Estimating Toxicity-Related Biological Pathway Altering Doses for High-Throughput Chemical Risk Assessment

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Impact Statement

Important inputs to chemical risk assessments are estimates of the highest allowable exposure levels that are protective of human health. Typical acceptable exposure values such as the Reference Dose (RfD) are based on expensive and time consuming animal toxicity tests. Non-animal based methods to estimate safe exposure levels would be beneficial because there are tens of thousands of existing chemicals with little or no animal testing data, and hundreds more chemicals introduced into commerce every year.

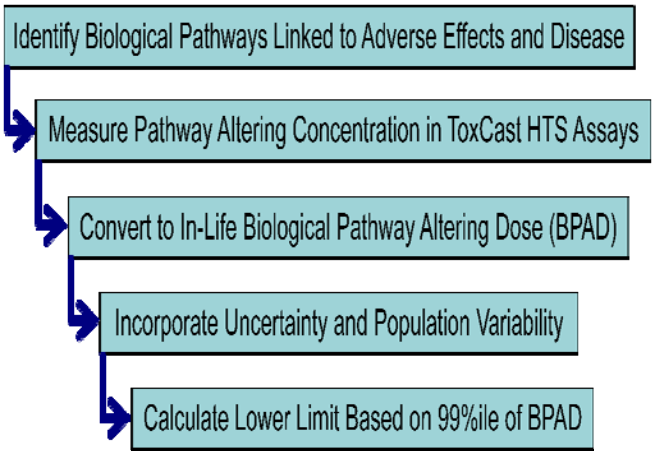
This paper presents an approach to use on data poor chemicals to derive screening-level estimates of allowable exposure levels. The method uses knowledge about how chemicals alter biological processes or pathways related to human disease. The proposed method for high-throughput chemical risk assessment (HTRA) uses data from rapid chemical screens to estimate exposures that would alter biological pathways in a way that could potentially lead to toxicity or disease.

Study Description

A proposed HTRA approach for chemicals is presented that focuses on biological pathways linked to adversity and disease. The approach combines results from ToxCast and Tox21 High-Throughput Screening (HTS) assays with data on metabolism and pharmacokinetic modeling to estimate exposure levels reasonably expected to be without risk of chemically induced disease in human populations. The proposed HTRA approach is essentially a five-step process (FIGURE 1) that calculates a Biological Pathway Altering Dose (BPAD) useful in estimating acceptable exposure levels.

1. Identify pathways linked to adverse outcomes: Biological pathways are a key connection between mode of action based risk assessment and HTS. This approach starts by identifying known targets (genes, proteins) and pathways linked to disease.
2. Measure chemical activity in concentration-response: The next step is to use ToxCast HTS data to determine the concentration of a chemical that can perturb the biological pathway in cells. This is termed the Biological Pathway Altering Concentration (BPAC).
3. Convert HTS concentration-response to human dose-response: Using metabolic measurements and pharmacokinetic models, the BPAD is calculated.
4. Incorporate population variability and uncertainty: All measurements and estimates are subject to uncertainty and population variability. The HTRA model incorporates both of these in a manner analogous to traditional risk assessments.
5. Estimate lower limit for pathway perturbation: The final step is to estimate a lower limit from the BPAD below which there is minimal risk of the toxicity-related pathway being perturbed, the $BPADL_{99}$.

Figure 1- Proposed Five-Step Process for High Throughput Risk Assessment (HTRA).



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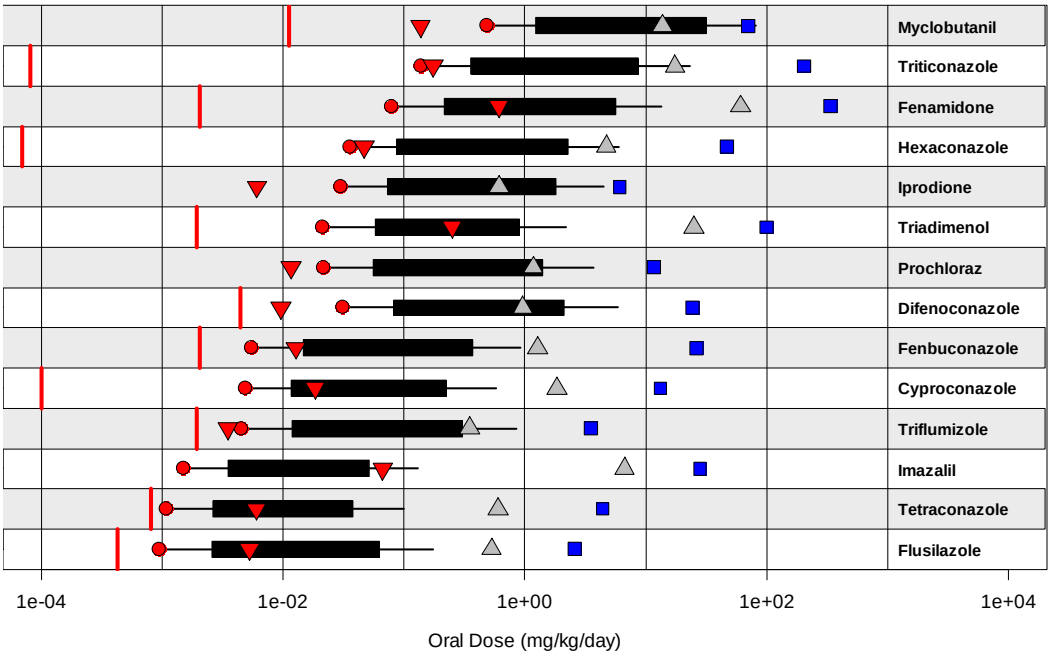

Figure 2 – Liver Toxicity Effect Levels

Figure Key

Red Circle=$BPADL_{99}$
Blue Box=Lowest Effect Level
Gray Triangle=No Effect Level
Red Triangle=NEL/100
Red Vertical Line= Estimated chronic exposure levels from food residues

Examples of this HTRA approach are presented for Bisphenol A, a chemical widely used in plastics, comparing estrogenicity measured by HTS to reproductive toxicity in animal studies. Rat reproduction tests resulted in a No Effect Dose of 50 mg/kg/day. Adjusted for uncertainty and variability, the no effect dose is 0.5 mg/kg/day and close to the HTRA lower limit, or $BPADL_{99}$ of 0. 16 mg/kg/day derived from six ToxCast estrogen receptor assays.

The second HTRA example for conazole fungicides compares rodent liver hypertrophy to interactions with the CAR and PXR receptor pathways. CAR and PXR respond to chemical exposures in ways that can lead to liver disease, and numerous ToxCast and Tox21 HTS assays measure chemical alterations in CAR and PXR pathways. The HTRA lower limits, or $BPADL_{99}$ calculated for 14 conazoles are compared to the No Effect Dose/100 for rodent liver hypertrophy in FIGURE 2. Most of the $BPADL_{99}$ for the conazoles are below and within a factor of 10 of the No Effect Dose/100.

Conclusions

This paper outlines an efficient and rapid method for providing screening-level estimates of acceptable exposure levels for data poor chemicals. There are a number of extensions and refinements that need to be carried out, but we believe that in time, the HTRA approach can be an important tool for addressing the backlog of chemicals in need of toxicity assessments. In addition, when combined with estimates of human exposure, the HTRA approach can be used to prioritize which chemicals need further toxicity testing and exposure monitoring.

Background

Many commodity chemicals in commerce have only undergone minimal safety testing as required by current US law. Toxicity testing conducted in animals is time-consuming, expensive and yields limited mechanistic information relevant to human disease. In an effort to improve existing chemical screening, US EPA's ToxCast and Tox21 projects are working to develop new ways to efficiently screen chemicals and prioritize limited testing resources toward those that have the greatest potential to cause hazard to human health. Legislation to overhaul the existing Toxic Substance Act is currently under discussion in the US Congress. This research was performed as part of the US EPA's Computational Toxicology Research Program.

Reference

Judson et al (2011) "Estimating Toxicity-Related Biological Pathway Altering Doses for High-Throughput Chemical Risk Assessment." *Chemical Research in Toxicology*, in press.

More Information: www.epa.gov/comptox

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