Evaluating the applicability of read-across tools and high throughput screening data for food relevant chemicals

Jalissa Wynder[1,5], Jerald Ovesen[2], Andrew Maier[2], Richard Judson[3], Nicole Kleinstreuer[4], Mansi Krishan[5]

[1]Molecular and Environmental Toxicology Center, University of Wisconsin, Madison, WI; [2]Department of Environmental Health, University of Cincinnati, Cincinnati, OH; [3]U.S. Environmental Protection Agency, Research Triangle Park, NC; [4]NIEHS, NICEATM, Durham, NC; [5]International Life Sciences Institute (ILSI) North America, Washington, DC

Background

Alternative toxicity methods to characterize the hazards of chemical substances have been proposed to reduce animal testing and efficiently screen thousands of chemicals. Relevant resources include large in vitro datasets from efforts such as the high-throughput screening (HTS) Tox21/ToxCast programs and read-across tools such as the Organization for Economic and Cooperation Development (OECD) QSAR toolbox. The goal of this work is to compare the result from traditional toxicity studies with predictions from these alternative testing methods for food relevant chemicals in ToxCast. We used computational models developed using Tox21/ToxCast high-throughput screening (HTS) data to predict the activity of food relevant chemicals against the estrogen receptor (ER) and androgen receptor (AR) pathways.

Experimental outline

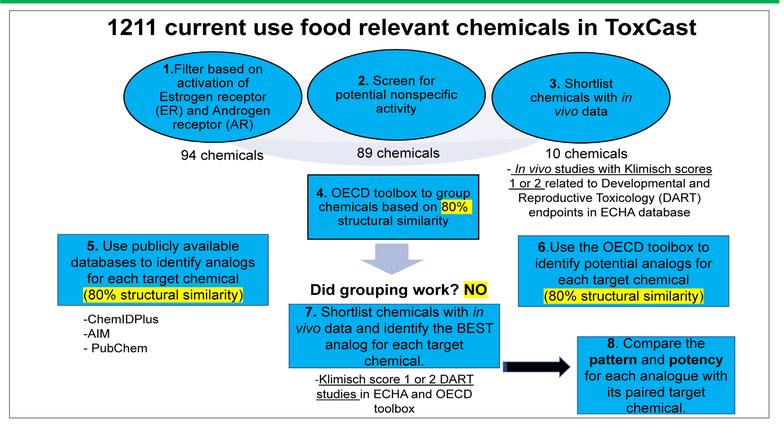


Figure 1. Experimental outline

1.We identified 94 putatively active estrogen-or androgen-active food relevant chemicals in ToxCast.

2.To reduce possible confounding from cytotoxicity and cell stress, the ER and AR model results were filtered based on observed *in vitro* cytotoxicity, which resulted in 89 putatively active, non-cytotoxic food relevant chemicals.

3.We further shortlisted the 89 putatively active, non-cytotoxic food relevant chemicals, based on the availability of *in vivo* data related to developmental and reproductive toxicity (DART).

4.This resulted in 10 putatively active, non-cytotoxic, DART related chemicals. Next, we compared the results from traditional toxicity studies with predictions from these alternative toxicity methods for food relevant chemicals in ToxCast.

Expanded methodology

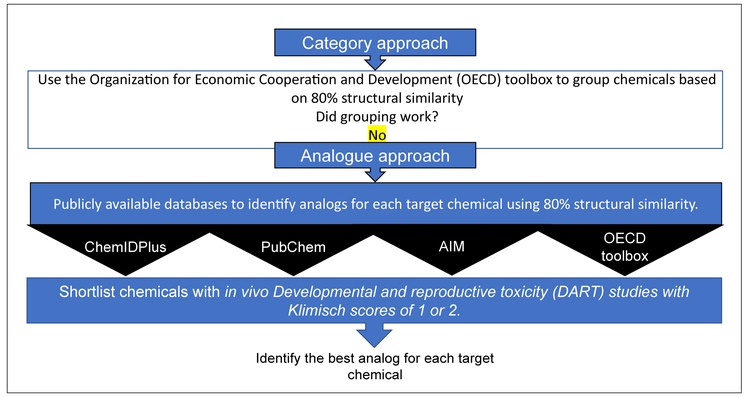


Figure 2. Proof of concept study

Structural similarity and similar mode of action were used to identify potential analogues for the 10 chemicals.

Results

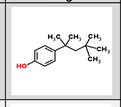
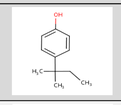
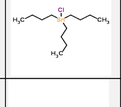
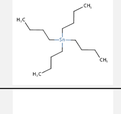
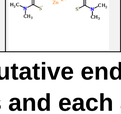
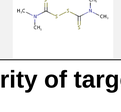
Target chemical name	Target chemical image	Food relevancy (*Karmaus et al. 2017*)	Classification from HTS computational models	Best analogue	% Similarity	Analogue images
1. 4-tert-octylphenol		Indirect food additive	ER agonist/AR antagonist	**4-tert-pentylphenol**	not indicated	
2. Tributyltin chloride		Indirect food additive	ER antagonist/AR antagonist	**Tetrabutyltin**	86.7	
3. Ziram		Pesticide residue	AR antagonist	**Thiram**	80	

Table 1. Putative endocrine activity and structural similarity of target chemicals and each analogue

Conclusions and future directions

- Using structural similarity and high quality *in vivo* data related to DART endpoints as our primary criteria, we identified 8 target chemicals for which the analogue approach could be employed.
- •In terms of DART endpoints, the analogue approach helped predict the potential endocrine activity of 3 out of 8 target chemicals.
- This study demonstrates that Tox21/ToxCast HTS assay data can be used for prioritization along with weight of evidence from read-across tools to evaluate food relevant chemicals, although the limitations in the approaches are evident

Results

	CASRN	Chemical name	% similarity	Similar Tox endpoints	Relative potency
1	**140-66-9**	**4-(1,1,3,3-Tetramethylbutyl) phennol**	**target**	acute toxicity	The analogue is more potent
	80-46-6	p-(1,1-dimethylpropyl) phenol	no indicated		
2	**1461-22-9**	**Tributyltin chloride**	**target**	acute toxicity, repeat dose tox, and sensitization	The target is more potent but they share similar potencies in other categories
	1461-25-2	Tetrabutyltin	86.7		
3	**137-30-4**	**Ziram**	**target**	irritation/corrosive, acute toxicity, sensitization	The target is more potent but they share similar potencies in other categories
	137-26-8	Thiram	80		

Table 2. High quality *in vivo* data for each target chemicals and its respective analogue

	CASRN	Chemical name	% similarity	Similar DART endpoints	Relative potency	H code DART classification
1	**140-66-9**	**4-(1,1,3,3-Tetramethylbutyl) phennol**	**target**	DART	similar potency	none
	80-46-6	p-(1,1-dimethylpropyl) phenol	no indicated			
2	**1461-22-9**	**Tributyltin chloride**	**target**	additional study details required	n/a	Repro. 1B H360
	1461-25-2	Tetrabutyltin	86.7			Repro. 1B H360; Repro. 2 H361
3	**137-30-4**	**Ziram**	**target**	DART	more potent	none
	137-26-8	Thiram	80			
H360: may damage fertility or unborn child; H361: suspected of damaging fertility or unborn child						

Table 3. Comparison of DART potencies for each target chemical and its respective analogue

Acknowledgments

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