



U.S. EPA Strategic Plan to Promote the Development and Implementation of Alternative Test Methods

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Predictive Models for Acute Oral Systemic Toxicity
Workshop

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Statutory Mandate

In 2016, TSCA was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act:

- new requirements and deadlines for actions related to the regulation of new and existing chemical substances.
- new Section 4 (h) entitled ***Reduction of Testing on Vertebrates***
- **Section 4(h)2 – Develop Strategic Plan**



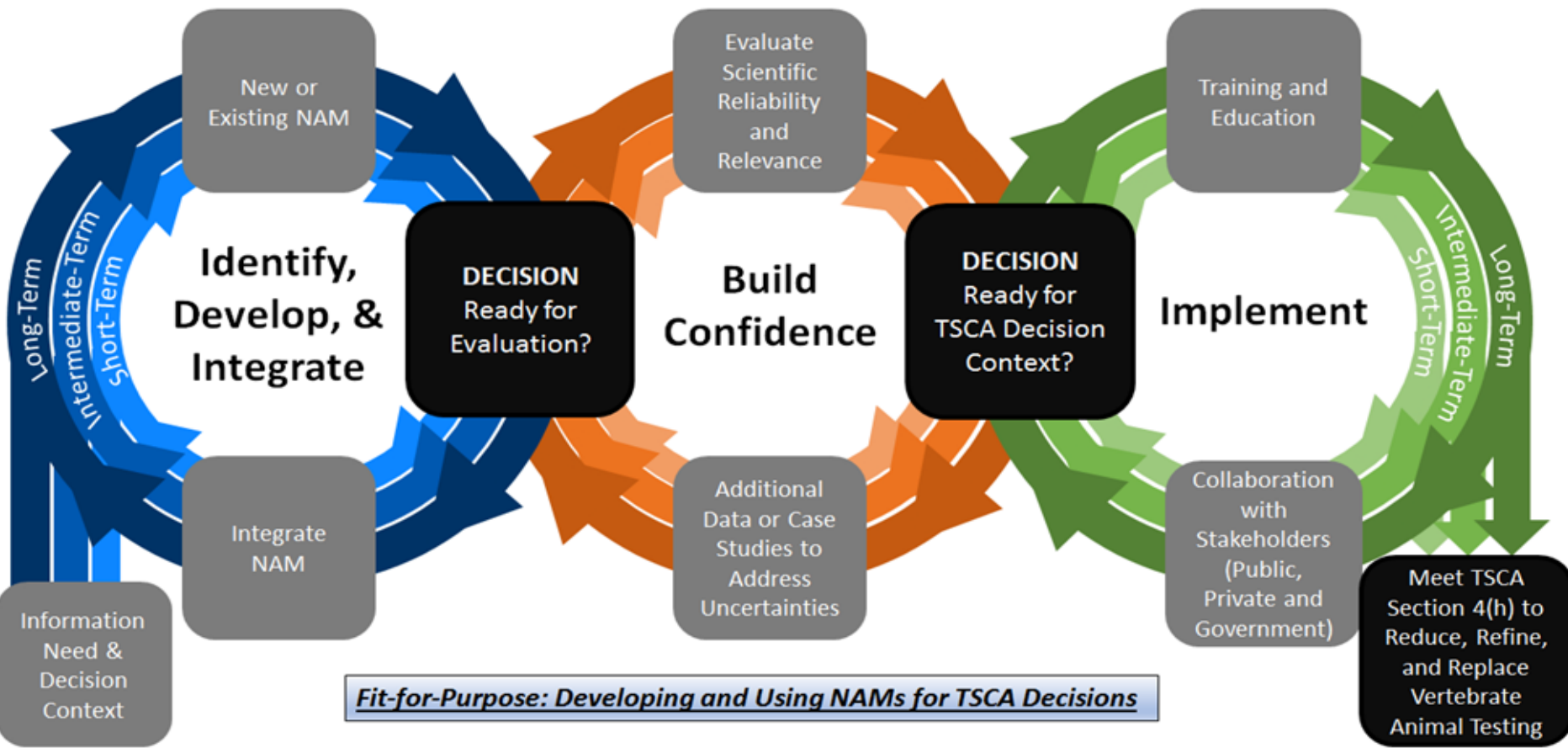
Overview of Draft Strategic Plan

1. Identification, Development and Integration of New Approach Methodologies (NAMs)*
2. Establishing Scientific Relevance, Reliability and Confidence
3. Importance of Training, Education and Collaboration
4. Implementation of NAMs Under TSCA
 - Commitment of time and resources through the establishment of the TSCA NAM Team (TNT)

** EPA views the term New Approach Methodologies as equivalent to alternative test methods and strategies*



Fig. 1 Core Components of EPA Strategic Plan to Develop and Implement New Approach Methodologies (NAMs) in TSCA





Use of NAMs for TSCA –Decision Context

- New chemicals program has been using NAMs for years
 - ECOSAR, OncoLogic, EPISuite, New Chemical Categories Document, SAR/QSAR/Read-Across
- EPA will consider NAMs for:
 - Screening candidates for prioritization
 - Prioritization
 - Risk evaluation
- Use will be fit-for-purpose



Identification, Development and Integration of NAMs (1)

- Identification and Development of NAMs
 - Chemical Characterization
 - Important to determine critical aspects of hazard, dosimetry, exposure and environmental fate/persistence
 - Examples of NAMs currently used - EpiSuite, OECD QSAR Toolbox
 - Hazard Identification and Characterization
 - *in chemico*, *in silico*, *in vitro*, others
 - Examples of NAMs currently used– ECOSAR, OncoLogic, AIM (all new chemicals); ToxCast and Tox21 for screening for prioritization



Identification, Development and Integration of NAMs (2)

- Identification and Development of NAMs
 - Dosimetry and In Vitro-In vivo Extrapolation (IVIVE)
 - Developing and using tools to perform IVIVE
 - Limited examples of NAMs currently used
 - Characterizing Exposure to Humans and the Environment
 - Examples of NAMs currently used – ChemSTEER (environmental release and occupational exposure), CEM (consumer exposure), E-FAST (exposure to general population and environmental organisms)



Identification, Development and Integration of NAMs (3)

- Integration of NAMs: Frameworks and Weight of Evidence
 - Section 26(h) and (i) – use of Weight of Evidence (WoE) and Best Available Science
 - Section 4(h) – “information of equivalent or better scientific quality” (than traditional animal models)
 - Various frameworks for Integrating or combining NAMs:
 - Adverse Outcome Pathway (AOP)
 - Integrated Approaches to Testing and Assessment (IATA)
 - Defined Approach (DA)
 - Other considerations based on a tiered approach (examples – endocrine program approach)



Establishing Scientific Relevance, Reliability and Confidence of NAMs (1)

- Framework (OECD Guidance Document 34):
 - Relevance – regulatory need/usefulness and associated limitations
 - Reliability - reproducibility
 - Transparency (i.e., release of data sets and performance characteristics)



Establishing Scientific Relevance, Reliability and Confidence of NAMs (2)

- Criteria (largely based on Casati et al., 2017)
 - Decision context defined
 - Where possible, NAM should be mechanistically and biologically relevant
 - Criteria for selecting reference or training chemicals
 - Reliability be considered in context of its use and accepted best practices
 - NAM transparently described and all information is publicly available
 - Uncertainty described to fullest extent possible
 - Evaluation and implementation by third parties must be possible
 - NAM should under go independent scientific review



Education, Training and Collaboration

- NAMs and the new advancements in science (biology, chemistry, non-vertebrate animal test methods) need to be understood for proper application under TSCA
- Ensuring that EPA scientists, the regulated community, and interested stakeholders are properly training to understand and use NAMs is critical to the success of implementing Section 4(h) of TSCA (including public outreach)
- EPA will continue to collaborates with multiple domestic and international partners on the development and use of NAMs for regulatory purposes.



Implementation

- Current-near term activities and needs (next three years)
- Intermediate term objectives (3-5 years)
- Long term goal



Implementation: Near-Term (Next Three Years) – Building a TSCA NAM Foundation

- i. Continue to Implement NAMs to Evaluate Hazard, Exposure and Environmental Fate for New and Existing Chemicals
- ii. Review Existing NAMs and Create and Maintain a List as required.
 1. Publish list – June 2018
 2. Review other existing NAMs according to Chapter 5 criteria
- iii. Identify and Maintain Most Requested/Needed Studies for New and Existing Chemicals – Retrospective Analysis
- iv. Identify and Curate Available Existing TSCA Information on NAMs (and Traditional Test Data) – CBI; TSCA In-House Inventory Analysis



Implementation: Near-Term (Next Three Years) (cont.)

- v. Use of NAMs to identify candidates for prioritizing existing chemicals
- vi. Begin development of Scientific Information Technology (IT) Platform
- vii. Collaborate with partners and stakeholders to identify NAMs for further development (including case studies through TNT)



Implementation: Intermediate-Term Objectives (3-5 years)

- i. Progress towards use of NAMs for prioritization and risk evaluation (several possibilities identified: toxicological threshold of concern (TTC); encouraging voluntary submitters to use NAMs; possible use of NAMs in designing safer chemicals.
- ii. Maintaining the expansion of the TSCA NAM List
- iii. Developing and maintaining educational and outreach goals for regulatory scientists, end-users and the public
- iv. Continue collaboration with partners and stakeholders to identify NAMs for further development



Implementation: Long-Term

- EPA's long-term goal is to move towards making TSCA decisions (conducting prioritization and risk evaluations for new and existing chemicals) with NAMs in order to reduce and eventually eliminate vertebrate animal testing for TSCA.



Next Steps

- Draft Strategic Plan released on March 7
 - including response to public comments from November 2nd, 2017 meeting
- Public Meeting took place yesterday - **Tuesday, April 10th** in Washington, DC
- Comments on the Plan will be accepted through **April 26th** (45-day comment period)
- Final will be published by **June 22, 2018**



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