# Use of Threshold of Toxicological Concern (TTC) with High Throughput Exposure Predictions as a Risk-Based Screening Approach to Prioritize More Than Seven Thousand Chemicals

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**ABSTRACT**

A risk-based prioritization approach using the Threshold of Toxicological Concern (TTC) combined with high-throughput exposure (HTE) modelling is presented. We started with 7968 chemicals with previously calculated population median oral daily intakes characterized by an upper 95% credible interval (UCI) (Wambaugh et al., 2014; Ref 1). Substances were profiled using the TTC workflow of Kroes et al (2004; Ref 2)) taking into account the known TTC exclusions and structural alerts. Modelled UCI daily exposures calibrated using NHANES data were compared to the appropriate class-specific TTC. For Cramer Class I, 0 of 1294 substances had UCIs greater than the TTC; for Cramer Class II 0 of 332 had UCIs above the TTC; for Cramer Class III 58 of 3214 UCIs were greater than the TTC; and for cholinesterase inhibitors 1 of 102 had a UCI above the TTC. For the 1853 chemicals with genotoxicity structural alerts, modeled UCI exposures for the vast majority exceeded the TTC of 0.15 µg/day (using median exposure values, only 79 were above the TTC). Using the ICH (2014; Ref 3) TTC value for mutagenic impurities of 1.5 µg/day (corresponding to an individual excess lifetime cancer risk of $1x10^{-5}$), the UCI exposure values of 333 substances were greater than this TTC (using the median exposure values 19 were above the ICH TTC). For substances that exceed TTCs, we discuss options for subsequent evaluation depending on the decision context. Overall, this analysis indicates that TTC and HTE are potentially useful as a pragmatic first step in a risk-based prioritization approach for chemical safety evaluations. *This poster does not reflect EPA policy.*

**PROBLEM FORMULATION AND APPROACH**

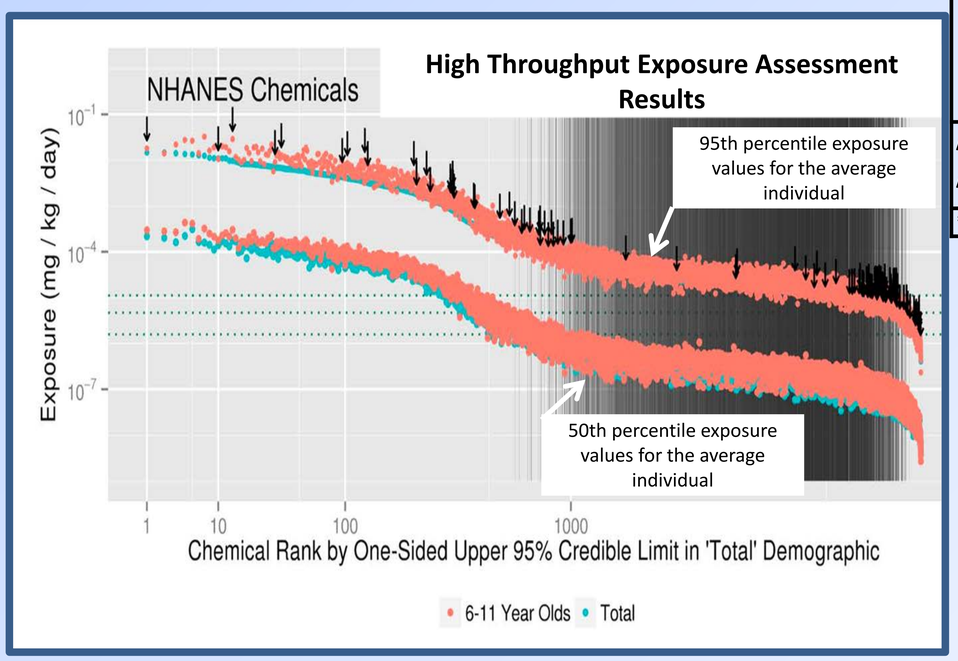
- Risk-based priority setting and screening level safety evaluations require information on both hazard and exposure.
- Chemical-specific robust toxicity data & chemical-specific exposure info are not readily available for a significant number of the approximately 15,000 chemicals in commerce.
- We demonstrate 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 over 7000 chemicals in commerce.

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

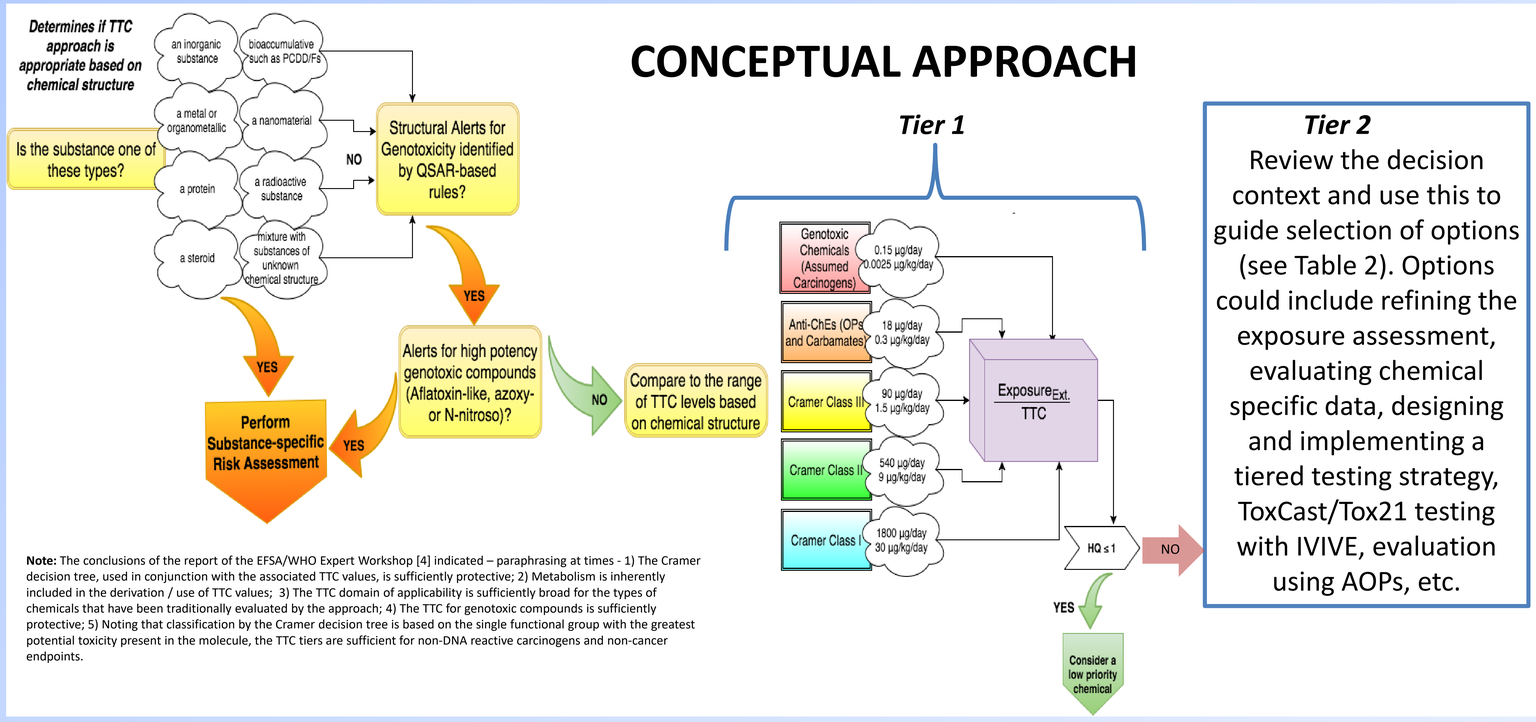
Consistent with the principles of chemical thermodynamics, the ubiquitous use of chemical products in modern life means that people are exposed to chemicals as part of normal everyday activities. The degree of exposure depends upon the product, uses and habits and practices. Potential health risks will 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 are unlikely to 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."[4] 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. Subsequently, extensive analyses of sub-chronic, chronic, reproductive and developmental toxicity studies resulted in the development of TTC values for three structural classes of chemicals.[2,4-6] The TTC approach continues to evolve with increasing use of QSAR and structural alerts to assign chemicals to particular classes.[7,8]

**High Throughput Exposure Assessment Methodology**

This analysis used the predicted exposure values from Wambaugh et al., 2014 [1] 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.[1]




## CONCEPTUAL APPROACH




**Note:** The conclusions of the report of the EFSA/WHO Expert Workshop [4] 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.

## Table 1. Prioritization results

Chemical structures were found for 7699 chemicals using the EPA CompTox dashboard (https://comptox.epa.gov/dashboard). Inorganics, bioaccumulative substances etc. were identified using the Kroes et al (2004) workflow module contained within Toxtree v2.5 (Ideaconsult Ltd), the OECD Toolbox's 'structure type' profiler and Leadscope structural features (www.leadscope.com). Organophosphates and carbamates were identified using Toxtree and Leadscope. Genotoxic alerts were identified using the OECD Toolbox v3.4 and Cramer structural classes were identified using Toxtree v2.5.

| TTC category | # of chemicals | TTC in µg/kg-day for 60 kg Adult | Substances Exceeding the TTC (HQ > 1) | |
|---|---|---|---|---|
| | | | UCI Exposure Value (count) | Median Exposure Value (count) |
| Excluded from the TTC approach | 904 | Not applicable | | |
| Cramer class III | 3214 | 1.5 µg/kg-day | 2% (58) | 0 |
| Cramer class II | 332 | 9.0 µg/kg-day | 0 | 0 |
| Cramer class I | 1294 | 30 µg/kg-day | 0 | 0 |
| Anti-ChEs | 102 | 0.3 µg/kg-day | 1% (1) | 0 |
| Genotoxic alerts | 1853 | Kroes 0.0025 µg/kg-day | 94% (1740) | 4% (79) |
| | | ICH 0.025 µg/kg-day | 18% (333) | 1% (19) |

## Table 2. Possible next steps for prioritized substances (i.e. substances with predicted exposures > TTC)*

| TTC Category | Possible Next Steps |
|---|---|
| Cramer Class I, II III | • Refine the exposure assessment using suitable models for specific conditions of use, populations and activities<br>• Evaluate existing chemical specific data, determine sufficiency of the information for a chemical-specific screening level risk assessment for systemic toxicity<br>o If additional hazard information is needed, consider HTS (ToxCast/Tox21); Read-Across, IATA, etc. (If HTS indicates potential specific molecular targets, determine if an existing AOP may be utilized to improve understanding of potential hazards) |
| Genotoxicity Alerts | • Refine the exposure assessment using suitable models for specific conditions of use, populations and activities<br>• Evaluate existing chemical specific data, determine sufficiency of the information for a chemical-specific screening level risk assessment for genotoxicity<br>o If additional information is needed, consider conducting genotoxicity screening tests of the chemical (e.g., Ames assay, gene mutation assay in mammalian cells, in vitro micronucleus, in vivo mammalian genetox)<br>o Evaluate potential modes of action using HTS (ToxCast/Tox21) screening assays to identify potential molecular initiating events associated with existing AOPs |
| Anti-cholinesterase Alerts | • Refine the exposure assessment using suitable models for specific conditions of use, populations and activities<br>• Review principles and procedures for selection of appropriate endpoints for assessing potential hazards to humans exposed to anticholinesterase pesticides and design a tiered testing strategy |

*The decision context should guide the selection of options, therefore these possible next steps should be considered illustrative, not exhaustive.

## Future Activities/ Additional Research

The TTC concept continues to evolve. The concept of internal TTC has been proposed as a screen for internal exposures [9,10]; 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.[11]

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