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Using ToxCast™ to Predict Chemicals Potential for Developmental, Reproductive and Vascular Development Toxicity

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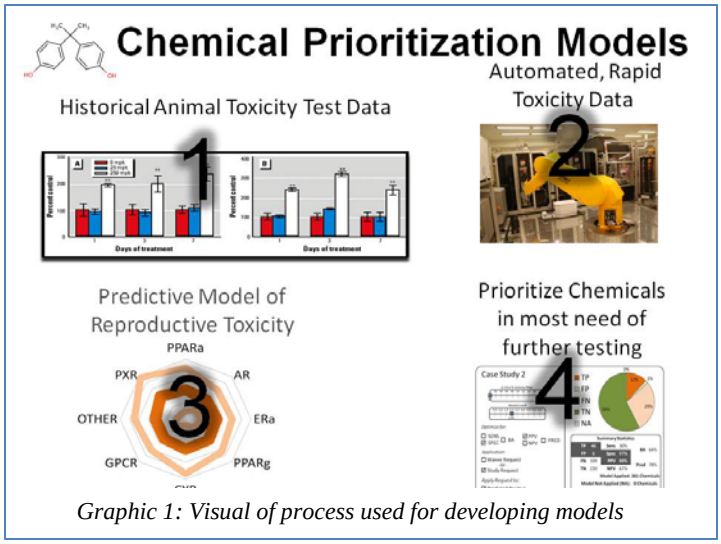
Tens of thousands of chemicals are currently in commerce, and hundreds more are introduced every year. Because there are so many chemicals—and since traditional chemical toxicity tests using animals is expensive and time consuming—only a small fraction of chemicals have been fully assessed for potential risk.

In 2007, EPA scientists began working on ToxCast, a research project to identify and prioritize potentially toxic chemicals using rapid, automated tests called *in vitro* assays. ToxCast is currently examining over 1,000 chemicals from a broad range of sources, including pesticides, industrial and consumer products, food additives and failed drugs that were never released to the market.

Recently, EPA scientists published papers describing first generation predictive models (see graphic 1 for process of developing models) using ToxCast data. These models show how the ToxCast concept can be used to predict the potential for certain chemicals to be toxic to embryonic development, male and female reproductive function, and vascular development. The models support continued development of this new approach to chemical safety assessment.



Graphic 1: Visual of process used for developing models

Developmental Toxicity Predictor

The study coupled traditional animal toxicity data from rats and rabbits with data from ToxCast's rapid, automated High Throughput Screening or HTS) assays to study the toxic effects of chemicals on prenatal development.

- The HTS assays used by ToxCast could distinguish between chemicals that affect rat versus rabbit development effects.
- Key biological signaling associated with developmental toxicity identified by ToxCast assays included those regulating cellular growth and differentiation as well as inflammatory signaling.

Reproductive Toxicity Predictor

The study compared ToxCast HTS data to rat multi-generation toxicity results to determine if ToxCast could be used to help identify which chemicals are potential reproductive toxicants. In applying this model to two situations, the positive economic impact of using ToxCast to prioritize chemicals for subsequent traditional testing showed a significant cost savings in the ability to detect reproductive toxicants

- The model utilized ToxCast chemicals with rat multi-generation reproductive toxicity test results and identified which chemicals are potential reproductive toxicants.
- Biological features of the model included activity of reproductive hormones,

drug metabolizing enzymes in the liver and several cell signaling pathways.

- For those chemicals that were shown to be active in the HTS assays, the model was able to distinguish chemicals that were and were not reproductive toxicants with an accuracy of 80%.

Vascular Development Predictor

The study mined the ToxCast HTS assay data and identified signatures for potential chemical disruption of blood vessel formation and remodeling, which it then tested using compounds known to be detrimental to vascular development.

- There was a strong correlation between animal developmental toxicity data and ToxCast HTS assays used in positively identifying Vascular Disruptor Compounds (VDCs).
- This model identified important biological features in inflammatory pathways, intercellular matrix r*emodelin*g and cellular growth signaling, and indicates that ToxCast data could help target animal testing by relying on *in vitro* assay signatures to identify potentially hazardous chemicals.

Conclusion

The four papers summarized here demonstrate the potential of ToxCast to cheaply and quickly identify *potentially hazard* chemicals and prioritize them for additional testing. Each study used ToxCast HTS assays to predict whether a chemical would produce adverse health effects in traditional animal based toxicity tests.

These results are very encouraging for continued development of prediction models. Model usage will ultimately be based on acceptance by the scientific and regulatory communities and the public that the predictions are accurate enough to protect human health.

As ToxCast increases the number of chemicals screened and the number of available tests, scientists will continue to enhance the development and application of modern scientific tools to efficiently protect human health and the environment from the effects of harmful chemicals.

References

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Originating Organization for Fact Sheet

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