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

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* *The views expressed in this presentation are those of the author[s] and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

Statutory Mandate: TSCA Section 4(h)(1)

- Prior to requesting testing using vertebrates:
  - Consider *reasonably available existing information*, and
  - Encourage and facilitate (Section 4(h)(1)(B)(I, ii and iii):
    - "Scientifically valid test methods and strategies that reduce or replace use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions;
    - The grouping of 2 or more chemical substances into scientifically appropriate categories…; and
    - The formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests…"

Statutory Mandate: TSCA Section 4(h)2 – The Strategic Plan

4(h)(2) - ***Implementation of Alternative Testing Methods***—To promote the development and timely incorporation of new scientifically valid test methods and strategies that are not based on vertebrate animals, the Administrator ***shall—***

Six points…(only one mentioned here)

4(h)(2)**(C)** - Requirement for ***"a list***...of particular alternative test methods or strategies the Administrator has identified that do not require new vertebrate animal testing…"

From the OPPT NAM Website

2. Maintain and regularly update a list of NAMs per Section 4(h)(2)(C)

- EPA published a list of NAMs in June of 2018 and committed to updating the list at least once a year. The first update was released in December 2019. *Additionally, EPA plans to release a draft proposal on a process for selecting which NAMs will be included on future versions of the list. This draft proposal will be released for public comment in 2020.*

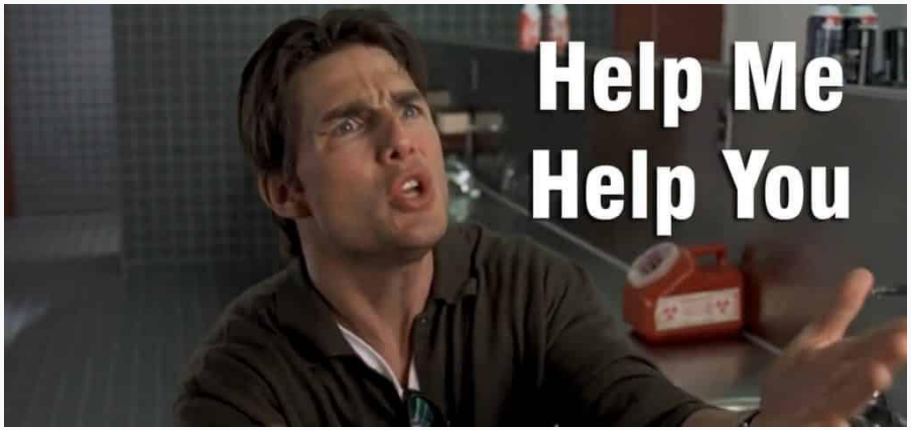
So, How Does a NAM Get on the TSCA List?

- There are organizations/entities that evaluate and “approve” NAMs (e.g., OECD Test Guideline Program, ICCVAM, ECVAM)
- But there may be other NAMs useful for TSCA decisions
- We would like to propose some ideas on how NAMs could be considered for inclusion in the TSCA Section 4(h)(2)(c) List

Practical Goals for NAM Nomination

Get lots of good NAMs added to the list

1. Encourage NAM nominations from a diversity of sources
2. Provide guidance as what EPA wants from a NAM for TSCA
   - How might we use it? What are the risk decision scenarios under TSCA?
   - What do we need for it to be usable? How do those differ by scenario?
   - What are the minimal performance criteria for acceptance/use?



What does the Perfect NAM Nomination Look Like?

- Method does not rely upon intact animals
- Provides relevant data that seamlessly integrates in TSCA regulatory activities:
  - Risk assessment (screening-level) of new chemicals
  - Risk evaluation of existing chemicals
  - Prioritization of existing chemicals
- Provides quantitative data
- Covers the diversity of TSCA chemical space
- Highly predictive of known values (ground-truthing)
- Reproducible
- Transferrable/Accessible
- Transparent

What are We Likely to Get?

Expectations vs. Reality

NAM Nomination versus Evaluation

Who Might Nominate a NAM for TSCA Use?

- U.S. EPA
- Other U.S. Federal Agencies
- International Agencies
- Groups advancing alternatives to animal tests
- TSCA submitters (regulated industry)
- Consultation firms specializing in TSCA support
- Companies with assays, models and other tools seeking to repurpose and commercialize for TSCA compliance

* NAM sources will have differing expertise, incentives and familiarity with TSCA

NAM Nominations- a Distillation

- What are the Critical Elements for a Nomination?
  - Nominal Information
    - What is it?
  - Development History
    - How was it developed and by whom?
  - Method Description
    - How does it work? What are the steps involved?
  - Relevance
    - Does it predict anything useful for decisions about TSCA chemicals?
  - Reliability
    - Can we trust the output and justify our decisions based on it use?

Critical Element #1: Nominal Information

- NAM name
- Nominating Official/Organization
- NAM Category:
  - *In chemico* (abiotic chemical reactivity methods)
  - *In silico*
    - Analog identification
    - Predictive model
    - Quantitative-structure activity relationship (QSAR)
    - Read-across
    - Other in silico
  - *In vitro*
    - 3-D/Organotypic
    - 2-D/Cell-based
    - Cell-free
    - Other in vitro
  - Integrative method (e.g. IATA, Defined Approach)
  - Other

Critical Element #2: Development History

- NAM Developer
- Development Release Date (year)
- Original Method Publication (authors, year, journal, pmid/doi)
- Current Version (number and date)

Critical Element #3: Method Description

- Provide a brief description of the method protocol/steps.
- Describe the endpoint(s) measured, modeled, or predicted.
- What type(s) of values are reported?
- Describe any calculation methods used.
- If NAM is model, please describe the feature/descriptor set and modeling method used.
- Describe the throughput and resource intensity for the current version of the NAM (i.e. cost per sample, samples processed per day).

Critical Element #4: Relevance

- We provide the OECD Guidance (2005) definition in the Strategic Plan (Section 5, p. 19):
  - Relevance- the ability of a test method to measure or predict an effect/target of interest as well as the regulatory need, usefulness of the alternative method(s) and associated limitations of the test method.
- In the criteria listed in the Strategic Plan (Section 5, p. 20):
  1. The decision context should be clearly defined.
  2. Where possible, the NAMs should be mechanistically and/or biologically relevant to the hazard being assessed. The chemical domain of applicability of the NAMs should also be defined to determine relevance to the TSCA chemical landscape.

Sub-Elements of Relevance

Decision Context

Endpoint ↔ Context

Chemical Coverage

Decision Context

Intended TSCA Risk Decision Context (check all that apply):

- ❑ Pre-prioritization
- ❑ Prioritization
- ❑ Risk evaluation
- ❑ Screening-level assessments

Endpoint ↔ Context

- ❑ Physical-Chemical Properties *
- ❑ Environmental Fate/Disposition
- ❑ Exposure/Monitoring
- ❑ Hazard- Ecotoxicology
- ❑ Hazard- Human Health

Endpoint ↔ Context

Provide a brief description with supporting references for any scientific rationale linking NAM endpoint(s) to the relevant TSCA decision context.

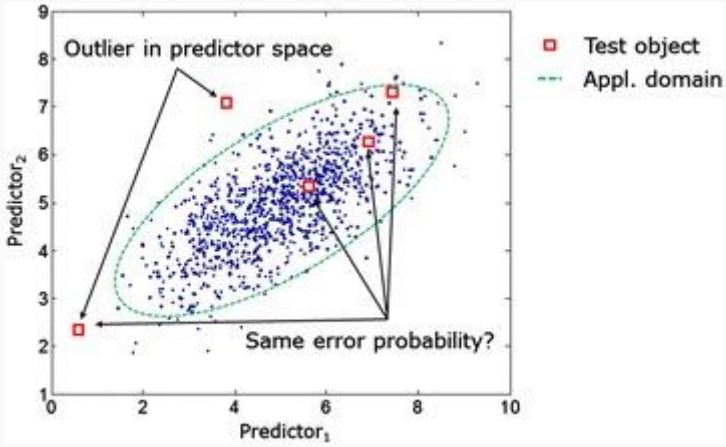
Does NAM endpoint(s) map to an existing adverse outcome pathway (AOP)? If so, how and to which AOP ?

Can the NAM endpoint be used qualitatively (e.g. hazard identification), quantitatively (e.g. establish a point of departure for hazard) for TSCA decisions?

Chemical Coverage

Describe the method used (if any) to define the chemical applicability domain of the NAM.

Describe any other chemical limitations to the NAM (e.g. DMSO solubility, vapor pressure, chemical classes known to produce false positive or false negative results).



Critical Element #5: Reliability

- We provide the OECD Guidance (2005) definition in the Strategic Plan (Section 5, p. 19):
  - Reliability- the extent of reproducibility of results from within (intra-) and among (inter-) laboratories over time, when performed using the same standardized protocol
- In the criteria listed in the Strategic Plan (Section 5, p. 20):
  3. Criteria for selecting reference or training chemicals should be defined and supporting information should be adequately referenced.
  4. The reliability of the NAM should be considered within the context of intended use and accepted best practices within the given field and the variability of the existing animal model.
  5. The NAMs should be transparently described and information made available to the public (e.g., any datasets are publicly available and its known limitations are clearly described). Information claimed as CBI may not allow public accessibility of all information in some cases.
  6. Uncertainty should be described to the fullest extent possible; both independently and compared to the existing animal model (if possible).
  7. The NAMs should undergo an independent review in order to raise confidence in the approach.
  8. Access and use by third parties should be possible (i.e., the alternative approach must be readily accessible commercially and/or the relevant protocols should be available).

Sub-Elements of Reliability

Reference Chemicals

Reproducibility

Predictivity

Transparency

Reference Chemicals

List the controls or standards used with the NAM and include supportive literature references and/or scientific rationale.

List all chemicals used to evaluate NAM performance with anticipated results, literature references and scientific rationale. This includes all reference chemicals, training sets and test sets.

Reproducibility

Describe the intra-laboratory reproducibility of the NAM and how quality assurance acceptance/rejection criteria were established.

Describe the limits of detection or quantification of the NAM.

Predictivity

Describe how NAM performance was evaluated using reference or training set chemicals with binary classifier statistics (or appropriate metric).

Describe any uncertainties or known limitations of the NAM (e.g. assay artifacts or interference, false positives/negatives, metabolic activity, dosing limits).

Transparency

Has the NAM been evaluated by outside users (beyond the developer)? If so, provide a list of outside users and describe the inter-laboratory reproducibility using control/reference chemicals.

Please provide documentation of any independent review(s) of the NAM that may have been performed (with documentation and references).

Describe any specialized or proprietary equipment, software or data that impedes NAM transfer to a third-party user.

Unresolved Questions

- What would motivate you to submit a NAM?
- If an integrated method (e.g. IATA) is submitted, do we need to evaluate the constituents independently or can we evaluate and adopt an integrated method comprised of unevaluated components?
- Can we include phys-chem methods as NAMs? Do NAMs necessarily need to replace an animal test to reduce animal testing?