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., EPA's ToxCast™), challenges arise interpreting HT 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 7968 chemicals. Because the well-established TTC approach uses hazard values derived from *in vivo* toxicity data, relevance to adverse effects is robust. We compared the conservative TTC (non-cancer) value of 90 µg/day (1.5 µg/kg/day) [1] to quantitative exposure predictions of the upper 95% credible interval (UCI) of median daily exposures for 7968 chemicals in 10 different demographic groups [2]. Results indicate: (A) none 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 an UCI that exceeded the TTC for any group. However, these median exposure predictions do not cover highly exposed (e.g., occupational) populations. Additionally, we propose an expanded risk-based screening workflow that comprises a TTC decision tree that includes screening compounds for structural alerts for DNA reactivity, OPs & carbamates as well as a comparison with bioactivity-based margins of exposure (Wetmore et al., Toxicol. Sci., 2015). This TTC risk-based screening approach may be useful in a modernized TSCA as the first step in risk-based prioritization. Subsequent steps for substances not deprioritized by this TTC method could include analysis using HTS bioactivity/ mechanistic screening, read-across 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

- Risk-based priority setting and screening level safety evaluations require information on both hazard and exposure.
- Chemical-specific robust toxicity data & chemical-specific exposure info are not readily available for a significant number of the ca. 15,000 chemicals in commerce.
- We demonstrate an approach that uses TTC for hazard values coupled with chemical-specific high-throughput exposure prediction values to enable risk-based priority setting/screening for several thousand chemicals in commerce .

Use of TTCs in Lieu of Chemical-Specific Exposure Guidance Values

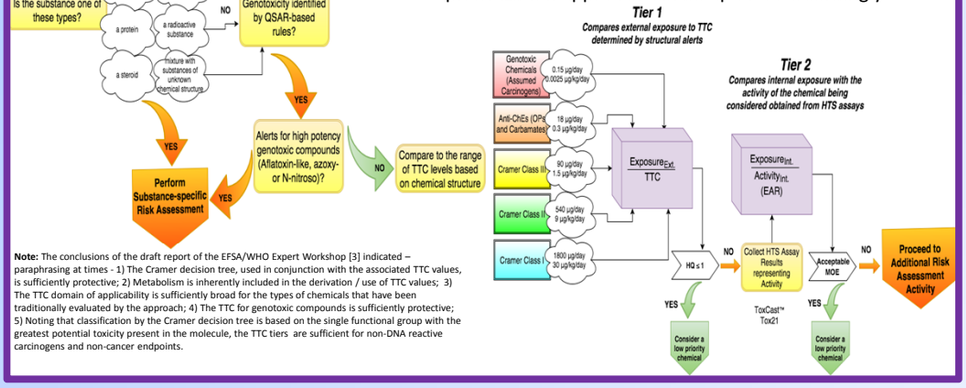
Consistent with the principles of chemical thermodynamics, the ubiquitous use of chemical products in modern life means that people are exposed to chemicals as part of normal everyday activities. The degree of exposure depends upon the product, uses and habits and practices. Potential health risks will depend on the magnitude, frequency, and duration of exposure, ADME and inherent toxicity of each chemical. Here we employ the TTC in lieu of chemical specific health guidance values such as a 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, conservatism was deliberately built into TTCs, thus enabling conclusions that exposure below a TTC will not produce any appreciable risk to human health. "The TTC approach as currently applied is 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 regulation value of 1.5µg/day which was derived based on an analysis of carcinogenicity potency data.

High Throughput Exposure Assessment Methodology

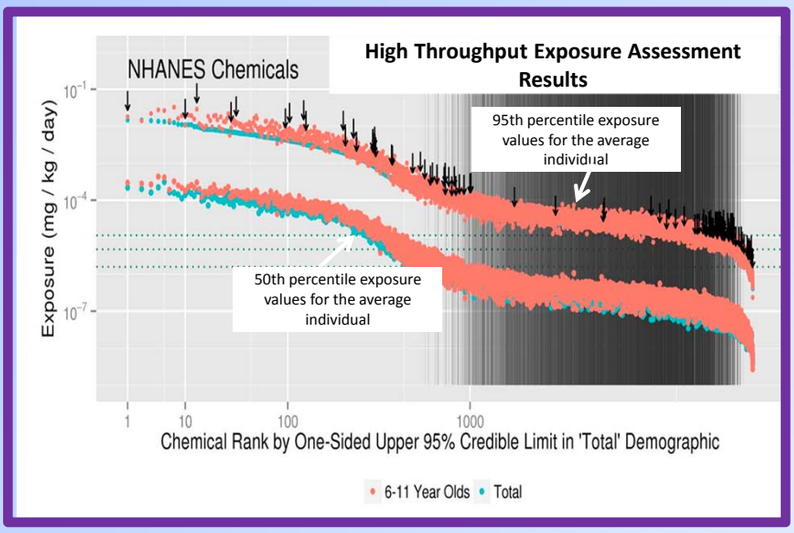
This analysis used the predicted exposure values from Wambaugh et al., 2014 [2] Wambaugh and coauthors developed a rapid heuristic model that enabled prediction of potential human exposure to the many thousands of chemicals for which little or no exposure data are available. To the left is the ranking and prioritization of 7968 chemicals with respect to the upper 95% predicted exposure (mg/kg/day) for the total U.S. population and for children aged 6–11. For each chemical the lower circle indicates the median and the upper circle indicates the 95% UCI for predicted exposures (mg/kg BW/day) for the average individual. Arrows indicate the chemicals inferred from the NHANES data. The horizontal dotted lines respectively indicate the 25%, median, and 75% limit of detection for NHANES chemicals. Demographic-specific predictions for the 7968 chemicals are extrapolated from these NHANES chemicals.[2]

CONCEPTUAL APPROACH

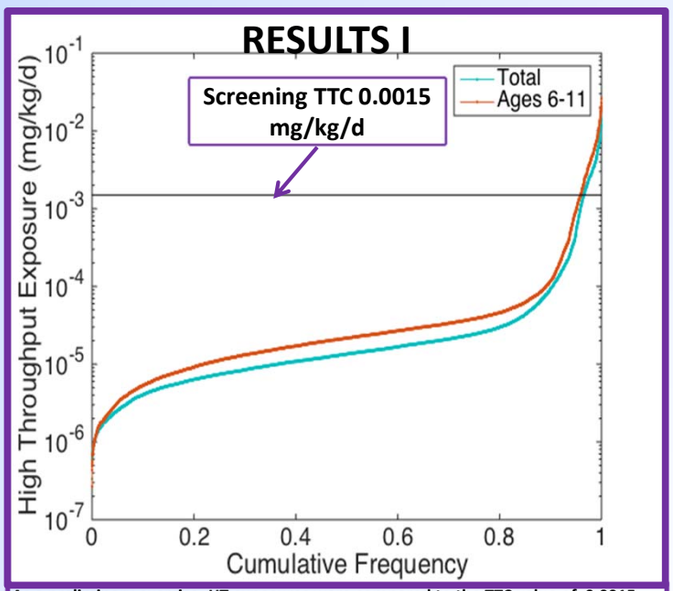
As work continues to update and refine the TTC approach, this prioritization approach can be updated accordingly



Note: The conclusions of the draft report of the EFSA/WHO Expert Workshop [3] indicated – paraphrasing at times - 1) The Cramer decision tree, used in conjunction with the associated TTC values, is sufficiently protective; 2) Metabolism is inherently included in the derivation / use of TTC values; 3) The TTC domain of applicability is sufficiently broad for the types of chemicals that have been traditionally evaluated by the approach; 4) The TTC for genotoxic compounds is sufficiently protective; 5) Noting that classification by the Cramer decision tree is based on the single functional group with the greatest potential toxicity present in the molecule, the TTC tiers are sufficient for non-DNA reactive carcinogens and non-cancer endpoints.



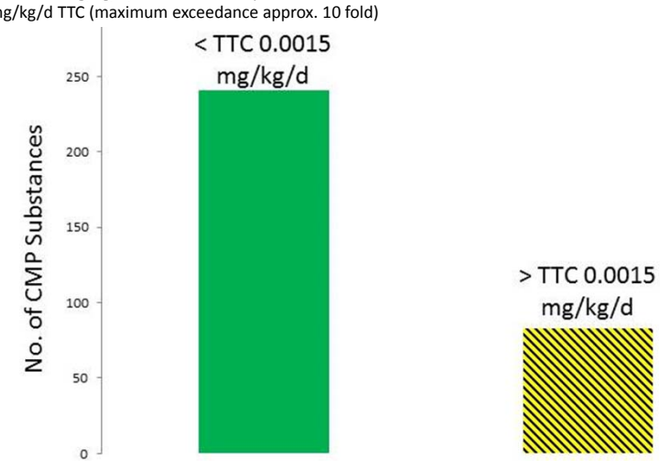
RESULTS I



As 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 genetox structural alerts. ➔ None of the median values for any chemical in any demographic group is above the this TTC and less than 5% of the 95th percentile values for any chemical in any demographic group are above this TTC.

RESULTS II: 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 exposures for 83 of the 324 substances exceeded the 0.0015 mg/kg/d TTC (maximum exceedance approx. 10 fold)



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:**
  (1) 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; (3) 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]

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COI Statement: The authors had complete control over the design, conduct, interpretation, and reporting of the analyses; this poster is solely the responsibility of the authors and does not necessarily reflect the views or policies of their employers. T. Simon received funding to support this research from the ACC. G. Patlewicz and J. Wambaugh are employed by EPA. S. Felter is employed by Procter and Gamble, a consumer product manufacturer. R. Becker is employed by ACC, a trade association of U. S. chemical manufacturers.