EPA Protection Agency

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Office of Chemical Safety and
Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods

(Draft)

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1. Executive Summary

On June 22, 2016, the Toxic Substances Control Act (TSCA) was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act. The EPA Office of Pollution Prevention and Toxics (OPPT) is responsible for carrying out the mandate of TSCA; which includes a new subsection that requires the EPA to develop a Strategic Plan to promote the use and development of alternative test methods and strategies to reduce, refine or replace vertebrate animal testing (Section 4 (h), *Reduction of Testing on Vertebrates*).

In this document, the EPA outlines its Strategic Plan for the reduction of testing in vertebrates for chemicals regulated under TSCA. The organizing framework for the EPA's strategy to reduce vertebrate animal testing relies heavily on what have been termed new approach methodologies (NAMs). NAMs have been adopted as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment. Both new and existing chemicals subject to TSCA regulation cover a broad range of chemical space and lack standard information requirements. Therefore, the EPA recognizes that this Strategic Plan necessarily describes a multi-year process with incremental steps for adoption and integration of NAMs that are appropriate and fit-for-purpose for making TSCA decisions (e.g., identifying candidates for prioritization, prioritization, and risk evaluation). NAMs would include methods that evaluate hazard (human health and environmental), exposure, and environmental fate as well as different approaches to integrate NAMs for decision making; i.e., adverse outcome pathways, (AOP), integrated approaches to testing and assessment (IATA) and defined approaches (DA).

This Strategic Plan has three core components: (1) *identifying, developing and integrating* NAMs for TSCA decisions; (2) *building confidence* that the NAMs are scientifically reliable and relevant for TSCA decisions; and (3) *implementing* the reliable and relevant NAMs for TSCA decisions. The EPA has identified seven current/near-term (<3 years) needs and activities. Completing these activities will result in moving towards four intermediate-term (3-5 years) objectives. These time frames, needs and activities provide the basis for developing NAMs, establishing reliability and relevance criteria for the NAMs, and implementing NAMs to inform decisions made under TSCA.

The EPA's long-term goal is to move towards making TSCA decisions (conducting prioritization activities and risk evaluations for new and existing chemicals) with NAMs in order to reduce and eventually eliminate vertebrate animal testing for TSCA. Achieving this goal will require the EPA to maintain a high level of commitment to identifying, developing, and integrating NAMs for implementation under TSCA and to work closely with stakeholders at every step.

To ensure the success of this Strategic Plan, the EPA is proposing the development of an internal TSCA NAM Team (TNT) to take advantage of expertise and resources within the Agency. The TNT would oversee the implementation of this Strategic Plan and be responsible for collaboration with stakeholders and the public.

2. Introduction

The Toxic Substances Control Act (TSCA) was originally enacted in 1976 and serves as the nation's primary chemical management law. On June 22, 2016, TSCA was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (hereafter referred to as TSCA). The EPA Office of Pollution Prevention and Toxics (OPPT) is responsible for administering TSCA, which includes new requirements and deadlines for actions related to the assessment and regulation of new and existing chemical substances. It also includes a new subsection under Section 4 (*Testing of Chemical Substances and Mixtures*) that requires the EPA to develop a Strategic Plan to promote the use and development of alternative test methods and strategies to reduce, refine or replace vertebrate animal testing (Section 4 (h), *Reduction of Testing on Vertebrates*, see Appendix A).

Alternative test methods and *strategies* are two different descriptors that have a common goal. Reduction, refinement and replacement (the 3Rs) have been hallmark principles in defining alternative test methods for over 50 years (Russell and Burch, 1959). *Reduction* is simply using fewer animals in experimentation, *refinement* of animal use includes procedures to lessen or avoid pain and distress, and *replacement* is using non-animal test systems or phylogenetically lower species. Strategies, on the other hand, include using more than just toxicity test methods to characterize hazard. Examples include the use of analog/read across techniques and tiered testing approaches to characterize a given human health or environmental endpoint. Collectively, *alternative test methods* and *strategies* fit into a new term - *new approach methodologies* (NAM) that has recently been used.[1] NAMs have been adopted as a broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment. For the purposes of TSCA, the EPA recognizes this new term as being synonymous with "alternative test methods and strategies to reduce, refine or replace vertebrate animals".

This draft Strategic Plan was developed by OPPT in collaboration with the EPA's Office of Pesticide Programs (OPP), the Office of Research and Development (ORD)[2], and the Office of Science Coordination and Policy (OSCP). OPPT has also worked with members, agencies, and technical workgroups of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)[3] and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).[4] Internationally, the EPA is actively engaged in many efforts in collaboration with the Organization for Economic Cooperation and Development (OECD), European Chemicals Agency (ECHA), Health Canada and Environment and Climate Change Canada, and the International Cooperation on Alternative Test Methods (ICATM).[5] Finally, the EPA works closely with its stakeholders, including the regulated community, animal welfare groups and other non-governmental organizations (NGOs),

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[1] A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html

[2] Including representatives from the National Center of Computational Toxicology (NCCT), National Exposure Research Laboratory (NERL), and the Immediate Office of ORD.

[3] https://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/index.html

[4] https://ntp.niehs.nih.gov/pubhealth/evalatm/index.html

[5] https://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/international-partnerships/index.html#About-ICATM

academia, and non-profit organizations such as the Health and Environmental Sciences Institute (HESI).[6] and the Center for Alternatives to Animal Testing (CAAT).[7]

NICEATM and ICCVAM recently completed "A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Product"[8] (hereafter referred to as the NICEATM/ICCVAM Strategic Roadmap). The NICEATM/ICCVAM Strategic Roadmap discusses the critical importance of collaboration and public-private partnerships in developing NAMs that fit the needs of regulatory and industry end-users, sharing data across sectors, and supporting staff training. Consistent with the NICEATM/ICCVAM Strategic Roadmap, the EPA is committed to work closely and openly with diverse stakeholders from industry, academia, and NGOs to support the implementation of the Agency's Strategic Plan.

In writing this draft Strategic Plan, the EPA notes the rapidly evolving nature of NAM information that will be useful in prioritizing, and ultimately developing quantitative risk assessments for chemicals. This evolving nature of development lends itself to an iterative process of NAMs implementation for regulatory decision-making. Moreover, approaches for establishing confidence (i.e., validation) are evolving rapidly. This draft plan should be considered a dynamic, evolving document, considering the best available science at a moment in time. As required by TSCA Section 4(h)(2)(E), the EPA will provide a report to Congress every five years (beginning in 2021) describing the progress in implementing this Strategic Plan.

The EPA hosted an expert meeting on November 2nd, 2017 during which a conceptual approach to the Strategic Plan was presented. A docket is available with the meeting materials and public comments received through January 10th, 2018 (http://www.regulations.gov; docket number HQ-OPPT-2017-0559). This document is an initial draft of the required Strategic Plan that is being made available to the public for comment. It is available both on the OPPT website[9] as well as the public docket (http://www.regulations.gov; docket number HQ-OPPT-2017-0559). The EPA is also releasing a response to comments document which describes responses to comments received associated with the November 2, 2017 meeting. This document is also available in the docket. The Strategic Plan must be developed by June 22, 2018.

3. Amended TSCA & Organization of this Strategic Plan

Section 4 of TSCA, entitled *Testing of Chemical Substances and Mixtures*, refers to the EPA's authority to require health and environmental effects testing be conducted relevant to a determination of an unreasonable risk of injury to health or the environment (Section 4(a)(1)). When such testing is required, TSCA further requires the EPA "shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this title, the use of vertebrate animals in the testing of chemical substances or mixtures…" (Section 4(h)(1)). Section 4(h)(2)(A) states the EPA shall:

[6] http://hesiglobal.org/
[7] http://caat.jhsph.edu/
[8] https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html
[9] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

"…develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment of chemical substances or mixtures…"

Section 4(h)(2) (C) and (D) require the EPA to develop a list of NAMs to include in the Strategic Plan 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" along with criteria "for considering scientific reliability and relevance" of NAMs. Section 4(h)(2)(D) also requires the agency provide for public notice and comment on the contents of the plan. Section 4(h)(2)(F) requires the EPA to prioritize and carry out performance assessment, validation, and translational studies to accelerate the development of NAMs.

Under other provisions of TSCA,[10] the Agency may rely on testing for decision-making. Sections 5 and 6 of TSCA pertain to new chemicals and existing chemicals, respectively. Section 8, entitled *Reporting and Retention of Information*, has a subsection (e) which requires the Administrator to be notified of any substantial risk information.

Under Section 5(a)(3), the EPA determines that either: 1) the new chemical substance *presents an unreasonable risk* of injury to health or the environment; 2) the *information* available to the Administrator *is insufficient to make a reasoned evaluation* of the health and environmental effects, 3) the new chemical substance *may present an unreasonable risk* of injury to health or the environment, (4) the new chemical substance is or will *be produced in substantial quantities*, and such substance either enters or may be reasonably anticipated to enter the environment in substantial quantities or *there is or may be significant or substantial human exposure* to the substance, or (5) the new chemical substance is *not likely to present an unreasonable risk* of injury to human health or the environment.

Section 6 of TSCA has changed the way the EPA evaluates existing chemicals. Section 6(b), entitled *Risk Evaluations*, lays out in detail the requirement to prioritize chemicals (Section 6(b)(1)) for eventual risk evaluation. Section 6(b)(4) describes the risk evaluation process. The regulatory decision is to determine whether a chemical substance, under the conditions of use[11], presents an unreasonable risk of injury to health or the environment. There have been two rules published to describe the prioritization and risk evaluation processes.[12]

Section 8(e) requires notification to the Administrator when information becomes available to any person which reasonably supports the conclusion of substantial risk of injury to health or the environment. OPPT acknowledges that as NAMs are developed and used, there needs to be

[10] Sections 4(a) and (b) pertain to parts of TSCA relating to procedures and process on requiring information via a rule, order or consent agreement once a decision is made that the information is necessary to make a decision. This draft Plan is focused on developing and using NAMs and so the rule, order or consent agreement process will not be discussed.

[11] TSCA defines conditions of use as: "..the circumstances, as determined by the Administrator, under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." (TSCA Section 3(4)).

[12] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/how-epa-evaluates-safety-existing-chemicals

consideration of updating the TSCA Chemical Substantial Risk Notice guidance to reflect the potential role of NAMs in determination of risks.[13]

For both new and existing chemicals, the EPA is required to make determinations regarding whether a chemical substance presents an unreasonable risk of injury to human health or the environment. As risk-based decisions, there is a requirement for either a qualitative or quantitative risk assessment that characterizes exposure and hazard information.

Consistent with the statute Sections 4 (testing), 5 (new chemicals) and 6 (existing chemicals), the EPA will consider NAMs for the following TSCA decision contexts: screening candidates for prioritization, prioritization, and risk evaluation. These contexts follow the concept of "fit-for-purpose" which is interpreted to mean that a particular NAM may be suitable for one regulatory use and not others. In other words, one method does not fit all situations; and thus flexibility is necessary.

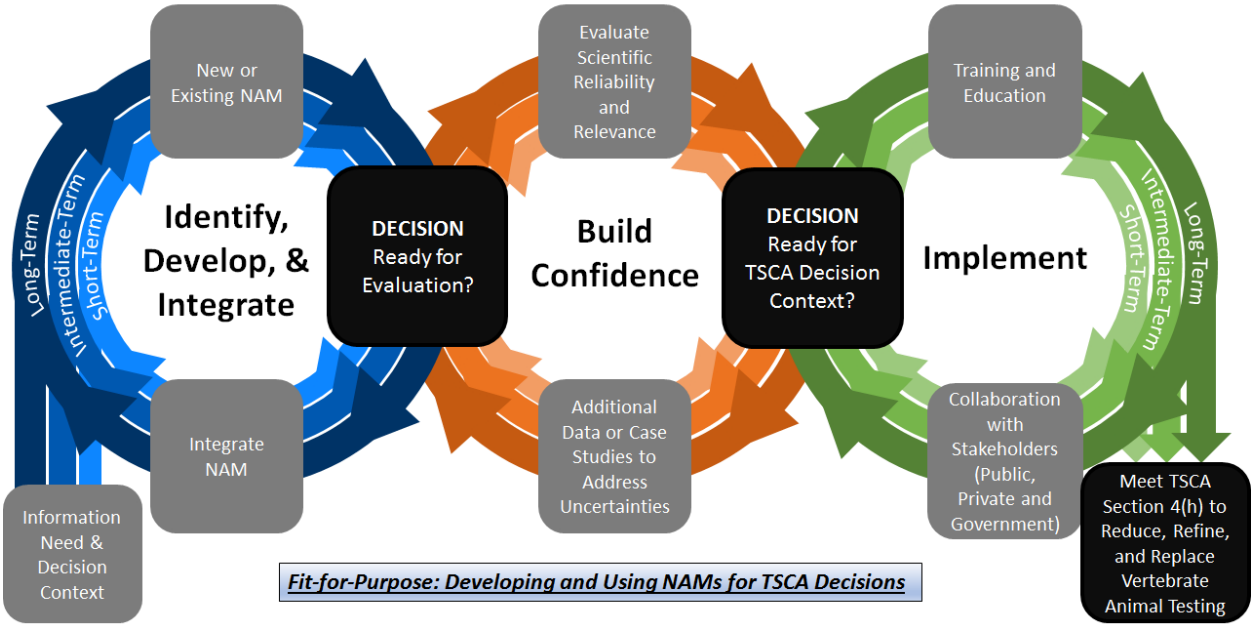
The EPA Strategic Plan is organized as follows:

- Chapter 4 - Identification, Development and Integration of NAMs – describes the first step in the strategy to identify, develop, and integrate NAMs for important regulatory endpoints or information needs in TSCA.
- Chapter 5 - Establishing Scientific Relevance, Reliability and Confidence of NAMs – outlines criteria to ensure that NAMs provide equivalent or better scientific quality and relevance to fulfill the legal requirements for the development and use of NAMs under TSCA.
- Chapter 6 - The Importance of Training, Education, and Collaboration – acknowledges the need for a training and education plan for scientists, the regulated community, interested stakeholders, and the public as an integral part of the implementation step in the strategy and encourages engagement with key stakeholders (e.g., formation of industry consortia) and US and international bodies (ICCVAM and OECD) regarding the development and use of NAMs
- Chapter 7 - Implementation of NAMs Under TSCA – provides the final step in the strategy for current and near-term, intermediate-term, and long-term activities to meet both the legal and scientific needs to achieve the mandate of Section 4(h).
- Chapter 8 - Conclusions and Next Steps – describes a plan to measure success and clear milestones to ensure implementation of the Strategic Plan is presented.

Figure 1 below shows the three core components central to this Strategic Plan: (1) *identification, development, and integration of NAMs*; (2) *building confidence* in NAMs by ensuring they are reliable and relevant for TSCA; and (3) *implementing* NAMs for TSCA prioritization and risk evaluation decisions.

[13] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/reporting-tsca-chemical-substantial-risk-notice

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



4. Identification, Development, and Integration of NAMs

The first step in the overall the EPA strategy combines the identification of existing NAMs and development of NAMs together with their integration to address the broad array of endpoints and chemicals regulated under TSCA. The TSCA-related NAMs generally fall into four categories including chemical characterization, hazard identification and characterization, dosimetry and *in vitro -in vivo* extrapolation, and exposure. The categories are outlined in the subsequent sections together with different frameworks for integrating the NAMs for different purposes and decisions. The identification and development of NAMs will be informed by the near- and intermediate activities outlined in Chapter 7. The EPA will carry out this step in the strategy through internal activities, collaborations with external research organizations and stakeholders, and international partnerships with other regulatory and research groups.

As there are no specific requirements to generate new health and safety information[14] to support new chemicals determinations under TSCA, the EPA has traditionally used a variety of NAMs either developed or available to evaluate important parameters to assess hazard, exposure and risk. These include EPA-developed NAMs[15] to predict physical/chemical properties, ecological hazard, carcinogenicity, as well as other methods and guidance to identify structural alerts for toxicity using structure-activity relationships (SAR) or quantitative SARs (QSARs),[16] use of

[14] The word "information" replaced the word "data" throughout amended TSCA.
[15] https://www.epa.gov/tsca-screening-tools
[16] Guidance documents and tools used include the OECD QSAR Toolbox and documents available at: http://www.oecd.org/chemicalsafety/risk-assessment/guidancedocumentsandreportsrelatedtoqsars.htm and at: http://www.oecd.org/env/ehs/oecdquantitativestructure-activityrelationshipsprojectqsars.htm

analogs/categories/read-across,[17] and estimates of exposure. The EPA has recently released a draft public document that provides an overview of the process and methods used to evaluate new chemicals under TSCA.[18]

TSCA mandates the EPA prioritize the existing chemicals in commerce to determine which are considered high priority candidates for risk evaluation under Section 6. A rule was published in June, 2017 and a public meeting was held on December 11, 2017 to discuss approaches to inform candidates for prioritization. At the public meeting, the EPA presented a document *(Discussion Document: Possible Approaches and Tools Identifying Potential Candidate Chemicals for Prioritization);*[19] which contains a section on the use of NAMs for identifying potential candidates for prioritization purposes.

a. Opportunities to Deploy and Develop NAMs for TSCA

i. Chemical Characterization

Chemical structure and physicochemical properties determine critical aspects of hazard, dosimetry, exposure, and environmental fate/persistence. In the absence of experimental data, NAMs that predict physicochemical properties are used to inform many decisions in TSCA new chemical reviews. The EPA uses different NAMs (e.g., EpiSuite, OECD QSAR Toolbox) that use structure to predict a range of physicochemical properties, such as water solubility and octanol: water partition coefficients (details in URLs and references in *Points to Consider* document).[20] Collectively, this information is used to predict absorption/bioavailability, distribution in the environment and other important parameters used to estimate hazard and exposure for characterization/risk assessment decisions (listing of tools and models used are at the OPPT website).[21] In Appendix B of this strategic plan, the EPA provides examples of existing NAMs that are currently used for chemical characterization.

Overall, many of the approaches rely on historical datasets and their utility depends on their domain of applicability, transparency and availability of the training and test data, characterization of uncertainty, and adherence to the OECD [Q]SAR validation principles (e.g., OECD Guidance Document 69).[22] The EPA supports public access to the datasets needed for predictive modeling as part of building scientific confidence and is one of the criteria listed "for considering scientific reliability and relevance" of NAMs under Section 4(h)(2). However, OPPT does use confidential business information (CBI) to regularly update and refine its models

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[17] OECD guidance/tools - http://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm; OPPT New Chemical Categories document - https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf

[18] The process is being updated and documented. See recent "Points to Consider" document that was presented in a Dec 6, 2017 public meeting - https://www.epa.gov/sites/production/files/2017-11/documents/draft_points_to_consider_11-09-17.final_.pdf

[19] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/possible-approaches-identifying-potential-candidates

[20] https://www.epa.gov/sites/production/files/2017-11/documents/draft_points_to_consider_11-09-17.final_.pdf

[21] https://www.epa.gov/tsca-screening-tools

[22] *Ibid* at footnote 16.

as this information, although not public, is critical to the Agency's mission of evaluating TSCA chemicals.

Apart from the identification and refinement of existing methods, the EPA supports the continued evolution and development of new methods that utilize chemical structure to predict physicochemical properties for unique substances and for chemical classes outside the domain of applicability of existing models. This will ensure the best available science is applied to decisions under TSCA. In the near- and intermediate-term activities identified in the Chapter 7 of this Strategic Plan, knowledge gaps will be assessed through interactions with stakeholders and used to guide future research and development objectives.

ii. Hazard Identification and Characterization

Toxicity testing is conducted to identify potential hazards a chemical can elicit and to characterize dose-response relationships for those hazards. Most current approaches are expensive, time-consuming, and may require traditional *in vivo* toxicity tests to extrapolate to humans (mammalian systems) or to environmental organisms (vertebrate, invertebrate and plant species). Among the existing NAMs for hazard identification, the EPA uses structure-based approaches such as ECOSAR to predict ecotoxicity and OncoLogic models to predict potential carcinogenicity as well as the Analog Identification Method (AIM) tool to identify appropriate analogs for hazard more generally.[23]

Apart from *in silico* and *in chemico* approaches that rely on chemical structure, experimental NAMs that use *in vitro* assays and computational modeling have also shown promise for hazard identification and characterization. The EPA uses non-guideline approaches in conducting risk assessment, including NAMs shown to be fit for specific purposes on a case-by-case basis. For example, chemicals could be prioritized, or candidates for prioritization identified, using data from the EPA's ToxCast and the Toxicology in the 21st Century (Tox21) consortium, the latter a federal collaboration among the National Institutes of Health, including the National Toxicology Program (NTP) at the NIEHS and the National Center for Advancing Translational Sciences, the EPA, and the Food and Drug Administration. Similarly, many industry laboratories routinely use *in vitro, in silico,* and *in chemico* approaches in research and development that are likely to provide relevant information in evaluating chemical hazard identification or characterization.

There are multiple national/international organizations which have been working to identify NAMs for hazard identification and characterization; including ICCVAM in the U.S., ECVAM in Europe, and the OECD.[24] These methods have been developed through traditional validation

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[23] *Ibid* at footnote 21.

[24] List of alternative methods accepted by US agencies through ICCVAM - https://ntp.niehs.nih.gov/pubhealth/evalatm/accept-methods/index.html and list of ICCVAM Guidance Documents: https://ntp.niehs.nih.gov/pubhealth/evalatm/accept-methods/guidance/index-2.html ; List of alternative methods listed as "regulatory acceptance/standards" completed according to the European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM) through its Tracking System for Alternative Methods towards Regulatory Acceptance (TSAR) - http://tsar.jrc.ec.europa.eu/ ; and List of alternative methods/strategies presented by health endpoints in the OECD - http://www.oecd.org/chemicalsafety/testing/oecdguidelineapproachbyendpoints.htm; and others such as Alttox.org –

approaches and have been heavily vetted and accepted and serve as examples that are important and useful for the U.S. and TSCA. Some NAMs have gone through the OECD Test Guideline process, which supports harmonization, consistency and acceptance by regulatory agencies around the world (the Mutual Acceptance of Data, or MAD).[25] The EPA will accept studies conducted under OECD guidelines.[26] A list of currently used NAMs is provided in Appendix B.

There are few endpoints typically relevant to TSCA decision making that are covered by existing, validated NAMs. For new and existing chemicals, few NAMs exist that reliably predict complex endpoints such as developmental, reproductive, and repeated-dose toxicity studies. In addition, the NAMs that do exist often do not provide predictions of points of departure that are needed for risk evaluation. As part of the near-term implementation activities, the EPA will be performing a retrospective analysis on the most requested studies and associated needs for NAMs when assessing new and existing chemicals. The results from this retrospective analysis will be used to inform research and development activities for hazard-related NAMs.

Innovation and progress in the development of NAMs is rapidly occurring. New technologies and methods are continually being developed that enable the evaluation of new pathways, cell types, tissues, and chemical interactions with biological systems or allow the evaluation to proceed more efficiently or cost-effectively. In addition, biological knowledge continues to evolve to enable both the development of novel *in vitro* assays as well as to inform the development of better computational models that integrate *in vitro*, *in vivo*, and *in silico* data. The development of novel NAMs for hazard identification and characterization is an integral part of the strategy to address the knowledge gaps and target the replacement of studies most frequently requested by the EPA under TSCA.

The technical limitations of *in vitro* NAMs have been documented previously (Tice *et al.,* 2013). Although not a complete list, these technical limitations include inadequate coverage of biological targets and pathways, reduced or distinct xenobiotic metabolism compared to *in vivo* responses, relatively simplified assays for inferring integrated physiological responses, and chemical compatibility (e.g., non-volatiles, specific solvents). Progress is being made in overcoming many of the technical limitations through advancements in the design and implementation of the *in vitro* test systems including increasing metabolic activity[27], expanding chemical compatibility, and more sophisticated culture systems (Low and Tagle, 2017). Alternative species models and systems-level computational models offer another potential path for addressing some of the technical limitations by incorporating or simulating tissue and organ-level responses (Planchart *et al.,* 2016; Leung *et al.,* 2016). For *in vitro* NAMs to provide information of equivalent or better scientific quality and relevance for TSCA, many of these technical limitations must be addressed.

table of validated and accepted alternative methods: http://alttox.org/mapp/table-of-validated-and-accepted-alternative-methods/

[25] http://www.oecd.org/chemicalsafety/testing/mutualacceptanceofdatamad.htm

[26] http://www.oecd.org/chemicalsafety/testing/

[27] https://www.challenge.gov/challenge/transform-tox-testing-challenge-stage-2/

iii. Dosimetry and *In Vitro* - *In Vivo* Extrapolation (IVIVE)

In risk evaluations, physiologically-based toxicokinetic (PBTK) or toxicokinetic (TK) modeling has been used to predict time course blood and tissue concentrations and relate tissue concentrations with the adverse effect. However, the development of such models is time and resource intensive and has traditionally required the use of vertebrate animals. The effective use of NAMs to inform risk-based decisions in TSCA will require consideration of *in vitro* disposition, *in vivo* dosimetry, and approaches that allow fit-for-purpose linkages to external exposure estimates. Currently within TSCA, the use of existing NAM for dosimetry and TK is limited. With the potential exception of evaluating bioavailability, few TK-related NAMs are listed as acceptable by national/international organizations; however, the EPA is aware that OECD has recently started a project to develop a guidance document on building PBTK models solely reliant on *in vitro, in chemico*, and *in silico* approaches which will be useful in advancing the implementation of NAM-based PBTK models.

The utilization of *in vitro* NAMs for hazard characterization is greatly enhanced by understanding the fate and movement of a chemical within the assay. Traditionally, estimates of *in vitro* potency have relied on nominal concentrations. However, for some chemicals, binding to plastic and protein, partitioning into *in vitro* constituents, and intracellular transport can result in potency estimates that vary significantly from the nominal concentration (Kramer *et al.,* 2015). Additional research in the development of NAMs is needed to identify and characterize generalizable principles of *in vitro* chemical disposition that can be applied across a broad chemical domain such as that under TSCA. The resulting information can then be incorporated into computationally predictive models, providing a systematic and defensible strategy to adjust *in vitro* potency values.

TK is essential for translating *in vitro*-derived potency values into an external administered dose required to achieve internal concentrations equivalent to these potency values. Existing NAMs have focused on simplified models that use a few pharmacokinetic factors, with values derived using *in vitro* experimental assays. Other pharmacokinetic considerations have been set to conservative assumptions (e.g., 100% absorption) or parameterized based on relatively simple estimates (e.g., urinary excretion) (Wetmore *et al.,* 2015). Population variability is typically incorporated into these models based on known distributions for each of the key parameters.

In the near- and intermediate-term activities identified in Chapter 7 of this strategic plan, knowledge gaps will be assessed and used to guide future research and development objectives. Among those knowledge gaps, application of the appropriate TK NAMs across the TSCA chemical landscape will require additional development of a portfolio of *in silico* and *in vitro* NAMs that predict key pharmacokinetic factors. Despite successes with the simplified TK-related NAM, this approach is not sufficiently predictive across the entire chemical space covered by TSCA (Wambaugh *et al.*, 2015). Novel *in silico* and *in vitro* NAM covering additional pharmacokinetic processes of absorption, distribution, and metabolism or refinements to existing NAM addressing unique characteristics for chemicals under TSCA will need to be developed. Similarly, tiered approaches to efficiently evaluate the broad range of required chemicals across multiple domains and TSCA decision contexts will need to be considered.

iv. Characterizing Exposure to Humans and the Environment.

TSCA requires consideration of exposure and conditions of use[28] in conjunction with hazard when performing both prioritization (existing chemicals) and risk evaluations (new and existing chemicals). While exposure-related NAMs may not directly replace vertebrate animal testing, they may help inform which chemicals may pose low risk concerns to human or environmental health and which animal tests may not be necessary due to exposure considerations. The EPA *Discussion Document: Possible Approaches and Tools Identifying Potential Candidate Chemicals for Prioritization*[29] provides a list of possible tools/approaches for NAMs the EPA may use in identifying candidate chemicals for prioritization and in the prioritization process for existing chemicals under TSCA. For new chemicals, the EPA uses a variety of existing tools[30] to estimate environmental releases/occupational exposure (ChemSteer), consumer (CEM), general population and environmental exposure to chemicals (E-FAST), and environmental distribution and persistence (EpiSuite). Appendix B provides a starting list of existing NAMs that are acceptable for characterizing exposure.

The knowledge gap analysis in Chapter 7 of the Strategic Plan will help inform specific needs in developing exposure-related NAMs. Advances in computational modeling and applications of machine learning methods are transforming exposure modeling, providing quantitative exposure estimates using minimal data (Isaacs *et al.,* 2014; Wambaugh *et al.,* 2014), predicting functional use and product composition (Phillips *et al.,* 2017), and allowing systematic and data-driven discoveries of critical exposure trends and patterns (Egeghy *et al.,* 2016). These advances can help inform conditions of use, thus enhancing TSCA risk-based prioritization and risk evaluation decisions. Despite the rapid evolution of exposure-related NAMs, specific improvements would enable broader application with TSCA. These improvements include expanding the chemical domain of the biomonitoring data used to calibrate the high-throughput exposure models, expansion of databases that provide product composition and use (including use patterns for specific subpopulations), development of high throughput exposure models for occupational settings, and expansion of ambient chemical release information for refinement of human and environmental exposure estimates.

b. Integration of NAMs: Relevant Frameworks (AOP, IATA, Defined Approaches, Tiered Testing, Pathway Analysis)

TSCA Section 26(h) and (i) require development of weight of evidence (WOE) evaluations using standards consistent with the best available science, technical procedures, measures, methods, protocols, methodologies, or models. Therefore, the EPA needs scientifically supportable approaches for developing WOE for the use and implementation of NAMs. In addition, stated

[28] Section 3(4) defines conditions of use as: "…the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of."

[29] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/possible-approaches-identifying-potential-candidates

[30] https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-exposure-and-fate-under-tsca#fate

throughout Section 4(h) is the requirement that NAMs need to provide "information of equivalent or better scientific quality…" than the traditional animal models. To accomplish this objective, the integration of NAMs will be a critical component of the first step in the EPA strategy to enable the prediction of complex toxicological responses, cover the broad chemical space covered under TSCA, and address the various types of uncertainty.

There are currently a variety of approaches for integrating NAMs as part of WOE or as alternatives for an existing *in vitro* and *in vivo* studies used in decision making. One approach for integrating NAMs is the adverse outcome pathway (AOP) framework, which describes the linkage (or potential linkage) between a molecular initiating event with progressive levels of biological organization at the individual or population level and provides a generalizable, chemical agnostic approach for organizing the key events that occur leading to a specific adverse outcome (Ankley *et al.,* 2010). The EPA supports the continued development of AOPs as an organizational framework for endpoints and responses relevant to TSCA. The EPA participates in the development of the OECD AOP Knowledgebase which includes the AOP wiki, Effectopedia, AOP Xplorer, and Intermediate Effects database which provide storage, evaluation, and linkage of information related to AOPs.[31]

Another means of combining NAMs is OECD's Integrated Approaches to Testing and Assessment (IATA). OECD defines an IATA as "a structured approach that strategically integrates and weighs all relevant data to inform regulatory decisions regarding potential hazard and/or risk and/or the need for further targeted testing and therefore optimizing and potentially reducing the number of tests that need to be conducted."[32] IATA follow an iterative approach to answer a question in a specific regulatory context, aware of the need for the acceptable level of uncertainty associated with the decision context (OECD, 2017). Similar to Section 26 of TSCA, the overall assessment process within IATA is based on WOE, which by definition uses expert judgment in the weighing of the different pieces of information.

A more structured, rule-based approach to integrating NAMs is the defined approach (DA)[33]. DAs are based on fixed sources of information (e.g., an *in vitro* assay and computational model) and a fixed interpretation of results from those information sources. Thus, DAs emphasize predictions which are rule-based and separate from predictions/approaches that are based on expert judgment. The fixed nature of DAs, where they may be available, should facilitate their potential use under the OECD mutual acceptance of data (MAD) program. Thus, where IATA are designed to be flexible and adaptable to particular regional requirements or regulatory statutes, DAs are proposed to fill a different, rule-based need where possible. For example, recently the key events in the skin sensitization AOP have provided the foundation for the integration of multiple *in vitro, in chemico,* and *in silico* NAMs to predict skin sensitization DAs as a replacement for the local lymph node assay in mice (Casati *et al.,* 2017).

Apart from integrating NAMs to predict complex toxicological responses, combining NAMs in tiered approaches may also enable more efficient testing of a large number of chemicals. High

[31] http://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm

[32] Report of the Workshop on a Framework for the Development and Use of Integrated Approaches to Testing and Assessment. 2015. OECD Series on Testing and Assessment No. 215

[33] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)28&doclanguage=en

throughput *in vitro* NAMs could be used to cast a broad biological net to capture potential hazards associated with chemical exposure. Alternative species, more complex *in vitro* culture systems, and/or *in silico* NAMs could then be integrated as a second tier to further refine the biological target or mode-of-action; ultimately linking a chemical with a putative AOP or apical effect. The integration of NAMs in a tiered testing approach would be an important component in the overall strategy to evaluate the thousands of chemicals regulated under TSCA and reduce the requirement for animal testing by targeting subsequent *in vivo* toxicity testing.

The integration of multiple NAMs for the same molecular target or the same pathway may also provide a means for increasing scientific confidence in a chemical response. Each assay and technology has a domain of applicability and a defined false negative and false positive rate. By integrating multiple NAMs, the domain of applicability can be broadened and the false negative and false positive rates reduced. For example, the EPA has incorporated an integrated battery of high-throughput *in vitro* screening assays and computational model of the ER pathway activity for prioritization and screening of endocrine bioactive compounds. Multiple assays were used to encompass different points of the pathway, and different technologies were used in order to avoid findings that may result from noise or assay interference (Browne *et al.,* 2015). This model has undergone a performance-based validation and was determined to be an acceptable alternative to some of the Tier 1 low-throughput assays in the Endocrine Disruptor Screening and Testing Program (EDSP) program at the EPA[34]. Similar combinations of NAMs could be developed and used for high-priority targets or pathways in TSCA.

5. Establishing Scientific Relevance, Reliability and Confidence of NAMs: Development of Criteria for TSCA-related Decisions

As shown in Figure 1, the second of the three components in the overall strategy centers on *Building Confidence.* This involves the development of a framework and associated criteria for establishing scientific confidence in NAMs to ensure that various *in silico, in vitro*, and *in chemico* methods provide "equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment" as compared to vertebrate animal testing, as required in Section 4(h)(2)(A).

Multiple entities and individuals have proposed frameworks for building confidence and accelerating the use of NAMs (e.g., NICEATM/ICCVAM Roadmap; Patlewicz *et al*., 2013; Patlewicz *et al.,* 2015; Cox *et al.,* 2014). The OECD *Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (GD 34)*[35] states that "new test methods undergo validation to assure that they employ sound science and meet regulatory needs", "the validation process should be flexible and adaptable", and that performance must be "demonstrated using a series of reference chemicals" and "evaluated in relation to existing relevant toxicity data."

[34] https://www.epa.gov/endocrine-disruption
[35] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2005)14&doclanguage=en

The first component is *relevance*. OECD GD 34 defines relevance as encompassing the regulatory need, usefulness of the alternative method(s) and associated limitations of the test method. As such, relevance incorporates *fit for purpose* and *utilization* as a contextual evaluation and application of the NAM or integrated NAMs, and may include a WOE analysis of their use, based on all available evidence, for use in making qualitative or quantitative predictions.

Reliability is defined in GD34 as the extent of reproducibility of results from a test within and among laboratories over time, when performed using the same standardized protocol. However, demonstrating between-lab reproducibility is applicable only when developing a standardized protocol intended to be used by any naïve laboratory in any world region. Many *in vitro* NAMs are not amenable to transfer into naïve laboratories and the demonstration of reliability is therefore confined to assessment of within laboratory reproducibility. Reliability of *in silico* NAMs is derived from transparency and peer review.

Inherent in confidence building is the need for *transparency* such as the release of datasets used to develop the NAM and associated performance characteristics and release the computer code or explicitly define the computational models.

Casati *et al*. (2017) have proposed a framework for performance-based approaches in the evaluation of DAs for skin sensitization. The framework was initially proposed by members of ICATM and relies on a set of qualitative and quantitative information defined in the OECD document entitled *Guidance Document on the Reporting of Defined Approaches to be Used Within Integrated Approaches to Testing and Assessment* (OECD Guidance Document 255).[36] This work provides the foundation for international efforts to develop consensus on non-animal approaches towards the complete replacement of the laboratory animal studies commonly used to evaluate skin sensitization. The evaluation criteria proposed by Casati *et al.* (2017) were recently discussed in a Special Session of the OECD Working Group of the National Coordinators for the Test Guidelines Programme (WNT) for the project on Performance-Based Test Guideline on Defined Approaches for Skin Sensitization. The group agreed upon these principles as the basis for an evaluation framework to be applied to defined approaches.

Section 4(h)(2) requires the EPA develop criteria "for considering scientific reliability and relevance" of NAMs. Based on the framework outlined above, the following provides a reasonable set of criteria for use by the EPA under TSCA:

- The decision context should be clearly defined.
- Where possible, the NAMs should be mechanistically and/or biologically relevant to the hazard being assessed. If not possible, the chemical domain of applicability of the NAMs should be defined to determine relevance to the TSCA chemical landscape.
- Criteria for selecting reference or training chemicals should be defined and supporting information should be adequately referenced.
- The reliability of the NAM should be considered within the context of intended use and accepted best practices within the given field.

[36] http://www.oecd.org/publications/guidance-document-on-the-reporting-of-defined-approaches-to-be-used-within-integrated-approaches-to-testing-and-assessment-9789264274822-en.htm

- The NAMs should be transparently described and all information made available to the public (e.g., any datasets and modelling code are publicly available and its known limitations are clearly described). TSCA CBI restrictions may not allow public accessibility of all information all the time.
- Uncertainty should be described to the fullest extent possible.
- Evaluation and implementation by third parties must be possible (i.e., the alternative approach must be readily accessible commercially and/or the relevant protocols must be available).
- The NAMs should undergo an independent scientific review in order to raise confidence in the approach.

These criteria are important as a rubric for the EPA and others to consider as NAMs are being developed and evaluated. The EPA often receives information from new chemical submitters that may include NAMs that are new or different than what the Agency uses in the new chemicals program. In some cases, the EPA receives [Q]SAR estimates as outputs from proprietary programs with which the Agency does not have first-hand knowledge or experience. Applying the criteria outlined above for relevance and reliability helps industry (submitters), regulators and others evaluate NAMs for TSCA decisions.

Section 4(h)(2)(F) also requires the EPA to prioritize and carry out performance assessment, validation, and translational studies *to accelerate the development of NAMs*. The EPA views its collaborations with ICCVAM and NICEATM, internationally through engagement with organizations as OECD and ICATM as well as through public dialogue as meeting this requirement. Recently, the EPA has become a more active member of several ICCVAM technical workgroups, including a newly created one on read-across. ICCVAM technical workgroups perform a variety of tasks such as developing scoping documents on existing requirements and information needs across the federal government for a toxicological endpoint, and providing a mechanism for developers of NAMs to communicate with and receive strategic guidance from agency representatives.

6. The Importance of Education, Training and Collaboration:

Application of NAMS, such as high-throughput test systems and computational data, to regulatory decisions requires a parallel investment in a broad range of translational, outreach, training, and quality assurance activities. Ensuring that the EPA scientists, the regulated community, and interested stakeholders are properly trained to understand and use NAMs is critical as the EPA moves forward in its implementation of TSCA. Learning the new advancements in science (biology, chemistry, computational toxicology, non-vertebrate animal test methods) are necessary to use the NAMs effectively and confidently for new and existing chemical prioritization and risk-based decisions under TSCA.

The EPA envisions an active and engaged dialogue with researchers, the regulated community, and other stakeholders as NAMs and their use are developed. For example, the development of information technology tools provides an efficient means to assemble and integrate NAM information related to health and environmental hazard, exposure and risk. The general engagement of the scientific community will be augmented by the development of customized training sessions for stakeholders. Education and training will cover both use and interpretation

of the information as well as the specific tools such as dashboards and workflows. Finally, similar to the *NICEATM/ICCVAM Strategic Roadmap*, one of the key goals is the need to connect end users (i.e., regulators) with the developers of NAMs.

Since the publication of the 2007 National Research Council (NRC) report (NRC,2007), the development and use of NAMs has relied heavily on collaborative efforts. In fact, TSCA encourages the EPA to work with both ICCVAM and OECD specifically (Section 4(h)(2)(A)(vii)); and further identifies a role for the EPA to work with industry (the formation of industry consortium (Sections 4(h)(1)(B)(iii) and 4(h)(2)(A)(viii)).

The EPA expects to expand its collaborative efforts on NAMs in the coming years. In addition to collaborating within and across the U.S. and international government authorities, the EPA will collaborate across sectors (public, private, academic, non-profit, animal welfare groups) to meet the goal of Section 4(h) of the amended TSCA.

7. Strategic Plan for Implementation of NAMs Under TSCA

The EPA has published NAM implementation strategies for pesticides and the endocrine program under FIFRA[37] and EDSP[38,39], respectively. In this Strategic Plan, the EPA builds on those plans, as well as the NICEATM/ICCVAM Strategic Roadmap, but with a focus on commercial chemicals and TSCA. TSCA covers a much broader range of chemical space and there are no standard information requirements from which to draw or begin implementation.

Chapters 4 and 5 in this document provide the background on the science and potential use of NAMs under TSCA, highlighting the internal use of NAMs in the EPA's new chemicals program. Chapter 6 documents the need for the EPA to enhance the training of its scientists, managers, and other stakeholders about NAMs that are being developed and evaluated and thus may be candidates for their potential use for TSCA decisions. Furthermore, Chapter 6 recognizes that the EPA, while already engaged in multiple collaborative efforts (e.g., ICCVAM, OECD), needs to build upon them to ensure the success of this Strategic Plan and the mandate of Section 4(h) of TSCA.

This chapter describes the activities that need to be done to implement this strategy. The activities are centered around three core components as presented in Figure 1, and for which timelines are provided below and in Table 1 that are sensitive to the requirements in the law. The EPA recognizes that this Strategic Plan is a multi-year process with incremental steps for adoption and integration of NAMs for TSCA decisions (e.g., identifying candidates for prioritization, prioritization, and risk evaluation). As such, a key activity in this Strategic Plan will be to identify evolving NAMs and prioritize further development (leading to regulatory acceptance) of NAMs that are of potential interest to TSCA regulatory outcomes (i.e., fit-for-purpose).

The EPA has identified current and near-term (<3 years) and intermediate-term (3-5 years) regulatory and research needs and activities based on Section 4(h) of TSCA. These time-frames,

[37] EPA Office of Pesticide Programs Strategic Vision for Adopting 21st Century Science Methodologies
[38] EPA Endocrine Disruptor Screening Program (EDSP) in the 21st Century
[39] Endocrine Disruptor Screening Program for the 21st Century: Work Plan

needs and activities provide the basis for developing NAMs, establishing reliability and relevance to establish confidence in the NAMs, and finally using the NAMs for TSCA decisions.

An important part of any Strategic Plan is to look to the future. The EPA's long-term goal is to move towards making TSCA decisions (conducting prioritization activities and risk evaluations for new and existing chemicals) with NAMs in order to reduce and eventually eliminate vertebrate animal testing for TSCA. Achieving this goal will require the EPA to maintain a high level of commitment to identifying, developing, and integrating NAMs for implementing under TSCA as described here and to work closely with stakeholders at every step.

Finally, to ensure success of this Plan, the EPA is proposing the development of a TSCA NAM Team (TNT) to take advantage of experts/resources within the Agency. The proposed members of the team include, but not be limited to, experts from OPPT, OPP, OSCP and ORD.

a. Current to Near-Term Needs and Activities: Building a TSCA NAM Foundation (Now-3 years)

TSCA Section 4(h)(1) states the EPA shall reduce and replace the use of vertebrate animals in testing – to the extent practicable and scientifically justified (language throughout Section 4(h)) - for decisions (identifying candidates for prioritization, prioritization, and risk evaluation) for both new and existing chemicals.

TSCA mandates the EPA prioritize existing chemicals in commerce to determine which are considered high and low priority candidates for risk evaluation under Section 6. A rule was promulgated in June 2017 and a public meeting was held on December 11, 2017 to discuss approaches to inform the identification of candidates for prioritization. At the public meeting, the EPA presented a document *(Discussion Document: Possible Approaches and Tools Identifying Potential Candidate Chemicals for Prioritization);*[40] which contains a section on the use of NAMs for identifying potential candidates for prioritization purposes.

In identifying near-term needs and activities, the EPA envisions these next few years as modernizing its knowledge base on NAMs for their potential regulatory use under TSCA. This will also be the basis for the EPA's plans to continue and expand on its collaborative efforts inside and outside the government, and to put more effort into the important process of training and educating regulatory and industry end-users. Thus, there are seven near-term activities identified:

i. Continue to Implement NAMs to Evaluate Hazard, Exposure and Environmental Fate for New and Existing Chemicals

The EPA has a long history of using NAMs, such as QSAR and read across, for new chemicals to qualitatively describe hazard (i.e., a possible positive or negative result for a given health or

[40] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/possible-approaches-identifying-potential-candidates

environmental endpoint), exposure (i.e., estimating occupational and consumer exposures, as well as environmental releases for evaluating exposure to the general human population and ecological receptors), and environmental fate (i.e., distribution and persistence). The EPA needs to build upon these and identify other NAMs that meet the criteria outlined in Chapter 5. For example, some endpoints such as skin sensitization, eye and skin irritation, and mutagenicity have existing OECD guidelines for NAMs which meet the EPA's needs.
TIMELINE: ***Ongoing***

ii. Review Existing NAMs & Create and Maintain a List per Section 4(h)(2)(C)

Section 4(h)(2)(C) requires the EPA develop a list of specific 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".

There are a number of national/international governmental organizations which have been working to identify NAMs; including ICCVAM in the U.S., ECVAM in Europe and the OECD.[41] All three organizations have various lists and levels of information related to accepted NAMs, NAMs under evaluation, and NAMs being developed. Methods and approaches that are on one or more of these accepted lists have been through a vetting process that accounts for *relevance* and *reliability* for the stated purpose of the method or approach.

Appendix B is the working list as required under TSCA Section 4(h)(2)(C), and it includes NAMs currently used by the EPA in TSCA.

The EPA views this current list as a snapshot in time. It is envisioned that one of the central functions of the newly formed TSCA NAM Team will be to establish a systematic and transparent process to update and maintain the list. Chapter 5 in this Strategic Plan provides a framework for principles that could be used to refine and define criteria for relevance and reliability for NAMs to be eligible for placement on the TSCA NAM List.

In making decisions related to using NAMs under TSCA (i.e., fit-for-purpose for prioritization, hazard, exposure or risk-based characterization), it will be important to be both flexible and scientifically rigorous. Flexibility is important because there are few specific information requirements for evaluating chemicals under TSCA. Thus, submitters (and regulators) can use appropriate information that would be best for a given chemical and use scenario. The EPA envisions receiving, and asking, for information using NAMs. In terms of scientific rigor, Section 26(h) of TSCA mandates the use of Scientific Standards in making decisions under

[41] List of alternative methods accepted by US agencies through ICCVAM - https://ntp.niehs.nih.gov/pubhealth/evalatm/accept-methods/index.html and list of ICCVAM Guidance Documents: https://ntp.niehs.nih.gov/pubhealth/evalatm/accept-methods/guidance/index-2.html; List of alternative methods listed as "regulatory acceptance/standards" completed according to the European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM) through its Tracking System for Alternative Methods towards Regulatory Acceptance (TSAR) - http://tsar.jrc.ec.europa.eu/ ; and List of alternative methods/strategies presented by health endpoints in the OECD - http://www.oecd.org/chemicalsafety/testing/oecdguidelineapproachbyendpoints.htm

Sections 4, 5, and 6 of the law. These sections pertain to testing, new chemicals and existing chemicals, respectively.

In considering both Section 26(h) and Section 4(h)(2) (C) and (D), the EPA provides the list in Appendix B as available and currently used NAMs for use under TSCA. The EPA will also evaluate information submitted/available that is both relevant and reliable (as described in Chapter 5 of this plan) for a given TSCA decision context (i.e., prioritization, hazard, exposure or environmental fate characterization). For example, in addition to the three organizations mentioned above, there are NAMs available in other fora (ToxCast[42], Tox21[43]) that may fit TSCA needs.

TIMELINE:

1. *The EPA will publish a list of NAMs per Section 4(h)(2)(C) on an EPA-dedicated website tailored to TSCA.* ***(June, 2018)***
2. *In the near term, the EPA TNT, potentially in collaboration with other experts inside and outside the Agency, will conduct its first review of other existing NAMs according to criteria to be developed using the principles provided in Chapter 5.* ***(First Quarter 2019)***

iii. Identify and Maintain Most Requested/Needed Studies for New and Existing Chemicals Under TSCA

The EPA reviews approximately 800-900 new chemical submissions (premanufacture notifications, PMNs) and various types of exemption requests per year. The EPA requests information, when needed, for a variety of human health and environmental endpoints for new chemicals. Prior to the 2016 amendments to TSCA, studies were requested for existing chemicals via a rule-making process.

The TSCA NAM Team (TNT) will retrospectively identify and evaluate the studies requested in the past, for both new and existing chemicals, in order to better document what types of outcomes and what categories of chemicals are of most relevance to TSCA. This retrospective will be made available to stakeholders, the research community, and the public and will be used to support the future development of NAMs to fit the needs of the EPA. The new chemicals program will also collect this information prospectively. In 2019, the EPA will begin to conduct 20 risk evaluations per year and will simultaneously begin to prospectively catalogue the information requested and justification for such information pertaining to Section 4(h) of TSCA.

TIMELINE: *Retrospective analysis* ***(Second Quarter 2019)***

iv. Identify and Curate Available Existing TSCA Information on NAMs (And Traditional Test Data)

Over the past few decades, industry has submitted NAM information (*in vitro* studies, QSAR analyses, analog/read across/category analyses, *in silico* predictions, etc) to the EPA; largely in

[42] https://www.epa.gov/chemical-research/toxcast-dashboard
[43] https://ncats.nih.gov/tox21/about/goals

support of new chemical submissions. Virtually all of this information is confidential business information (CBI), and thus is not available to the general public. This information also includes *in vivo* test data on many chemicals. The EPA views this as an untapped trove of information that needs to be mined, curated and used to better develop new chemical category documents and NAMs in general for the TSCA-specific chemical space.

The TNT will begin to identify, catalog and analyze this information ("TSCA In-House Inventory") for all decision-contexts (for both new and existing chemicals) as this information becomes available. This analysis will be made publicly available, to the extent possible with CBI, to advance the development and implementation of NAMs.
TIMELINE: *TSCA In-House Inventory analysis* ***(Second Quarter 2019)***

v. Use of NAMs to Identify Candidates for Prioritizing Existing Chemicals for TSCA Risk Evaluation

Various NAMs are part of the initial EPA proposal to identify candidates for prioritizing existing chemicals under TSCA Section 6. The EPA is required to prioritize at least 20 high, and at least 20 low, priority chemicals by approximately the end of December, 2019. The EPA expects NAMs will play an increasing role in identifying candidates for prioritization over the next few years.
TIMELINE: Ongoing

vi. Begin Development of Scientific Information Technology Platforms

A key element of this Strategic Plan is the development of an information technology (IT) platform that is specific to TSCA. In addition to combining all appropriate in-house and public information, the TSCA consolidated information infrastructure will focus on developing more efficient IT tools for leveraging available chemical information. Current efforts include expanding deployment of scientific data and translating tools developed by ORD and third parties for use by TSCA.
TIMELINE: Ongoing

vii. Collaborate with Partners and Stakeholders to Identify NAMs for Further Development

The information obtained from Chapter 7(a) (iii) and (iv) of this Strategic Plan will be particularly useful to identify where the EPA (and others) should work towards identifying and developing appropriate approaches (possible test methods and the use of AOP, IATA and DA frameworks) that need further development to meet TSCA Section 4(h) needs for NAMs.

The EPA anticipates that during this near-term time period there may be knowledge gaps identified and used to focus possible research/testing on NAMs using Sections 4(h)(2)(A)(vii) (formation of industry consortia) and 4(h)(2)(F) (prioritize NAMs for performance assessment and translational studies to accelerate the development of appropriate NAMs).

OPPT will also work closely with ORD and others inside and outside the EPA to enhance collaborative efforts for identifying research needs for NAMs specifically for TSCA. Since the

passage of the TSCA amendments, the EPA has become an active member of several ICCVAM technical workgroups (skin sensitization, developmental and reproductive toxicity, IVIVE) and initiated the creation of the new ICCVAM technical workgroup on read-across. ICCVAM technical workgroups perform a variety of tasks such as developing scoping documents on existing requirements and information needs across the federal government for a toxicological end point, and providing a mechanism for developers of NAMs to communicate with and receive strategic guidance from agency representatives. The EPA is also participating in a steering committee as part of the National Institutes of Health (NIH) Small Business Innovation Research (SBIR) Program Phase IIB Validation of Organotypic Human Airway Models and Assay Methods for *In Vitro* Inhalation Toxicology Screening, Validate EpiAirway™, EpiAlveolar™ and macrophage models as alternatives for OECD TGs 403 and 436 (acute inhalation toxicity).

The EPA's TNT will oversee collaborations with partners and stakeholders to ensure that NAMs are developed to fit the needs of TSCA. For example, the EPA will host workshops, webinars, and other meetings as well as conduct case studies on the use of NAMs under TSCA (retrospectively and prospectively). Finally, the EPA anticipates engaging specifically with the newly formed Science Advisory Committee on Chemicals (SACC) on a regular basis on the development and use of NAMs under TSCA.

TIMELINE:

1. *EPA participation in collaborative efforts* ***(Ongoing)***
2. *Case Studies through TNT* ***(Ongoing)***

b. Intermediate-term Objectives: Building a Future TSCA with NAMs (3-5 years)

In 2021, the EPA is required to submit a report to Congress on the progress made on implementation of this Strategic Plan. The EPA expects this report to represent the transition of moving from near-term *needs and activities* towards intermediate-term *objectives*. In the near-term timeframe, the EPA is building the TSCA NAM foundation. The outcome of the retrospective and prospective analyses described in above (Chapter 7.a.iii and 7.a.iv) are important in directing future development and integration of NAMs. Also, the EPA will begin to receive new information submitted under TSCA (Section 4(h), in general, as well as Section 4(h)(3), which requires industry and others who voluntarily submit information to consider use of NAMs). As this information is being collected, the EPA will be able to more systematically and strategically develop and implement NAMs

The seven near-term activities identified above will lay the groundwork for moving towards the following four intermediate-term objectives:

i. Progress Towards Use of NAMs for Prioritization and Risk Evaluation

As our knowledge of, and confidence in, NAMs (*in chemico*, *in vitro* and *in silico* methods as well as the various frameworks such as AOPs, DAs, IATAs) grow, they will improve the process of identifying candidates for prioritization. Similarly, the NAMs will be used to make hazard, exposure, environmental fate characterization decisions for the risk evaluation of new chemicals and possibly existing chemicals.

Specific objectives which would be useful for prioritization and risk evaluation could include: evaluation of the utility of the toxicological threshold of concern (TTC) approach for priority setting; expansion of existing new chemical categories; and identification of new categories for the new chemical categories document.

Other objectives include: (1) provide encouragement for voluntary submitters of information to the EPA under TSCA Section 4(h)(3) about how NAMs could significantly reduce private and public resources (time and money) for bringing chemicals into US commerce; and (2) identifying the critical role that NAMs can play in designing safer chemicals (i.e., green chemistry).
TIMELINE: *3-5 Years*

ii. Maintaining the Continual Expansion of the TSCA NAM List

The process to identify, develop, and integrate NAMs for implementation will continue in this timeframe as new technologies are developed. It is anticipated that the evolution of the science of evaluating mixtures, various ecological endpoints and nanomaterials will be evaluated in this time frame.
TIMELINE: *3-5 Years*

iii. Developing and Maintaining Educational and Outreach Goals for Regulatory Scientists, End-Users and the Public

The EPA plans to implement a variety of tools to educate regulatory scientists, end-users, and the general public about NAMs and their use under TSCA. This is necessary to both build and provide confidence to all parties that the development and use of NAMs will not diminish the EPA mission to protect human health and the environment. Some possible examples of fulfilling this objective include: (1) workshops, courses and webinars for technical stakeholders; (2) possible certificate program for end-users (similar to the Sustainable Futures program); and (3) outreach to schools (K-12 as well as colleges); etc.
TIMELINE: *3-5 Years*

iv. Continue Collaboration with Partners and Stakeholders to Identify NAMs for Further Development

The EPA believes the development of NAMs for regulatory use will continue to be important and as the science improves – as well as the regulatory implementation of their use under TSCA – the near-term needs will lead to focused objectives for research.
TIMELINE: *3-5 Years*

c. Long-Term Goal: Reduce and Eventually Eliminate Vertebrate Animal Testing (?? years)

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

EPA to maintain a high level of commitment to identifying, developing, and integrating NAMS for implementation under TSCA as described here and to work closely with stakeholders at every step. Importantly, all the near-term needs and activities and the intermediate-term objectives will necessarily continue over time as needed. Thus, at this time, it is not possible to identify a time-frame when vertebrate animal testing will be eliminated; but it is an important – and ultimately achievable – goal.

8. Conclusions & Next Steps

Section 4(h)(2)(A) of the amended TSCA presents the requirements for developing the Strategic Plan. The opening words represent the goal for the EPA and this Strategic Plan:
"…to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment of chemical substances or mixtures…"

Using the framework in Figure 1 and the near and intermediate term activities presented in Chapter 7; Table 1 presents the steps the EPA will follow to implement this Strategic Plan.

As the EPA develops and implements this Strategic Plan, it is important to keep the agency's mission in mind: to protect human health and the environment. The use of NAMs under TSCA does not diminish this mission, rather it is a call to achieve it through new and better science-based methods and approaches. With this Strategic Plan, the EPA is embarking on a journey to improve the science and confidence in regulating new and existing chemicals in US commerce through the development and use of NAMs.

As required by Section 4(h)(2)(E), the EPA will provide a report to Congress every five years (beginning in 2021) describing the progress in implementing this Strategic Plan.

Table 1: Steps to Implement TSCA Strategic Plan on NAMs[1]			
Figure 1 Component → / Time Frame ↓	*Identify, Develop and Integrate NAMs*	*Build Confidence (Ensuring Relevance and Reliability)*	*Implementing NAMs under TSCA*
Near Term (Now – 3 Years)	Develop List of NAMs (TSCA Section 4(h)(2)(C) **(June, 2018)**	Review Existing NAMs **(1st Qtr, 2019)**	Continue Using NAMs for new (evaluation) and existing (prioritization) chemicals (**Ongoing)**
	Identify requested information (Retrospective Analysis) **(2nd Qtr., 2019)**	Maintaining Database of Requested Information (**Ongoing)**	
	Identify TSCA In-House Inventory and Maintain Internal CBI Files **(2nd Qtr, 2019)**	Maintaining Database of TSCA In-House Inventory (**Ongoing)**	
	Building IT Platform (**Ongoing)**		
	Developing Case Studies (**Ongoing)**		
	Identify Knowledge Gaps/Research Needs that are TSCA-Specific (**Ongoing)**		
Intermediate (3-5 Years)		Expand and Maintain the List of NAMs (**Ongoing)**	NAMs will increasingly be used in prioritization activities and in quantitative risk evaluation (**Ongoing)** NAMs will build upon the New Chemicals Category document (**Ongoing)**
	Develop and Maintain Educational and Outreach Goals ***(Ongoing)***		
	Identify Knowledge Gaps/Research Needs that are TSCA-Specific ***(Ongoing)***		
Long Term	Move towards making TSCA decisions (conducting prioritization activities and risk evaluations for new and existing chemicals) with NAM to reduce and eventually replace use of vertebrate animal testing.		

[1]Collaboration with a variety of stakeholders as well as education and training of regulators and stakeholders will be consistent throughout the implementation of this Strategic Plan. A TSCA NAM Team will be established to ensure the successful implementation of this Strategic Plan.

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Appendix A Reduction of Testing on Vertebrates (15 U.S.C. §2603(h))

SEC. 4. TESTING OF CHEMICAL SUBSTANCES AND MIXTURES.

(Note: Text for sections a through g are not presented):

(a) TESTING REQUIREMENTS

(b) TESTING REQUIREMENT RULE, ORDER, OR CONSENT AGREEMENT

(c) EXEMPTION.

(d) NOTICE.

(e) PRIORITY LIST.

(f) REQUIRED ACTIONS.

(g) PETITION FOR Protocols and Methodologies FOR THE DEVELOPMENT OF Information

(h) Reduction of Testing on Vertebrates. —

(1) In General —The Administrator shall reduce and replace, to the extent practicable, scientifically justified, and consistent with the policies of this title, the use of vertebrate animals in the testing of chemical substances or mixtures under this title by—

(A) prior to making a request or adopting a requirement for testing using vertebrate animals, and in accordance with subsection (a)(3), taking into consideration, as appropriate and to the extent practicable and scientifically justified, reasonably available existing information, including—

(i) toxicity information;

(ii) computational toxicology and bioinformatics; and

(iii) high-throughput screening methods and the prediction models of those methods; and

(B) encouraging and facilitating—

(i) the use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions under this title;

(ii) the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category; and

(iii) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests, provided that such consortia make all information from such testing available to the Administrator.

(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—

(A) not later than 2 years after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing and provide information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment of chemical substances or mixtures through, for example—

(i) computational toxicology and bioinformatics;

(ii) high-throughput screening methods;

(iii) testing of categories of chemical substances;

(iv) tiered testing methods;

(v) in vitro studies;

(vi) systems biology;

(vii) new or revised methods identified by validation bodies such as the Interagency Coordinating Committee on the Validation of Alternative Methods or the Organization for Economic Co-operation and Development; or

(viii) industry consortia that develop information submitted under this title;

(B) as practicable, ensure that the strategic plan developed under subparagraph (A) is reflected in the development of requirements for testing under this section;

(C) include in the strategic plan developed under subparagraph (A) a list, which the Administrator shall update on a regular basis, of particular alternative test methods or strategies the Administrator has identified that do not require new vertebrate animal testing and 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;

(D) provide an opportunity for public notice and comment on the contents of the plan developed under subparagraph (A), including the criteria for considering scientific reliability and relevance of the test methods and strategies that may be identified pursuant to subparagraph (C);

(E) beginning on the date that is 5 years after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, and every 5 years thereafter, submit to Congress a report that describes the progress made in implementing the plan developed under subparagraph (A) and goals for future alternative test methods and strategies implementation; and

(F) prioritize and, to the extent consistent with available resources and the Administrator's other responsibilities under this title, carry out performance assessment, validation, and translational studies to accelerate the development of scientifically valid test methods and strategies that reduce, refine, or replace the use of vertebrate animals, including minimizing duplication, in any testing under this title.

(3) Voluntary Testing—

(A) In General—Any person developing information for submission under this title on a voluntary basis and not pursuant to any request or requirement by the Administrator shall first attempt to develop the information by means of an alternative test method or strategy identified by the Administrator pursuant to paragraph (2)(C), if the Administrator has identified such a test method or strategy for the development of such information, before conducting new vertebrate animal testing.

(B) Effect of Paragraph—Nothing in this paragraph shall, under any circumstance, limit or restrict the submission of any existing information to the Administrator.

(C) Relationship to Other Law—A violation of this paragraph shall not be a prohibited act under section 15.

(D) Review of Means—This paragraph authorizes, but does not require, the Administrator to review the means by which a person conducted testing described in subparagraph (A).

Appendix B List of NAMs as Required Under TSCA Section 4(h)(2)(C)

This is a draft, working list and EPA is particularly interested in feedback regarding content and organization.

TSCA Section 4(h)(2)(C) requires the Strategic Plan include a list, "which the Administrator shall update on a regular basis, of particular alternative test methods or strategies the Administrator has identified that *do not require new vertebrate animal testing*…." (emphasis added).

As explained in the narrative portion of this Plan, there are many organizations with lists of NAMs at various stages of development with the goal of regulatory acceptance (see Chapter 7.a.ii). For the six tables in this Appendix, EPA presents NAMs (i.e., test methods and approaches) which *do not require new vertebrate animal testing:*

- Table B-1 presents nine different tools/models/approaches to estimate hazard and exposure currently used by OPPT.
- Table B-2 lists 24 test methods which are not *in vivo* vertebrate animal protocols that have been accepted for human health testing under the OECD program.
- Table B-3 is a listing of 19 OECD Guidance and Review Documents pertaining to NAMs (called "non-testing methods" by the OECD)
- Table B-4 is a listing of ten OECD Guidance and Review Documents on frameworks and approaches to applying NAMs for human health hazard/risk decisions (called "testing for human health" by the OECD).
- Table B-5 – provides the single OECD Guidance Document describing non-guideline in *vitro* methods for testing for Endocrine Disruptors
- Table B-6 - is a listing of the eight OECD Guidance and Review Documents pertaining to the development of Performance Standards for the development of NAMs

B-1. EPA-Specific (Based on Experience with TSCA)

NAM	Parameter Assessed
Ecological Structure-Activity Relationships Program (ECOSAR)	Hazard - *In silico* tool to predict aquatic hazard
OncoLogic	Hazard - *In silico* tool to predict potential to cause cancer in humans
Analog Identification Methodology (AIM)	Hazard - Database tool to facilitate identification of analogs for read-across
Chemical Assessment Clustering Engine (ChemACE)	Hazard – Database tool to facilitate structural clustering
New Chemical Categories Document	Hazard – Documentation of TSCA chemical categories
Estimation Programs Interface (EPISuite)	Physical/chemical properties and environmental fate – multiple tools and models used to predict properties of chemicals
Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER)	Exposure – tools and models to estimate environmental releases and worker exposures
Exposure and Fate Assessment Screening Tool (E-FAST)	Exposure = tools and models to estimate consumer, general public and environmental exposures to chemicals.
Approaches to Estimate Consumer Exposure	Exposure – a variety of tools and models to estimate exposure to various consumer products and materials
URL sources: Hazard - https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-hazard-under-tsca#models ; Physical/Chemical Properties, Environmental Fate and Exposure - https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-exposure-and-fate-under-tsca#fate General Guidance on all approaches - https://www.epa.gov/tsca-screening-tools	

B-2. OECD Test Guidelines – Health Effects[44]

No.	Title	Original Adoption	Most Recently Updated
428	Skin Absorption: *in vitro* Method	13 April 2004	---
429	Skin Sensitisation: Local Lymph Node Assay	24 April 2002	22 July 2010
430	*in vitro* Skin Corrosion: Transcutaneous Electrical Resistance Test (TER)	13 April 2004	28 July 2015
431	*in vitro* Skin Corrosion: Reconstructed Human Epidermis (RHE) Test	13 April 2004	26 July 2016
432	*in vitro* 3T3 NRU Phototoxicity Test	13 April 2004	---
435	*in vitro* Membrane Barrier Test Method for Skin Corrosion	19 July 2006	28 July 2015
437	Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants	7 September 2009 (corrected in 2010) (corrected in 2017)	26 July 2013
438	Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants	7 September 2009 (corrected in 2017)	26 July 2013
439	*in vitro* Skin Irritation: Reconstructed Human Epidermis Test Method	22 July 2010	28 July 2015
442C	*In chemico* skin Sensitisation	5 February 2015	---
442D	*In vitro* Skin Sensitisation	5 February 2015	---
442E	*In vitro* Skin Sensitisation: In Vitro Skin Sensitisation assays addressing the Key Event on activation of dendritic cells on the Adverse Outcome Pathway for Skin Sensitisation	26 July 2016	9 October 2017
455	Performance-based Test Guideline for Stably Transfected Transactivation *in vitro* Assays to Detect Estrogen Receptor Agonists and Antagonists	7 September 2009	26 July 2016
456	H295R Steroidogenesis Assay	28 July 2011	---
458	Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals	26 July 2016	---
460	Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants	2 October 2012 (corrected in 2017)	

[44] Go to http://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm and click on "List of Adopted Test Guidelines Including Dates of Revisions

No.	Title	Original Adoption	Most Recently Updated
471	Bacterial Reverse Mutation Test	26 May 1983	21 July 1997
473	*in vitro* Mammalian Chromosome Aberration Test	26 May 1983 (corrected in 2016)	26 September 2014
476	*in vitro* Mammalian Cell Gene Mutation Tests using the Hprt and xprt genes	4 April 1984 (corrected in 2016)	28 July 2015
487	*in vitro* Mammalian Cell Micronucleus Test	22 July 2010 (corrected in 2016)	26 September 2014
490	*In vitro* Thymidine Kinase Mutation Test	28 July 2015 (corrected in 2016)	
491	Short-time Exposure for the Detection of Chemicals Causing Serious Eye Damage, and Chemicals Not Requiring Classification for Serious Eye Damage or Eye Irritation	28 July 2015 (corrected in 2017)	---
492	Reconstructed Human Cornea-like Epithelium for the Detection of Chemicals Not Requiring Classification and Labelling for Eye Irritation or Serious Eye Damage	28 July 2015 (corrected in 2017)	
493	Human Recombinant Estrogen Receptor Binding Assay	28 July 2015	---

B-3. OECD Adopted Guidance and Review Documents – Non-Testing Methods[45]

Guidance/Review Document	Title/Topic
ENV Monograph No 67:	Application of structure-activity relationships to the estimation of properties important in exposure assessment
ENV Monograph No 68:	Structure-activity relationships for biodegradation
No 49	Report from the expert group on (Quantitative) structure-activity relationships [(Q)SARs] on the principles for the validation of (Q)SARs
No 58:	Report on the regulatory uses and applications in OECD Member Countries of (Quantitative) structure-activity relationship [(Q)SAR] models in the assessment of new and existing chemicals
No 69:	Guidance documents on the validation of (Quantitative) structure-activity relationship [(Q)SAR] models
No 80	Guidance on grouping of chemicals
No 102:	The guidance document for using the OECD (Q)SAR application toolbox to develop chemical categories according to the OECD guidance on grouping chemicals
No 111:	Report of the expert consultation to evaluate an estrogen receptor binding affinity model for hazard identification
No 113:	Report of the focus session on current and forthcoming approaches for chemical safety and animal welfare
No 120 Part 1:	Report of the expert consultation on scientific and regulatory evaluation of organic chemistry mechanism-based structural alerts for the identification of DNA binding chemicals
No 120 Part 2:	Report of the expert consultation on scientific and regulatory evaluation of organic chemistry mechanism-based structural alerts for the identification of DNA binding chemicals
No 139 plus Addendum:	Report of the expert consultation on scientific and regulatory evaluation of organic chemistry mechanism-based structural alerts for the identification of protein-binding chemicals
Part 1, Part 2	No. 168: The adverse outcome pathway for skin sensitisation initiated by covalent binding to proteins:
No. 184:	Guidance document on developing and assessing adverse outcome pathways
No 193:	OECD guidance for characterising oleochemical substances for assessment purposes
No 194:	Guidance on grouping of chemicals, second edition
No. 255	Guidance Document on the Reporting of Defined Approaches to be Used Within Integrated Approaches to Testing and Assessment
No. 256	Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used Within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation, Annex 1, Annex 2
No. 260	Guidance Document for the Use of Adverse Outcome Pathways in Developing Integrated Approaches to Testing and Assessment (IATA)

[45] http://www.oecd.org/env/ehs/testing/seriesontestingandassessmentnon-testingmethodseggsarandgrouping.htm

B-4. OECD Adopted Guidance and Review Documents – Testing for Human Health[46]

Guidance/Review Document	Title/Topic
Pages 1-31; Pages 32-62	ENV Monograph No 36: Scientific criteria for validation of *in vitro* toxicity tests
No 34:	Guidance document on the validation and international acceptance of new or updated test methods for hazard assessment
No 129:	Guidance document on using cytotoxicity tests to estimate starting doses for acute oral systematic toxicity tests
Part 1, Part 2	No 168: The adverse outcome pathway for skin sensitisation initiated by covalent binding to proteins:
No 173:	Performance standards for stably transfected transactivation *in vitro* assays to detect estrogen agonists for TG 455
No 174:	Performance standards for the BG1Luc ER TA transactivation method to detect estrogen receptor antagonists
No 203:	Guidance document on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation
No. 214	Guidance Document on the *In Vitro* Syrian Hamster Embryo (SHE) Cell Transformation Assay
No. 231	Guidance Document on the I*n Vitro* Bhas 42 Cell Transformation Assay (BHAS 42 CTA)
No 263:	Guidance Document on an Integrated Approach on Testing and Assessment (IATA) for Serious Eye Damage and Eye Irritation

B-5. OECD Adopted Guidance and Review Documents –Testing for Endocrine Disruptors[47]

Guidance/Review Document	Title/Topic
No. 211[48]	Guidance Document for Describing Non-Guideline *In Vitro* Test Methods
No 207:	New scoping document on *in vitro* and *ex vivo* assays for the identification of modulators of thyroid hormone signaling

[46] http://www.oecd.org/env/ehs/testing/seriesontestingandassessmenttestingforhumanhealth.htm
[47] http://www.oecd.org/env/ehs/testing/seriesontestingandassessmenttestingforendocrinedisrupters.htm
[48] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)35&doclanguage=en

B-6. OECD Adopted Guidance and Review Documents – Performance Standards[49]

Guidance/Review Document	Title/Topic
No. 173:	Performance Standards for Stably Transfected Transactivation *In Vitro* Assays to Detect Estrogen Agonists for TG 455
No. 174:	Second Edition Performance Standards For Stably Transfected Transactivation *In Vitro* Assays To Detect Estrogen Receptor Antagonists
No. 213:	Performance Standards for Assessment of Proposed Similar or Modified *In Vitro* Skin Sensitisation ARE-NRF2 Luciferase Test Methods
No. 216	Performance Standards for the Assessment of proposed Similar or Modified *In Vitro* Reconstructed Human Cornea-like Epithelium (RHCE) Test Methods for Eye Hazard
No. 218	Performance Standards for the Assessment of Proposed Similar or Modified *In Vitro* Reconstructed Human Epidermis (RHE) Test Methods for Skin Corrosion Testing as described in TG 430
No. 219	Performance Standards for the Assessment of Proposed Similar or Modified *In Vitro* Reconstructed Human Epidermis (RHE) Test Methods for Skin Corrosion Testing as described in TG 431
No. 220	Performance Standards for the Assessment of Proposed Similar or Modified *In Vitro* Reconstructed Human Epidermis (RhE) Test Methods for Skin Irritation Testing as described in TG 439
No. 222	Performance Standards for the Human Recombinant Estrogen Receptor Binding Assay

[49] http://www.oecd.org/chemicalsafety/testing/performance-standards.htm