Identification of New Approach Methodologies (NAMs) for Placement on the TSCA Section 4(h)(2)(C) List: NAM Nomination Process

Introduction

On June 22, 2016, the Toxic Substances Control Act (TSCA) was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

TSCA Section 4(h)(2)(C) requires EPA to develop a list of alternative test methods or strategies that are "scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing." The current TSCA Section 4(h)(2)(C) list ("the List") is included on the EPA webpage. The *NAMs Strategic Plan* notes that EPA will update the List periodically and that there would be opportunities for stakeholders to participate in this process. This document outlines the process for nominating NAMs. EPA is dedicated to using gold standard science to inform our regulatory actions and to promoting the use of NAMs to fill data gaps during the regulatory process.

The science and technology of NAM development is rapidly evolving, and the List is not intended to be a complete account of all NAMs with potential applications in TSCA. EPA may choose to consider data from other NAMs not currently on this List to support an evaluation for a new or existing chemical.

As part of the nomination process, EPA will evaluate the appropriateness of a NAM for the intended regulatory application. A NAM included on the List may be deemed suitable for a specific TSCA decision context, but it might not be for others. EPA expects NAM data to be used in screening and evaluating new chemicals, pre-prioritizing and prioritizing existing chemicals, and risk evaluations. Additional risk assessment uses are possible, and EPA recommends consulting with the Agency on NAMs and alternative methods to best fulfill TSCA Section 4(h).

Process for Nominating NAMs

The TSCA NAMs Nomination Process utilizes a tiered approach designed to facilitate a transparent and efficient evaluation of the proposed methods. External Stakeholders initiate the nomination process by submitting a short description of their proposed methodology and alignment with the criteria for identifying NAMs provided in the NAMs Strategic Plan. This information should be submitted via email to NAMsNomination@epa.gov. The Agency will review the submission for completeness, evaluate that it meets the criteria outlined in the Strategic Plan and determine whether the nomination advances to the next tier of evaluation. This process ensures that thoroughly vetted and compliant NAMs are considered for further review, aligning with the gold standard science principles and are relevant to current regulatory needs.

Key considerations when submitting and reviewing NAMs include context of use, biological relevance, and reliability.

In considering context of use, EPA will focus on the intended application of the NAM for a specific TSCA risk assessment/evaluation context and/or endpoint and will include consideration of the:

1. Risk decision context: *e.g.,* screening-level assessment of new chemicals, pre-prioritization of existing chemicals, prioritization of existing chemicals, and risk evaluation of existing chemicals.
2. Endpoint: physicochemical properties, environmental fate/disposition, exposure/monitoring, ecological effects and human health effects.
3. Fit-for-purpose: Is the information provided by the NAM (*e.g.*, hazard identification, point-of-departure, etc.,) adequate for the TSCA risk decision context?

In considering biological relevance, EPA will focus on the following principles which are important for describing the relationship between the NAM and the TSCA endpoint/risk decision context including the:

1. Biological/mechanistic basis of the NAM (if applicable): an understanding of the biology and mechanisms leading to the endpoint, including considerations for the target species.
2. Reference chemicals: chemicals used in the development and evaluation of the NAM for which response in the test method or species are well characterized. Examples include positive/negative controls, as well as training and test set chemicals. Reference chemicals can include mono- and multi -substituent compounds.

In considering reliability, EPA will consider the following principles to assess the predictive capacity and robustness of the NAM and the implementation in TSCA:

1. Acceptance criteria and quality assurance: documentation of best practices and quality control related to experimental data, test system, experimental equipment, internal standards, acceptance/rejection criteria for experimental data, limits of detection and standard operating procedures (as applicable)[1].
2. Applicability domain: defines the types of chemicals for which the NAM results are considered acceptable.
3. Predictivity: evaluates NAM performance using appropriate reference chemicals and statistics/metrics; includes appropriate measures of goodness-of-fit, robustness and predictivity for statistical models; describes potential methodological limitations and uncertainties
4. Reproducibility: verification of results both within laboratories and between independent laboratories; description of any specialized/proprietary equipment that may impact the transferability of the NAM.
5. Independent review: description of the independent evaluation of the NAM via peer-reviewed journal, committee, or independent validation body.

[1] For additional information on acceptance criteria and quality assurance practices from the OECD for in vitro, in silico and omics data, refer to the Guidance Document on Good In Vitro Method Practices (GIVIMP) (OECD, 2018), the (Q)SAR Assessment Framework: Guidance for the regulatory assessment of (Quantitative) Structure Activity Relationship models, predictions and results based on multiple predictions (OECD, 2023b) and the Omics Reporting Framework (OORF): Guidance on reporting elements for the regulatory use of omics data from laboratory-based toxicity studies (OECD, 2023a).