Evaluation of Estrogenic Activity of Extractables reported in Cardiovascular Medical Device Submissions

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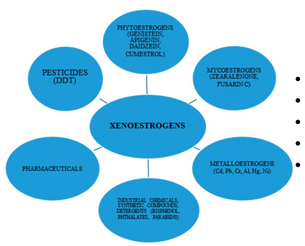
Abstract

There are increasing concerns about potential adverse effects from exposure to endocrine-active chemicals released from medical devices. ToxCast/Tox21 high-throughput screening (HTS) in vitro assays measuring perturbations in the Estrogen Receptor (ER) pathway are useful tools for identifying chemicals that have the potential to exert estrogenic activity. However, as of our knowledge, analysis of the estrogenicity profile of medical device relevant chemicals using ToxCast/Tox21 assay data has not yet been performed. The purpose of this research is to identify estrogen-active extractables reported in cardiovascular medical device submissions using ToxCast/Tox21 ER assays and predictions from in silico models trained on ToxCast/Tox21 ER assay data (i.e., Collaborative Estrogen Receptor Activity Prediction Project (CERAPP)). Organic chemicals reported in medical device extracts across 92 cardiovascular medical device submissions were obtained from the CDRH Image2000 database. Chemical identity (i.e., a CASRN) was provided for 4820 organic extractables, which correspond to 2125 unique chemicals. ToxCast/Tox21 ER agonist assay data and/or CERAPP predictions were identified for 807 out of the 2125 chemicals (38%). Of the 807, a total of 213 chemicals (26.4%) were active in at least one (1) ToxCast/Tox21 ER assay or predicted to be ER agonists by the CERAPP model. We further applied cytotoxicity and percentage activity filters across tested ToxCast/Tox21 assays and identified a subset of 92 chemicals that are more likely to be estrogen-active, based on activity in ≥ 50% ToxCast/Tox21 ER assays and/or ER agonist predictions by the CERAPP model. These data indicate that ToxCast/Tox21 ER in vitro assay data and predictions from the CERAPP model can be useful tools for screening estrogenic activity of extractables that are reported in medical device submissions, and possibly serve as an additional source of toxicological information for sponsors and regulators in medical device biological evaluations.

Introduction

- **Xenoestrogens** are exogenous chemicals or mixture of chemicals that interact with the estrogen receptor (ER) and mimic or block the action of endogenous estrogens.



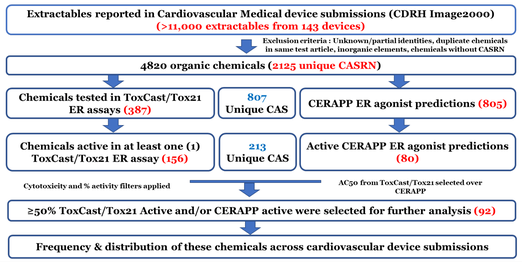
ADVERSE HEALTH OUTCOMES

- **Developmental defects**
- **Reproductive dysfunction**
- **Behavioral changes**
- **Metabolic dysfunction**
- **Susceptibility to disease (e.g., cancer)**

- Xenoestrogens are reported to migrate from medical devices manufactured with diverse materials.[1]
- Tools for screening estrogenic activity of chemicals:
  - **ToxCast/Tox21 assays:** High throughput screening (HTS) in vitro assays and computational approaches to identify, prioritize, and evaluate chemical safety.[2]
  - **Collaborative Estrogen Receptor Activity Prediction Project (CERAPP):** Computational models for prediction of ER activity trained on ToxCast/Tox21 ER assay data. CERAPP predictions are available for 32,000 chemical structures covering a broad range of chemical and product classes.[3]
- **Aim: Investigate the occurrence of xenoestrogens across cardiovascular medical device submissions using ToxCast/Tox21 ER assays and CERAPP agonist model predictions.**

Methods

Simplified schematic of the strategy



- CDRH Image2000 searches:
  - Search term: "toxicological risk assessment"; Medical Specialty: Cardiovascular (CV)
  - Chemical identity, CASRN, and quantity reported per device (µg/device) captured
- Quantity reported per device (µg/device) was used to calculate chemical concentration in the blood (µM) based on the assumption of bolus release and homogeneous distribution in the blood volume of an adult female:

$$\text{Concentration}(\mu M) = \left(\frac{\text{Reported quantity } (\mu g/\text{device})}{\text{M.W.} \times \text{Average Female Blood Volume (4.5L)}}\right)$$

- Chemical concentration in blood compared to median AC50 and AC10 values obtained from 24 ToxCast/Tox21 ER assays or CERAPP agonist model predictions (See Figure 2).

Results

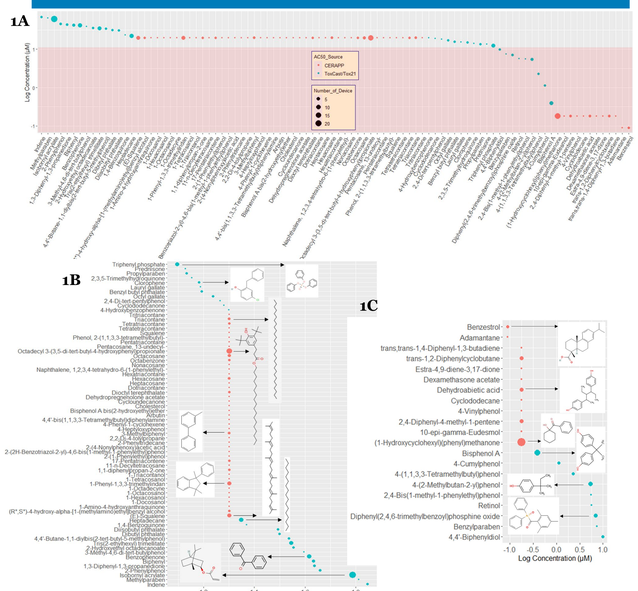


Figure 1A. 92 chemicals that are active in ≥50% ToxCast/Tox21 assays and/or CERAPP active; 1B. Lower potency: AC50 > 10 µM with representative chemicals ; 1C. Higher potency: AC50 ≤ 10 µM with representative chemicals.

The 92 estrogen-active chemicals were reported across 82 cardiovascular medical devices corresponding to 38 different FDA product codes.

Results

Chemical Name	CASRN	# Submissions	# Extracted Devices	# FDA Product Codes*
Isobornyl acrylate	5888-33-5	18	23	11 (DQX, DRS, KRA, KRD, MJN, NIP, NIQ, NKM, NPT, PNJ, PQK)
(1-Hydroxycyclohexyl)(phenyl)methanone	947-19-3	16	17	11 (DRS, DSQ, FPA, KRA, KRD, MIH, MJH, NKM, NPT, PNJ, PQK)
Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	2082-79-3	13	14	13 (DSQ, DYB, FPA, KRA, LWS, MJN, MWH, MXC, NIK, NIP, NKE, NKM, NPT)
Benzophenone	119-61-9	5	9	2 (DSQ, LOX)
Heptadecane	629-78-7	7	8	6 (DSQ, DSY, DXY, LWQ, MIH, NKM)
Tris(2-ethylhexyl) trimellitate	3319-31-1	7	7	7 (DRS, FPA, KFM, KRA, LPB, LWQ, NPT)
Bisphenol A	80-05-7	7	7	7 (DRS, DYB, KRA, LWS, MIH, MXC, OCM)
(E)-Squalene	111-02-4	6	6	5 (LWQ, LWS, MWH, NKM, NPT)
Triphenyl phosphate	115-86-6	6	6	6 (FPA, KRA, LWQ, LWS, NIK, NKE)
1-Phenyl-1,3,3-trimethylindan	3910-35-8	6	6	2 (DSQ, LWP)
Biphenyl	92-52-4	2	4	1 (LWQ)
4-(2-Methylbutan-2-yl)phenol	80-46-6	4	4	4 (DQY, DRS, LWQ, PQK)
Octacosane	630-02-4	3	4	3 (FPA, LDF, NKM)
Dehydroabietic acid	1740-19-8	3	3	3 (DSQ, LWQ, NKM)
Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	75980-60-8	2	3	1 (MUQ)
3-Methylbiphenyl	643-93-6	1	3	1 (MCW)
1,3-Diphenyl-1,3-propanedione	120-46-7	2	3	2 (KRA, NIQ)
trans-1,2-Diphenylcyclobutane	20071-09-4	3	3	3 (FPA, MXC, OCM)
2-Phenylphenol	90-43-7	3	3	3 (DTB, LWQ, PQK)
Hexacosane	630-01-3	2	3	2 (LDF, NKM)
Triacontane	638-68-6	2	3	2 (LDF, NKM)
2,4-Diphenyl-4-methyl-1-pentene	6362-80-7	2	3	2 (DSQ, LWQ)
Octyl gallate	1034-01-1	2	2	1 (NPT)
Indene	95-13-6	2	2	2 (KFM, MCW)
Propylparaben	94-13-3	2	2	2 (LWR, MWH)
4,4'-Biphenyldiol	92-88-6	2	2	1 (MIH)
4,4'-Butane-1,1-diylbis(2-tert-butyl-5-methylphenol)	85-60-9	2	2	1 (MIH)
1,1-diphenylpropan-2-one	781-35-1	2	2	1 (MIH)
4-Cumylphenol	599-64-4	2	2	2 (MXC, ONU)
4-(1,1,3,3-Tetramethylbutyl)phenol	140-66-9	2	2	2 (DQY, DRS)
Dibutyl phthalate	84-74-2	2	2	2 (DRS, LWS)
Benzestrol	85-95-0	2	2	2 (DQY, DRS)
Dioctyl terephthalate	4654-26-6	2	2	2 (DSY, MIH)
2-Hydroxyethyl octadecanoate	111-60-4	1	2	1 (DQY)
Octabenzone	1843-05-6	2	2	1 (ONU)
Clorophene	120-32-1	2	2	2 (DTB, LWQ)
Tetratriacontane	14167-59-0	2	2	2 (LWQ, NKM)
17-Pentatriacontene	6971-40-0	2	2	2 (LWQ, NKM)
(R*,S*)-4-hydroxy-alpha-[1-(methylamino)ethyl]benzyl alcohol	365-26-4	1	2	1 (NIQ)
Diisobutyl phthalate	84-69-5	2	2	2 (DXY, PNJ)
Benzyl butyl phthalate	85-68-7	2	2	2 (DSQ, DXY)

*https://www.fda.gov/medical-devices/classify-your-medical-device/download-product-code-classification-files

Table 1. Most frequently reported estrogen-active extractables across devices. A total of 41 estrogen-active extractables, reported at least twice across devices, are shown. Higher potency chemicals (AC50 ≤ 10 µM) are highlighted in red.

41 out of the 92 estrogen-active chemicals are reported at least twice across 76 devices and 35 FDA product codes. Devices classified under FDA product codes LWQ, NKM, NPT contain higher number of estrogen-active chemicals.

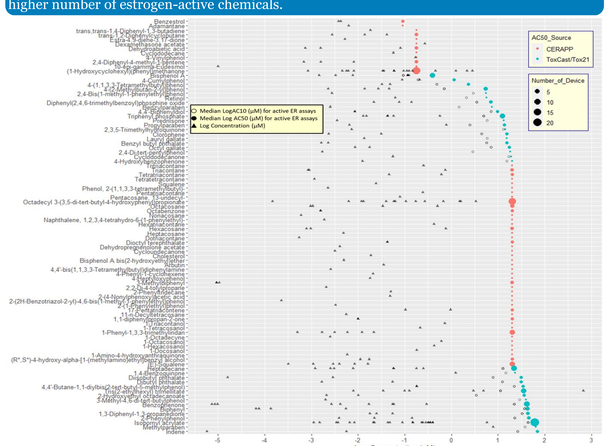


Figure 2. Concentration of chemicals in female adults compared to median AC50 values.

The blood concentrations for the majority of the 92 estrogen-active extractables are lower than their respective AC50 or AC10 values.

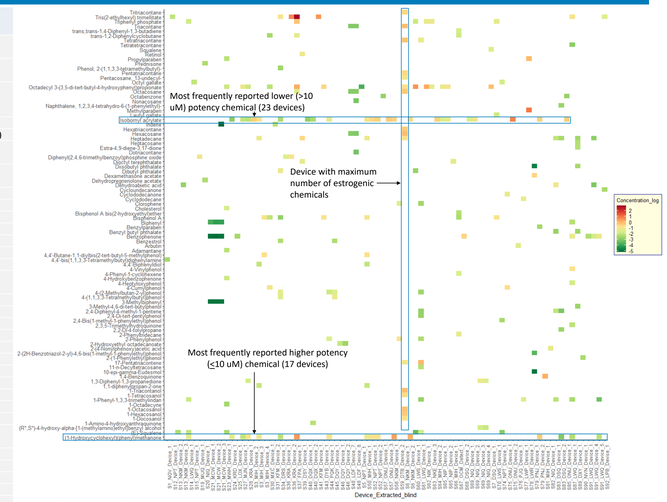


Figure 3. Distribution of chemicals active on 50% ToxCast/Tox21 and/or CERAPP active across medical device extracts.

- Estrogen-active extractables are reported at quantities ranging from 0.003 to 1,645,946 µg/device, which correspond to blood concentrations of 5.74E-06 to 668.9 µM in adult females, respectively.
- Some devices contain a combination of various estrogenic chemicals. For example, **S6_NKM_Device_1** contains 16 different xenoestrogens.

Summary & Future Plans

1. The 92 estrogen-active chemicals were reported in 82 out of 143 cardiovascular medical devices (57% devices).
2. The majority of the chemicals (71/92 chemicals; 77%) are low potency xenoestrogens with AC50 values higher than 10 µM.
3. 21 of 92 chemicals have AC50 values lower than 10 µM, which include bisphenol A and (1-hydroxycyclohexyl)(phenyl)methanone.
4. The concentration for the majority of the estrogen-active chemicals are below the AC10/AC50 values.
5. The number of estrogen-active chemicals ranged from 1 to 16 chemicals per device; therefore, additive effects of xenoestrogen mixture should be addressed to further understand their toxicity.
6. Future Plans:
   - Estimation of ER activity of mixtures of estrogen-active chemicals across devices using concentration-addition model.
   - Measuring estrogenic activity of medical device material extracts in an in vitro ER-based transcriptional activation assay.

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References

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