human			old
NVS_NR_mERa	NVS_NR	Esr1	estrogen receptor	nuclear receptor NVS	mouse			old
OT_ER_ERaERa_0480	OT	ESR1	estrogen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_ER_ERaERa_1440	OT	ESR1	estrogen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_ERa_EREGFP_0120	OT	ESR1	estrogen receptor	nuclear receptor OT	human	cervix	HeLa	old
OT_ERa_EREGFP_0480	OT	ESR1	estrogen receptor	nuclear receptor OT	human	cervix	HeLa	old
OT_ERa_ERELUC_AG_1440	OT	ESR1	estrogen receptor	regulation of gene expression	chinese hamster	ovary	CHO-K1	new
OT_ERa_ERELUC_ANT_1440	OT	ESR1	estrogen receptor	regulation of gene expression	chinese hamster	ovary	CHO-K1	new
TOX21_ERa_BLA_Agonist_ratio	Tox21_BLA_Agonist	ESR1	estrogen receptor	nuclear receptor Tox21	human	kidney	HEK293T	old
TOX21_ERa_BLA_Antagonist_ratio	Tox21_BLA_Antagonist	ESR1	estrogen receptor	nuclear receptor Tox21 ant	human	kidney	HEK293T	old
TOX21_ERa_LUC_BG1_Agonist	Tox21_LUC_Agonist	ESR1	estrogen receptor	nuclear receptor Tox21	human	ovary	BG1	old
TOX21_ERa_LUC_BG1_Antagonist	Tox21_LUC_Antagonist	ESR1	estrogen receptor	nuclear receptor Tox21 ant	human	ovary	BG1	old
OT_ER_ERaERb_0480	OT	ESR1,ESR2	estrogen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_ER_ERaERb_1440	OT	ESR1,ESR2	estrogen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_ER_ERbERb_0480	OT	ESR2	estrogen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_ER_ERbERb_1440	OT	ESR2	estrogen receptor	nuclear receptor OT	human	kidney	HEK293T	old
OT_ERb_ERELUC_ANT_1440	OT	ESR2	estrogen receptor	regulation of gene expression	chinese hamster	ovary	CHO-K1	new

PPARG

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
ATG_PPARg_TRANS_up	ATG_TRANS	PPARG	ppar signaling	nuclear receptor ATG	human	liver	HepG2	old
NVS_NR_hPPARg	NVS_NR	PPARG	ppar signaling	nuclear receptor NVS	human			old
TOX21_PPARg_BLA_Agonist_ratio	Tox21_BLA_Agonist	PPARG	ppar signaling	nuclear receptor Tox21	human	kidney	HEK293T	old
TOX21_PPARg_BLA_antagonist_ratio	Tox21_BLA_Antagonist	PPARG	ppar signaling	nuclear receptor Tox21 ant	human	kidney	HEK293	old

RAR family

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
ATG_RARa_TRANS_up	ATG_TRANS	RARA	nuclear receptor ATG	nuclear receptor ATG	human	liver	HepG2	old
NVS_NR_hRAR_Antagonist	NVS_NR	RARA	nuclear receptor NVS	nuclear receptor NVS	human			old
NVS_NR_hRARa_Agonist	NVS_NR	RARA	nuclear receptor NVS	nuclear receptor NVS	human			old
ATG_DR5_CIS_up	ATG_CIS	RARA RARB RARG	nuclear receptor ATG	nuclear receptor ATG	human	liver	HepG2	old
TOX21_RAR_LUC_Agonist	Tox21_BLA_Agonist	RARA RARG	regulation of transcription factor activity	regulation of transcription factor activity				new
TOX21_RAR_LUC_Antagonist	Tox21_LUC_Antagonist	RARA RARG	regulation of transcription factor activity	regulation of transcription factor activity				new
ATG_RARb_TRANS_up	ATG_TRANS	RARB	nuclear receptor ATG	nuclear receptor ATG	human	liver	HepG2	old
ATG_RARg_TRANS_up	ATG_TRANS	RARG	nuclear receptor ATG	nuclear receptor ATG	human	liver	HepG2	old

TGFB1

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
ATG_TGFb_CIS_up	ATG_CIS	TGFB1	inflammation up	inflammation up	human	liver	HepG2	old
BSK_BE3C_TGFb1_down	BSK_down	TGFB1	inflammation down	inflammation down	human	lung	bronchial epithelial cell	old
BSK_KF3CT_TGFb1_down	BSK_down	TGFB1	inflammation down	inflammation down	human	skin	keratinocytes and foreskin fibroblasts	old
BSK_BE3C_TGFb1_up	BSK_up	TGFB1	inflammation up	inflammation up	human	lung	bronchial epithelial cell	old
BSK_KF3CT_TGFb1_up	BSK_up	TGFB1	inflammation up	inflammation up	human	skin	keratinocytes and foreskin fibroblasts	old

TP53

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
APR_HepG2_p53Act_1h_dn	APR_dn	TP53	apoptosis down	apoptosis down	human	liver	HepG2	old
APR_HepG2_p53Act_24h_dn	APR_dn	TP53	apoptosis down	apoptosis down	human	liver	HepG2	old
APR_HepG2_p53Act_72h_dn	APR_dn	TP53	apoptosis down	apoptosis down	human	liver	HepG2	old
APR_HepG2_p53Act_24h_up	APR_up	TP53	apoptosis up	apoptosis up	human	liver	HepG2	old
APR_HepG2_p53Act_72h_up	APR_up	TP53	apoptosis up	apoptosis up	human	liver	HepG2	old
APR_HepG2_p53Act_1h_up	APR_up	TP53	apoptosis up (remove)	apoptosis up	human	liver	HepG2	old
ATG_p53_CIS_up	ATG_CIS	TP53	apoptosis up (remove)	apoptosis up	human	liver	HepG2	old
TOX21_p53_BLA_p1_ratio	Tox21_BLA_Agonist	TP53	apoptosis up	apoptosis up	human	intestinal	HCT116	old
TOX21_p53_BLA_p2_ratio	Tox21_BLA_Agonist	TP53	apoptosis up	apoptosis up	human	intestinal	HCT116	old
TOX21_p53_BLA_p3_ratio	Tox21_BLA_Agonist	TP53	apoptosis up	apoptosis up	human	intestinal	HCT116	old
TOX21_p53_BLA_p4_ratio	Tox21_BLA_Agonist	TP53	apoptosis up	apoptosis up	human	intestinal	HCT116	old
TOX21_p53_BLA_p5_ratio	Tox21_BLA_Agonist	TP53	apoptosis up	apoptosis up	human	intestinal	HCT116	old

Stress pathways, Example of Assays

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
APR_HepG2_OxidativeStress_1h_dn	APR_dn		oxidative stress down	oxidative stress down	human	liver	HepG2	old
APR_HepG2_OxidativeStress_24h_dn	APR_dn		oxidative stress down	oxidative stress down	human	liver	HepG2	old
APR_HepG2_OxidativeStress_72h_dn	APR_dn		oxidative stress down	oxidative stress down	human	liver	HepG2	old
APR_HepG2_StressKinase_1h_dn	APR_dn		oxidative stress down	oxidative stress down	human	liver	HepG2	old
APR_HepG2_StressKinase_24h_dn	APR_dn		oxidative stress down	oxidative stress down	human	liver	HepG2	old
APR_HepG2_StressKinase_72h_dn	APR_dn		oxidative stress down	oxidative stress down	human	liver	HepG2	old
APR_HepG2_OxidativeStress_24h_up	APR_up		oxidative stress up	oxidative stress up	human	liver	HepG2	old
APR_HepG2_OxidativeStress_72h_up	APR_up		oxidative stress up	oxidative stress up	human	liver	HepG2	old
APR_HepG2_OxidativeStress_1h_up	APR_up		oxidative stress up (remove)	oxidative stress up	human	liver	HepG2	old
APR_HepG2_StressKinase_1h_up	APR_up		oxidative stress up (remove)	oxidative stress up	human	liver	HepG2	old
APR_HepG2_StressKinase_24h_up	APR_up		oxidative stress up (remove)	oxidative stress up	human	liver	HepG2	old
APR_HepG2_StressKinase_72h_up	APR_up		oxidative stress up (remove)	oxidative stress up	human	liver	HepG2	old
TOX21_ESRE_BLA_ratio	Tox21_BLA_Agonist	ATF6	ER stress	ER stress	human	cervix	HeLa	old
ATG_MRE_CIS_up	ATG_CIS	MTF1	oxidative stress up (remove)	oxidative stress up	human	liver	HepG2	old
ATG_NRF2_ARE_CIS_up	ATG_CIS	NFE2L2	oxidative stress up	oxidative stress up	human	liver	HepG2	old
ATG_NRF1_CIS_up	ATG_CIS	NRF1	oxidative stress up	oxidative stress up	human	liver	HepG2	old
ATG_SREBP_CIS_up	ATG_CIS	SREBF1	ER stress	ER stress	human	liver	HepG2	old
ATG_Xbp1_CIS_up	ATG_CIS	XBP1	ER stress	ER stress	human	liver	HepG2	old

Mitochondria, Example of Assays

assay	source_group	intended_target	biological_process	biological_process_2	organism	tissue	cell_short_name	version
APR_HepG2_MitoMass_1h_dn	APR_dn		mitochondrial disruption down	mitochondrial disruption down	human	liver	HepG2	old
APR_HepG2_MitoMass_24h_dn	APR_dn		mitochondrial disruption down	mitochondrial disruption down	human	liver	HepG2	old
APR_HepG2_MitoMass_72h_dn	APR_dn		mitochondrial disruption down	mitochondrial disruption down	human	liver	HepG2	old
APR_HepG2_MitoMembPot_1h_dn	APR_dn		mitochondrial disruption down	mitochondrial disruption down	human	liver	HepG2	old
APR_HepG2_MitoMembPot_24h_dn	APR_dn		mitochondrial disruption down	mitochondrial disruption down	human	liver	HepG2	old
APR_HepG2_MitoMembPot_72h_dn	APR_dn		mitochondrial disruption down	mitochondrial disruption down	human	liver	HepG2	old
APR_Hepat_MitoFxnI_1hr_dn	APR_hepat_dn		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_1hr_MEAN_dn	APR_hepat_dn		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_24hr_dn	APR_hepat_dn		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_24hr_MEAN_dn	APR_hepat_dn		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_48hr_dn	APR_hepat_dn		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_48hr_MEAN_dn	APR_hepat_dn		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_1hr_MEAN_up	APR_hepat_up		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_1hr_up	APR_hepat_up		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_24hr_MEAN_up	APR_hepat_up		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_24hr_up	APR_hepat_up		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_48hr_MEAN_up	APR_hepat_up		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_Hepat_MitoFxnI_48hr_up	APR_hepat_up		mitochondrial depolarization	mitochondrial depolarization	rat	liver	hepatocyte	new
APR_HepG2_MitoMass_24h_up	APR_up		mitochondrial disruption up	mitochondrial disruption up	human	liver	HepG2	old
APR_HepG2_MitoMass_72h_up	APR_up		mitochondrial disruption up	mitochondrial disruption up	human	liver	HepG2	old
APR_HepG2_MitoMass_1h_up	APR_up		mitochondrial disruption up (remove)	mitochondrial disruption up	human	liver	HepG2	old
APR_HepG2_MitoMembPot_1h_up	APR_up		mitochondrial disruption up (remove)	mitochondrial disruption up	human	liver	HepG2	old
APR_HepG2_MitoMembPot_24h_up	APR_up		mitochondrial disruption up (remove)	mitochondrial disruption up	human	liver	HepG2	old
APR_HepG2_MitoMembPot_72h_up	APR_up		mitochondrial disruption up (remove)	mitochondrial disruption up	human	liver	HepG2	old
NVS_ENZ_rMAOAC	NVS_ENZ	Maoa	mitochondrial disruption up	enzyme blocking	rat	brain		old
NVS_ENZ_rMAOAP	NVS_ENZ	Maoa	mitochondrial disruption up	enzyme blocking	rat	liver		old
NVS_ENZ_rMAOAC_Activator	NVS_ENZ_Activator	Maoa	mitochondrial disruption down	enzyme anti-blocking	rat	brain		old
NVS_ENZ_rMAOAP_Activator	NVS_ENZ_Activator	Maoa	mitochondrial disruption down	enzyme anti-blocking	rat	liver		old
NVS_ENZ_rMAOBC	NVS_ENZ	Maob	mitochondrial disruption up	enzyme blocking	rat	brain		old
NVS_ENZ_rMAOBP	NVS_ENZ	Maob	mitochondrial disruption up	enzyme blocking	rat	brain		old
NVS_ENZ_rMAOBC_Activator	NVS_ENZ_Activator	Maob	mitochondrial disruption down	enzyme anti-blocking	rat	brain		old
NVS_ENZ_rMAOBP_Activator	NVS_ENZ_Activator	Maob	mitochondrial disruption down	enzyme anti-blocking	rat	brain		old
TOX21_MMP_ratio_down	Tox21_BLA_Agonist		mitochondrial disruption down					old
Tox21_MitochondrialToxicity_ratio	Tox21_BLA_Agonist		mitochondrial disruption up	mitochondrial disruption up	human	liver	HepG2	old
TOX21_MMP_ratio_up	Tox21_BLA_Agonist		mitochondrial disruption up					old
NVS_MP_hPBR	NVS_MP	TSPO	mitochondrial disruption up	mitochondrial disruption up	human	intestinal		old
NVS_MP_rPBR	NVS_MP	Tspo	mitochondrial disruption up	mitochondrial disruption up	rat	kidney		old
TOX21_MMP_fitc	Tox21_LUC_Agonist		mitochondrial depolarization	mitochondrial depolarization	human	liver	HepG2	new
TOX21_MMP_rhodamine	Tox21_LUC_Agonist		mitochondrial depolarization	mitochondrial depolarization	human	liver	HepG2	new