Use of Threshold of Toxicological Concern (TTC) with High Throughput Exposure Predictions as a Risk-Based Screening Approach of Several Thousand Commodity Chemicals

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ABSTRACT

Although progress has been made with HT (high throughput) biological activity profiling (e.g., DNA ToxCast™), challenges arise interpreting or reporting results in the context of adversity & converting HT assay concentrations to equivalent human exposures for the broad domain of commodity chemicals. Here, we propose using Threshold of Toxicological Concern (TTC) as a risk screening method to evaluate exposure ranges derived from NHANES for 786 chemicals. Because the well-established TTC approach uses hazard values derived from animal toxicity data, reliance on adverse effects is reduced. We compared the conventional TTC (non-carcinogenic values) of 0.0015 mg/kg ± 1.5 µg/kg to quantitative exposure predictions of the upper 95% credible interval (UCI) of median daily exposures to 786 chemicals in 30 different demographic groups. Results indicated that some of the median values of credible interval of exposure for any chemical in any demographic group was above the TTC, & [b] fewer than 5% of chemicals had a UCI that exceeded the TTC for any group. However, these median exposure predictions do not cover heavily exposed (e.g., occupational) populations. Additionally, we propose an expanded HT-based screening workload that combines a TTC decision tree that includes screening compounds for structural alerts for DNA and developmental toxicity with the EPI suite of computational methods for chemical and dosimetric risk predictions. The use of the NHANES data for other purposes (beyond the scope of this manuscript) was deprioritized; therefore, this HT method could include analysis using HT-based mechanistic screening, read access as part of integrated testing or exposure refinement. Disclaimer: The views expressed are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

PROBLEM FORMULATION AND APPROACH

We test the use of TTC derived values coupled with chemical-specific high throughput exposure predictions to evaluate risk-based priority setting.

Use of TTCs in the Evaluation of Chemical-Specific Exposure Guidance Values Consistent with the principles of chemical thermodynamics, the adoption of use of chemical products is a matter of public health; people are exposed to chemicals as part of normal daily living, occupational, and recreational activities and practices. Potential health risks will depend on the magnitude, frequency, and duration of exposure. AMEs and internal toxicity of each chemical. Here we apply the TTC in lieu of chemical-specific health guidance values such as Reference Dose (RfD) or Tolerable Daily Intake (TDI). The TTC approach was developed for chemicals where human exposure is estimated to be low and chemical-specific toxicological data are lacking. From a regulatory science perspective, conservation was deliberately built into the TTC, thus enabling conclusions that exposure below a TTC will not produce any appreciable risk to human health. The TTC approach is currently applied in a valid, science-based screening tool useful for the prioritization of chemicals and for more general applications in chemical risk assessment.[3] The approach initially used a single threshold of a log -5 g/kg/day which was expanded on a continuum of log -15 potency data.

High Throughput Exposure Assessment Methodology

This analysis used the predicted exposure values from Wambaugh et al. [2014][2] Wambaugh and coauthors developed a rapid heuristic model that enabled prediction of potential human exposure to the many thousands of chemicals for which little or no exposure data are available. To the left is the screening and prioritization of 786 chemicals with respect to the upper 95% predicted exposure (mg/kg/day) for the total U.S. population and for children ages 0-11. For each chemical the lower circle indicates the median and the upper circle indicates the 95% UCI for predicted exposures (mg/kg/day). For the average individual, arrows indicate the chemicals derived from the NHANES data. The horizontal dotted lines respectively indicate the 20%, median, and 75% limit of detection for NHANES chemicals. Demographic-specific predictions for the 786 chemicals are extrapolated from these NHANES’s results.[2]

RESULTS I: Third Phase of Canada’s CMP

• Of the 1550 CMP Chemicals, Wambaugh et al. 2014 results provided oral human exposure predictions for 324 substances
• Of these 324, the 95% oral exposures for 241 substances (70%) were below the screening level TTC of 0.0015 mg/kg/d. The 95% oral exposure for 83 of the 324 substances exceeded the 0.0015 mg/kg/d TTC (maximum exceedance approx. 10 fold).<

CONCEPTUAL APPROACH

As work continues to update and refine the TTC approach, this prioritization approach can be updated accordingly.

RESULTS II: Third Phase of Canada’s CMP

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• A preliminary exercise, HT exposures were compared to the TTC value of 0.0015 mg/kg/d (Cramer Class III). Note: we did not yet screen out organophosphates or compounds for genotoxic structural alerts. None of the median values for any chemical in any demographic group is above the TTC and less than 5% of the 95th percentile values for any chemical in any demographic group are above this TTC.

Future Activities/Additional Research

• In the future, we plan to run to screen for structural alerts and then re-screen using the full set of TTC values. As experienced is gained, additional tiers may be added (such as a Tier 3 fit for purpose in vitro cellular assays; a Tier 4 IATA, etc.)
• The TTC concept continues to evolve. The concept of internal TTC has been proposed as a screen for internal exposures [8,9]; additional research is needed to determine these values.
• (3) Research is needed to derive internal concentrations consistent with the 5th percentile of external exposure NOAELs or PODs for a range of substances. This includes an understanding of metabolism and the ultimate toxicant (parent or metabolite) for substances in the TTC database; [2] In vitro-to-in vivo extrapolation (IVIVE) will be needed to convert external exposure to internal concentration for comparison with the internal TTC; (c) The IVIVE methods that have been developed for comparison of internal activity concentrations from ToxCast™ and other high throughput data sources will need to be expanded to cover a broader domain of chemistries.[10]