Evaluation of the Medical Device Chemical Space in the ToxCast/Tox21 High-Throughput Screening (HTS) Program

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Abstract

ToxCast/Tox21 high-throughput screening (HTS) *in vitro* assays constitute a rapid and cost-effective platform for identifying potential chemical hazards relevant to medical devices by screening large chemical libraries for effects on biochemical endpoints, cellular processes, and phenotypes. The ToxCast/Tox21 HTS program covers chemical-induced biological effects on over 1,000 assay endpoints, including interaction with receptors, transporters, ion channels, enzyme inhibition, induction of cell stress, and cytotoxicity. Analysis of the bioactivity profile of medical device relevant chemicals in ToxCast/Tox21 assays has not been performed yet. The purpose of this project is to evaluate the medical device chemical space across the ToxCast/Tox21 HTS program, focusing on chemicals, which includes tentatively identified substances, reported to be present in polymers/plastics. A total of 1,226 chemicals associated with polymers/plastics were tested in ToxCast/Tox21 assays. These chemicals were cross-referenced against the CDRH's Image2K+ database to evaluate potential relevance for the medical device space. A total of 1,118 chemicals were reported in medical device submissions captured in the Image2000 database. Chemical bioactivity was evaluated across tested assay endpoints in the ToxCast/Tox21 platform and major biological targets were identified. This effort using ToxCast/Tox21 data will help identify potential hazards for chemicals suspected to leach from medical devices and may be an additional source of information for sponsors and regulators in the evaluation of medical device biocompatibility.

Introduction

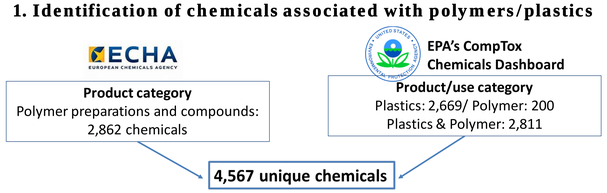
The Center for Devices and Radiological Health (CDRH/FDA) recommends biocompatibility evaluation of medical devices to evaluate the potential for the device to cause adverse biological responses. Biocompatibility endpoints that may be warranted for medical devices include cytotoxicity, sensitization, skin irritation, material-mediated pyrogenicity, hemocompatibility, implantation, systemic toxicity, genotoxicity, carcinogenicity, and reproductive/developmental toxicity. Some biocompatibility endpoints can be addressed by chemical characterization and toxicological risk assessment (TRA) of leachables/extractables. Medical device sponsors generally conduct non-targeted screening analysis of medical device extracts to identify chemical constituents that can be released from the device. The reported chemicals, which includes tentatively-identified substances, are used to inform toxicological risk assessment.

ToxCast/Tox21 HTS data may be useful for identifying potential hazards from chemicals released from medical devices. The purpose of this study is to evaluate the bioactivity of medical device relevant chemicals across the ToxCast/Tox21 platform and identify major biological targets/pathways targeted by medical device chemicals.

Materials and Methods

Identification of medical device relevant chemicals.

1. Identification of chemicals associated with polymers/plastics



2. Mapping chemicals associated with polymers/plastics to Tox21/ToxCast chemical library.

- Publicly available ToxCast/Tox21 files (InvitroDB_v.3.2)

1,226 out of 4,567 chemicals associated with polymers/plastics that were tested in ToxCast/Tox21 assays

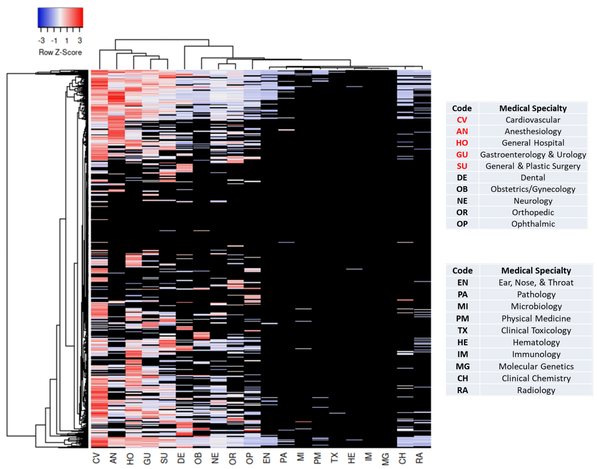
3. Bioactivity evaluation across ToxCast/Tox21 assays

- Assay endpoints retrieved for 1,226 chemicals that were tested in ToxCast/Tox21 assays
- Assay endpoints were mapped to biological targets (target genes)
- Bioactivity evaluated for chemical/assay pairs active below the cytotoxicity threshold (i.e., AC50 assay < median AC50 cytotoxicity burst assays).

4. Relevance of chemicals tested in ToxCast/Tox21 program to the medical device chemical space

- Searches in the CDRH's Image2K+ database for medical device submissions
- "CASRN AND toxic*" used as search terms to target the TRA section of submissions where leachables/extractables are reported.

1,118 out of 1,226 ToxCast/Tox21 chemicals reported in medical device submissions



Code	Medical Specialty
CV	Cardiovascular
AN	Anesthesiology
HO	General Hospital
GU	Gastroenterology & Urology
SU	General & Plastic Surgery
DE	Dental
OB	Obstetrics/Gynecology
NE	Neurology
OR	Orthopedic
OP	Ophthalmic

Code	Medical Specialty
EN	Ear, Nose, & Throat
PA	Pathology
MI	Microbiology
PM	Physical Medicine
TX	Clinical Toxicology
HE	Hematology
IM	Immunology
MG	Molecular Genetics
CH	Clinical Chemistry
RA	Radiology

Figure 1. Distribution of chemicals tested on ToxCast/Tox21 assays across medical device specialties.

- Toxcast/Tox21 chemicals were reported in > 14,000 medical device submissions (67% PMN, 9% IDE, 7% PMA, 6% MAF, and 11% other submission types).
- ToxCast/Tox21 chemicals were highly reported in cardiovascular device submissions, followed by general hospital, anesthesiology, gastroenterology & urology, general & plastic surgery, and dental medical specialties.

Results and Discussion

ToxCast/Tox21 assay activity

- 1,226 medical device relevant chemicals were tested in 4 to 1,134 ToxCast/Tox21 assays with a median of 351 tested assay endpoints.
- 1,104 chemicals were active in at least one ToxCast/Tox21 assay with a median number of 10 active assay endpoints.
- Application of the cytotoxicity threshold resulted in a slight reduction in the median number of active assay endpoints (7).

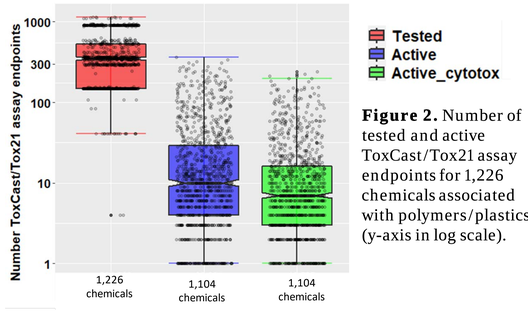


Figure 2. Number of tested and active ToxCast/Tox21 assay endpoints for 1,226 chemicals associated with polymers/plastics (y-axis in log scale).

Cytotoxicity

- Addressing cytotoxicity is required for all medical devices that have direct or indirect contact with the body.
- Top ranked cytotoxic chemicals based on median AC50 values from cytotoxicity burst assays contain carbamate_dithio and Sn_organo ToxPrint chemotypes.

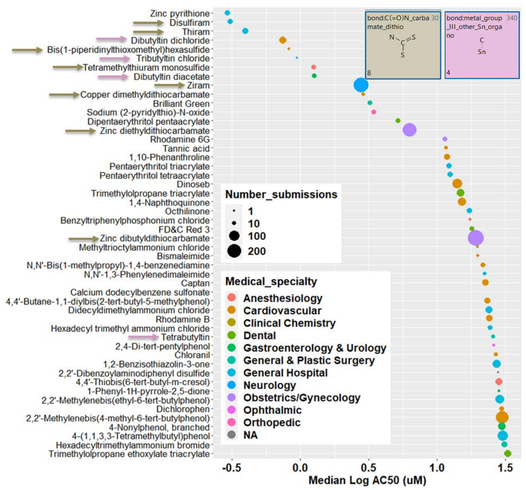


Figure 3. Top cytotoxic medical device chemicals. The color of the dot indicates the medical device specialty in which the chemical was most frequently reported. The size of the dot is proportional to the number of submissions.

Biological target families

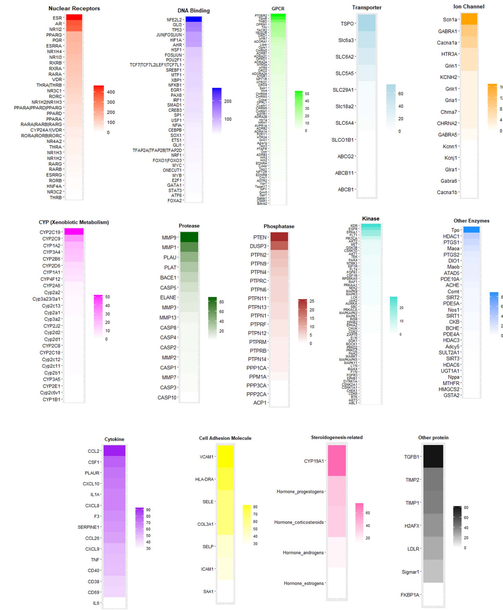


Figure 4. Number of medical device relevant chemicals active per biological target from ToxCast/Tox21 assays.

- ToxCast/Tox21 assays were mapped to 242 biological targets (target genes).
- Nuclear receptors and other transcriptions factors were biological families highly targeted by the chemicals. A total of 461 and 375 chemicals were active in at least one assay measuring perturbations in the estrogen receptor (ESR) and androgen receptor (AR) pathways, respectively.

Conclusion

- **ToxCast/Tox21 HTS data can be useful for:**
  - Identification of bioactivity for medical device relevant chemicals
  - Selection of safer materials of construction and manufacturing / processing materials
  - Insights into root cause of medical device failure in biocompatibility testing
- **Next steps:**
  - Linkage of bioactivity to toxicological endpoints of regulatory interest (e.g., systemic toxicity, carcinogenicity, developmental/reproductive toxicity) based on mode of action annotations provided in the NTP's Integrated Chemical Environment (ICE) website (https://ice.ntp.niehs.nih.gov/).