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Supplemental Material

Screening for Chemical Contributions to Breast Cancer Risk: A Case Study for Chemical Safety Evaluation

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Keywords for searches of assays in Tox21 and ToxCast

Searches were case insensitive
Keywords in the same group are separated by

genotoxicity:
mutation|chromosome|chromosomal|micronuclei|micronucleus|adduct|repair|genotox
proliferative signaling: autocrine|growth factor|TGF|insulin|prolifer|EGFR
limitless replication: immortal|telome
invading apoptosis: apoptosis|apopto|BH3
avoiding immune destruction: immune
tumor promoting inflammation: inflamm|sensitization
angiogenesis: angiogenesis|blood vessel|vascul|VEGF|VCAM
energy regulation: energy|hypoxia|mitochondri|glycolysis
metastasis and invasion: metastasis|chemotaxis|cell
adhesion|differentiation|migration|motility|invasion|HGF
growth suppression: suppressor|suppression|CDK|contact

estrogen: estrogen|estradiol|estriol|estrone
steroidogenesis: steroido|HSD|estrone sulfatase|hydroxysteroid dehydrogenase
AHR: ahr|aryl hydrocarbon
aromatase: aromatase|CYP19|CYP-19|CYP 19
androgen: androgen|testosterone|_AR_
thyroid: thyroid
progesterone: progesterone|progestin|progestagen|progestogen|pregnenolone
Her2: Her2|neu |cd340|P185|erbb2

breast: breast|mammary|MCF|MDA-kb2|T47D

cell cycle regulation: cell cycle|mitosis
xenobiotic metabolism:
xenobiotic|monooxygenase|oxidoreductase|transporter|glucuronosyltransferase
oxidative stress: oxidative

Table S1. Assays from ToxCast, Tox21, and the EPA Endocrine Disruptor Screening Program that Target Breast Cancer-Relevant Endpoints.

		ToxCast/Tox21		EDSP
Category	Endpoint/pathway	Assays [a]	In/from breast cells[b]	System
Steroid hormones	Estrogen receptor α	receptor binding/ dimerization/ transcriptional activity; proliferation in estrogen dependent breast cells	yes	in vitro and in vivo
	Estrogen receptor β	*protein dimerization (no receptor binding or transcriptional activity assays)*		[c]
	Androgen receptor	receptor binding/ coactivator recruitment/ transcriptional activity	yes	in vitro and in vivo
	Progesterone receptor	*receptor binding (no transcriptional activity assays)*	yes	
	Aromatase	*inhibition/activity (no expression assays)*	yes	in vitro
	Estrogen metabolism	CYP, SULT, other enzyme activity		
	Steroidogenesis (other)	steroid intermediate levels		in vitro
Other molecular targets involved in endocrine signaling and development	Thyroid receptor	receptor transcriptional activity/ binding		in vivo
	Thyroid (other)	--		
	Her2	--		
	Estrogen-related receptor	*receptor transcriptional activity (no reference compound)*		[c]
	Aryl hydrocarbon receptor	transcriptional activity		
	Prolactin	--		
	Growth factors	growth factor/cytokine (e.g. TGFb, IFN-g) expression; GF receptor (e.g. EGFR) kinase activity and expression [d]		
	PPAR (α, γ, δ)	receptor transcriptional activity/binding		
	ROR	transcriptional activity		
	Epigenetic programming	*histone deacetylation inhibition, mitochondrial function (few or no assays for other epigenetic endpoints)*		
Carcinogenesis	Genotoxicity	*p53, GADD45A levels; HCS DNA damage/ texture (no assays with consistent relationship to standard genotoxicity tests); cytotoxicity in DNA repair deficient cell lines; ATAD5*		
	Inflammation	CEPB, NF-KB activity; OPRL1, P2RY1 binding; CD 40, TNFa, cytokine (e.g. IL1a, IL8,cxcl9, cxcl10, ccl2) levels [d]		
	Xenobiotic metabolizing enzymes	CYP, SULT, UGT, other enzyme activity/expression [d]		
	Cellular stress (including oxidative)	transcriptional activity of stress-related proteins; HCS pH2AX; HCS pcJun [d]		
Other hallmarks of cancer	Evading growth suppressors	p53 levels; HCS pcJun; p38 inhibition [d]		
	Angiogenesis	HIF1a reporter gene assay; proliferation, vascular cell adhesion module (VCAM) in vascular cells; plasmogen activator-related protein (e.g. PLAT, PLAU, PLAUR, SERPINE, THBD) levels [d]		
	Cell cycle changes	mitotic arrest/cell cycle arrest; cell cycle related gene expression	yes	
	Activating tissue invasion and metastasis	cell adhesion/extracellular matrix-related (e.g. ICAM, VCAM, MMP1, PLAT) protein levels; PDE5A activation/inhibition, PPARa/PPARg binding, transcriptional activity [d]		
	Avoiding immune destruction	TCF/b-cat (T-cell specific) transcriptional activity; ISRE transcriptional activity; NF-kB transcriptional activity; proliferation, cytotoxicity, and protein levels in peripheral blood mononuclear cells [d]		
	Evading apoptosis	HCS apoptosis assays; caspase, PDE5, AR inhibition/activity; MYC, p53 protein levels [d]	yes	
	Replicative immortality	--[e]		
Mammary gland development	Morphology	--[f, g]		
	AR, ER in developing MG	--[f]		
Other organism-level endocrine effects	Reproductive development (e.g. AGD, nipple retention, pubertal timing)	--[f]		in vivo
	Circulating hormone levels	--[f]		in vivo

Italics indicate that there is an assay related to the endpoint, but that there are also some gaps.

[a] Several assays in ToxCast provide information about multiple cancer hallmarks; important assays may not be listed under every relevant pathway if they are listed elsewhere in this table.
[b] Indicates if any assays in the category are performed in breast cells, or in the case of cell free assays, using components derived from breast cells.
[c] In vivo estrogenicity tests may reflect some activity from these alternate receptors.
[d] Kleinstreuer et al. (2013) mapped many additional assays to these processes based on target genes' inclusion in Gene Ontology categories matching keywords related to the hallmarks of cancer.
[e] Kleinstreuer et al. (2013) list SIRT2 (involved in chromatin silencing at the telomere) under limitless replication/telomerase.
[f] No in vitro tests exist for these organ and organism-level endpoints, although validated in vivo tests are available.
[g] Protocols for evaluating the morphology of the developing mammary gland are available from the OECD (2008) and have been discussed by Rudel et al. (2011).

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