Using the New ICCVAM NAM Validation Guidance to Evaluate the Threshold of Toxicological Concern as a Computational NAM

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Prior to using New Approach Methodologies (NAMs) for evaluation of potential toxic effects of chemicals and products on human health and the environment, sufficient scientific confidence is needed to support a specific NAM in its intended application, whether for regulatory and/or non-regulatory assessments. Recently, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) published a Framework for the validation, qualification, and regulatory acceptance of NAMs to help developers and end-users build confidence in the use of specific NAMs for an intended purpose (ICCVAM, 2024[1]).

This research project will evaluate the Thresholds of Toxicological Concern (TTC) as a computational NAM for conducting risk-based prioritization and/or deriving surrogate human health risk assessment values according to the ICCVAM Framework to document the current status of confidence for the use of the TTC for these regulatory purposes. The project will include: a literature search, validation via the ICCVAM process for use of TTC as a computational NAM for risk-based prioritization and as a surrogate human health risk assessment (HHRA) value; and collaboration with scientific experts to evaluate the data and develop and publish a scientific manuscript. The manuscript will include a description of areas where further research should be considered to strengthen scientific confidence in the use of the TTC for priority setting and chemical safety evaluations to support product stewardship and regulatory decision making.

Implications: NAMs must be demonstrated to have sufficient scientific confidence for their intended applications, and scientific confidence frameworks (such as the ICCVAM Framework) provide a flexible, fit-for-purpose way to do this compared to traditional validation. The TTC has already been shown to be an efficient, cost-effective screening tool that can streamline the risk assessment process while still being public health protective (Simon et al., 2024[2]). However, now that ICCVAM has developed a Framework and guidance for evaluating the scientific confidence of NAMs, the TTC, like other NAMs, needs to be evaluated by applying the ICCVAM guidance to convince US federal regulatory authorities. If the TTC is shown to have sufficient scientific confidence for the two intended uses that will be evaluated in this project, then the barriers inhibiting the use of the TTC for priority setting and screening level risk evaluations in TSCA and other federal regulatory and product stewardship programs are anticipated to be significantly reduced or eliminated.

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[1] https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf
[2] https://pubmed.ncbi.nlm.nih.gov/38555099/