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

June 22, 2018

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DOCKET

Supporting information can be found in the public docket:
https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2017-0559

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ABBREVIATIONS

3Rs – Reduction, Refinement and Replacement
AIM – Analog Identification Method
AOP – Adverse Outcome Pathway
CAAT – Center for Alternatives to Animal Testing
CBI – Confidential Business Information
CEM – Consumer Exposure Model
ChemSTEER – Chemical Screening Tool for Exposures and Environmental Releases
DA – Defined Approach
ECHA – European Chemicals Agency
ECOSAR – Ecological Structure-Activity Relationships Program
EDSP – Endocrine Disruptor Screening and Testing Program
E-FAST – Exposure and Fate Assessment Screening Tool
EPA – Environmental Protection Agency
EPISuite™ – Estimation Programs Interface
ER – Estrogen Receptor
EURL-ECVAM – European Union Reference Laboratory for Alternatives to Animal Testing
FDA – Food and Drug Administration
FIFRA – Federal Insecticide, Fungicide and Rodenticide Act
HESI – Health and Environmental Science Institute
IATA – Integrated Approaches to Testing and Assessment
ICATM – International Cooperation on Alternative Test Methods
ICCVAM – Interagency Coordinating Committee on the Validation of Alternative Methods
ICE – Integrated Chemical Environment
IVIVE – In Vitro to In Vivo Extrapolation
LLNA – Local Lymph Node Assay
MAD – Mutual Acceptance of Data
NCATS – National Center for Advancing Translational Sciences
NAM – New Approach Methodologies
NCCT – National Center for Computational Toxicology
NERL – National Exposure Research Laboratory
NIEHS – National Institute of Environmental Health Sciences
NIH – National Institutes of Health
NGO – Non-Governmental Organization
NICEATM – NTP Interagency Center for the Evaluation of Alternative Test Methods
NTP – National Toxicology Program
OCSPP – Office of Chemical Safety and Pollution Prevention
OECD – Organization for Economic Cooperation and Development
OPP – Office of Pesticide Programs
OPPT – Office of Pollution Prevention and Toxics
ORD – Office of Research and Development
OSCP – Office of Science Coordination and Policy
PBTK – Physiologically-Based Toxicokinetics
PETA – People for the Ethical Treatment of Animals

POD – Point of Departure
QSAR – Quantitative Structure Activity Relationship
SACC – Science Advisory Committee on Chemicals
SAR – Structure Activity Relationship
SBIR – Small Business Innovation Research
TK - Toxicokinetics
TNT – TSCA NAM Team
TSCA – Toxic Substances Control Act
WOE – Weight of Scientific Evidence

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 mandates of TSCA; which includes a new subsection that requires EPA to 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), *Reduction of Testing on Vertebrates*).

In this document, EPA outlines its Strategic Plan for the reduction of testing in vertebrates for chemicals regulated under TSCA. The organizing framework for EPA's strategy to reduce vertebrate animal testing relies heavily on what have been termed new approach methodologies (NAMs). This phrase has been adopted as a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals. Both new and existing chemicals subject to TSCA regulation cover a broad range of chemical space and lack standard information requirements. Therefore, 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, risk evaluations for new and existing chemicals and other risk-based decisions). 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. EPA has identified eight current/near-term (<3 years) needs and activities. Completing these activities will result in moving towards five 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.

EPA's long-term goal is to move towards making TSCA decisions with NAMs in order to reduce, refine or replace vertebrate animal testing. Achieving this goal will require 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, EPA has established an internal TSCA NAM Team (TNT) to take advantage of expertise and resources within the Agency. The TNT will oversee the implementation of this Strategic Plan and be responsible for collaborating with stakeholders and the public.

The TSCA Section 4(h) List of NAMs can be found on the EPA webpage[1].

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 EPA to 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), *Reduction of Testing on Vertebrates*, see Appendix).

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-vertebrate animal test systems. 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 introduced (ICCVAM, 2018). This phrase has been adopted as a broadly descriptive reference to any technology, methodology, approach (including computational/in silico models (i.e., QSARs)), or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals. For the purposes of TSCA, EPA recognizes this new term (i.e., NAMs) as encompassing any "alternative test methods and strategies to reduce, refine or replace vertebrate animals."

[1] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

This Strategic Plan was developed by OPPT in collaboration with 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, 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, EPA works closely with its stakeholders, including the regulated community, animal welfare groups and other non-governmental organizations (NGOs), 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 Products" (ICCVAM, 2018) (hereafter referred to as the ICCVAM Strategic Roadmap). The 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 ICCVAM Strategic Roadmap, 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 Strategic Plan, EPA notes the rapidly evolving nature of NAM information that will be useful in, among other things, prioritizing, and ultimately developing quantitative risk evaluations for new and existing chemicals. This evolving nature of development lends itself to an iterative process of NAM implementation for regulatory decision-making. Moreover, approaches for establishing confidence (e.g., validation) are evolving rapidly. This Strategic 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), EPA will provide a report to Congress every five years (beginning in 2021) describing the progress in implementing this Strategic Plan.

The public process used to develop this Strategic Plan began when EPA hosted an expert meeting on November 2, 2017 during which a conceptual approach to the Strategic Plan was presented. A docket was created and used to receive public comments on the conceptual approach through January 10, 2018 (http://www.regulations.gov; docket number HQ-OPPT-2017-0559). This same docket was used to post a March 7, 2018 draft of this document, with a public comment period open until May 11, 2018. A public meeting to solicit comments was also

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[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
[6] http://hesiglobal.org/
[7] http://caat.jhsph.edu/

held on April 10, 2018 in Washington, DC. This Strategic Plan is available both on the OPPT website (U.S. EPA, 2017a) as well as the public docket (http://www.regulations.gov; docket number HQ-OPPT-2017-0559). EPA has also published a response to comments document which describes responses to comments received associated with the March 7, 2018 draft.

The TSCA Section 4(h) List of NAMs can be found on the EPA webpage[8].

3. TSCA & Organization of this Strategic Plan

There are various sections in TSCA that include animal testing-related provisions to which this Strategic Plan applies, the most prominent including Sections 4, 5, 6, and 8. Section 4 of TSCA, entitled *Testing of Chemical Substances and Mixtures*, refers to EPA's authority to require health and environmental effects testing be conducted in most cases relevant to a determination of an unreasonable risk of injury to health or the environment (Section 4(a)). [9] 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.

TSCA requires EPA to "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…" through prescribed measures (Section 4(h)(1)).

Section 4(h)(2)(A) states EPA shall:

"…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 ICCVAM or the OECD[10]; or
(viii) Industry consortia that develop information submitted under this title…"

Section 4(h)(2) (C) and (D) require 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

[8] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical
[9] Sections 4(a) and (b) include procedures and process on requiring information via a rule, order or consent agreement. This Plan is focused on developing and using NAMs and so the rule, order or consent agreement process will not be discussed.
[10] ICCVAM and OECD are abbreviated here, but spelled out in the law.

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 EPA to prioritize and carry out performance assessment, validation, and translational studies to accelerate the development of NAMs.

Under Section 5(a)(3), EPA determines that: 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 in the absence of sufficient information, (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 EPA evaluates existing chemicals. Section 6(b), entitled *Risk Evaluations*, lays out 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 under Section 6(b)(4) 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 (U.S. EPA, 2017b).

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 consideration of updating the TSCA Chemical Substantial Risk Notice guidance to reflect the potential role of NAMs in determination of risks (U.S. EPA, 2018c).

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

Consistent with Sections 4 (testing), 5 (new chemicals) and 6 (existing chemicals), EPA expects to consider NAMs for the following TSCA decision contexts, among others where testing issues may arise: screening candidates for prioritization, prioritization, risk evaluations and other risk-based decisions. 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.

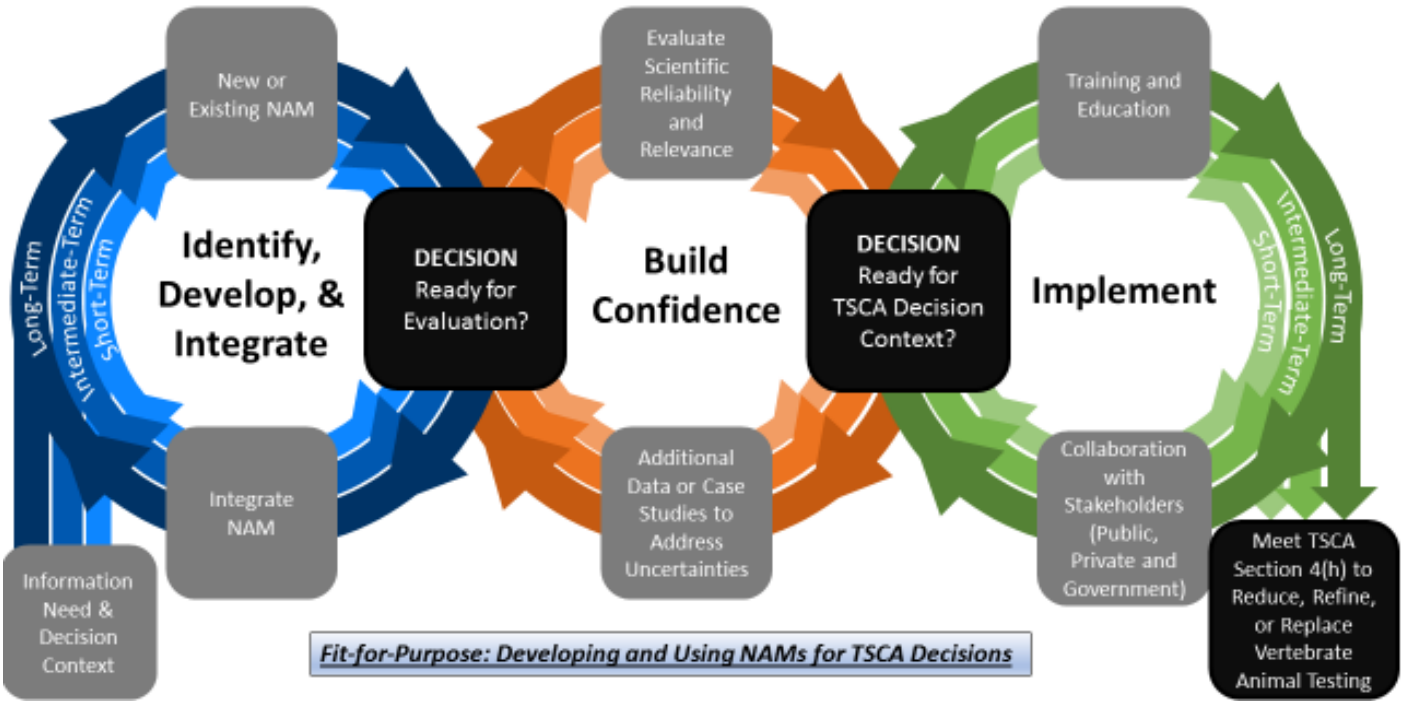
[11] TSCA defines conditions of use as: "...the circumstances, as determined by the Administrator, under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of." (TSCA Section 3(4)).

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 consistent with TSCA Section 4(h)(2)(C).
- Chapter 6 - The Importance of Training, Education, and Collaboration – acknowledges the need for training and education for EPA scientists and managers, 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) and the goals of this Plan.
- Chapter 8 - Conclusions and Next Steps – presents clear milestones to measure success and ensure implementation of the Strategic Plan.

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 decisions.

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 Strategic Plan 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: 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-term activities outlined in Chapter 7. The EPA will carry out this step in the Strategic Plan 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[12] to support new chemicals determinations under TSCA, 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 (U.S. EPA, 2018b) 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) (OECD, 2018a, b, 2014b), use of analogs/categories/read-across (OECD, 2017d, 2014a; EPA OPPT, 2010), and estimates of exposure. EPA has released a draft public document that provides an overview of the process and methods EPA generally expects to use to evaluate new chemicals under TSCA (U.S. EPA, 2017d).

TSCA mandates EPA prioritize existing chemicals to determine which are considered high or low priority candidates for risk evaluation under Section 6. A rule was published in June 2017 to establish the prioritization process 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)(U.S. EPA, 2017d)* 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. NAMs which describe physical chemical properties or exposure potential can help inform hazard testing for risk assessment including, for example, identifying chemicals that have low concerns to human or environmental health due to physical-chemical property or exposure considerations. In the absence of experimental data, NAMs that predict physicochemical properties are used to inform many

[12]The word “information” replaced the word “data” throughout amended TSCA.

decisions in TSCA new chemical reviews. 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) (U.S. EPA, 2017d). 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 are at the OPPT website)(U.S. EPA, 2018b). EPA provides a list of NAMs as required by Section 4(h)2(C) (hereafter referred to as the TSCA Section 4(h) List[13]), some of which may be used for chemical characterization .

Overall, many of the NAMs provided in the TSCA Section 4(h) List 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, 2014b). EPA supports public access to the datasets used to build predictive models as part of building scientific confidence; which is why such access is listed as one of the criteria "for considering scientific reliability and relevance" of NAMs in Chapter 5 of this plan. However, complete access may not be possible in some cases. For example, OPPT uses information claimed as confidential business information (CBI) to regularly update and refine its models 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, 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 development of appropriate information so that 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 *in vivo* toxicity tests to extrapolate to other mammalian species (including humans) or to environmental organisms (vertebrate, invertebrate and plant species). Among the existing NAMs for hazard identification, EPA uses structure-based approaches such as ECOSAR to predict ecotoxicity and OncoLogic to predict potential carcinogenicity as well as the Analog Identification Method (AIM) tool to identify appropriate analogs for hazard more generally (U.S. EPA, 2018b). In addition to *in silico* and *in chemico* approaches that rely on chemical structure, NAMs that use *in vitro* assays and computational modeling are being developed for hazard identification and characterization. EPA uses such

[13] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

approaches in conducting risk evaluations, including NAMs shown to be fit for specific purposes on a case-by-case basis. For example, in appropriate circumstances, chemicals could be prioritized, or candidates for prioritization identified, using data from EPA's ToxCast and the Toxicology in the 21st Century (Tox21) consortium; the latter being a federal collaboration among the National Institutes of Health, including the NIEHS Division of the National Toxicology Program (NTP) and the National Center for Advancing Translational Sciences (NCATS), EPA, and the Food and Drug Administration (FDA). 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., EURL-ECVAM in Europe, and the OECD.[14] These methods have been developed through traditional validation 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)(OECD, 1989, 1981). EPA will accept studies conducted under OECD guidelines. The TSCA Section 4(h) List[15] includes many OECD guideline studies.

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 (POD) that are needed for risk evaluation. As part of the near-term implementation activities, 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 of most relevance to EPA under TSCA. This may also inform the concept of combining traditional (*in vivo*) information with NAMs to address a POD or hazard identification question.

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

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[14] List of alternative methods accepted by US agencies through ICCVAM - https://ntp.niehs.nih.gov/pubhealth/evalatm/accept-methods/index.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 – table of validated and accepted alternative methods: http://alttox.org/mapp/table-of-validated-and-accepted-alternative-methods/

[15] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

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 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[16], expanding chemical compatibility, and more sophisticated culture systems (Low and Tagle, 2017). Alternative (non-vertebrate where possible) 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 (Leung et al., 2016; Planchart 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.

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 likely include 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 NAMs 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.

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

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

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; Wetmore, 2015). Population variability is typically incorporated into these models based on known distributions for each of the key parameters; which is a key point in attempting to understand effects on potentially exposed or susceptible subpopulations as is required under TSCA.

In the near- and intermediate-term activities identified in Chapter 7 of this Strategic Plan, knowledge gaps will be identified 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., 2018). Novel *in silico* and *in vitro* NAMs 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.

Under TSCA, EPA considers exposure and conditions of use[17] in conjunction with hazard when performing both prioritization and risk evaluations for existing chemicals and risk-based decisions for new 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 (U.S. EPA, 2017d)* provides a list of some possible tools/approaches for NAMs EPA may use in identifying candidate chemicals for prioritization under TSCA. For new chemicals, EPA uses a variety of existing tools (U.S. EPA, 2018b) to estimate environmental releases/occupational exposure (ChemSteer), consumer (CEM), general population and environmental exposure to chemicals (E-FAST), and environmental distribution and persistence (EpiSuite™), all of which are in the TSCA Section 4(h) List.

The knowledge gap analysis discussed in Chapter 7 of the Strategic Plan informs identification of specific needs in developing exposure-related NAMs. Advances in computational modeling and applications of machine learning methods are transforming exposure modeling[18], 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

[17] 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."

[18] See ExpoCast at https://www.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research

and data-driven discoveries of critical exposure trends and patterns (Egeghy et al., 2016). These advances can help inform TSCA 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) requires use of scientific information, technical procedures, measures, methods, protocols, methodologies, or models consistent with the best available science. Section 26(i) requires decisions under sections 4, 5 and 6 to be based on the weight of the scientific evidence (WOE). Therefore, EPA needs scientifically supportable approaches for making decisions based on WOE using NAMs. In addition, stated throughout Section 4(h) is the priority for identifying NAMs that 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 using, or integrating, NAMs as part of WOE or as alternatives for existing *in vitro* and *in vivo* studies used in decision making. Generally speaking, these approaches can be organized under the OECD's Integrated Approaches to Testing and Assessment (IATA) framework. 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" (OECD, 2017a). 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, 2017c). 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.

An IATA can be built using the adverse outcome pathway (AOP) framework, which describes the linkage (or potential linkage) between a molecular initiating event and a specific adverse outcome at the individual or population level, with progressive levels of biological organization (Ankley et al., 2010). These linkages are termed "key events" and provides a generalizable, chemical agnostic approach for organizing a biologically relevant continuum from exposure to effect. EPA supports the continued development of AOPs as an organizational framework for endpoints and responses relevant to TSCA. EPA participates in the development of the OECD AOP Knowledgebase which includes the AOP wiki, Effectopedia, AOP Xplorer, and Intermediate Effects databases which provide storage, evaluation, and linkage of information related to AOPs (OECD, 2017a).

A more structured, rule-based approach to integrating NAMs is the defined approach (DA) (OECD, 2017b). Defined approaches 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, defined approaches emphasize predictions which are rule-based and separate from predictions/approaches that are based on expert judgment. The fixed nature of defined approaches, 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, defined approaches 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 defined approaches as a replacement for the local lymph node assay (LLNA) in mice (Casati et al., 2017). The EPA has taken this information and approach and has developed a policy in which LLNA studies will, generally, no longer be requested under TSCA or FIFRA (U.S. EPA, 2018a).

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 throughput *in vitro* NAMs could be used to cast a broad biological net to capture potential hazards associated with chemical exposure. Non-vertebrate 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 estrogen receptor (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 (U.S. EPA, 2015). Similar combinations of NAMs could be developed for use 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 "information of equivalent or better scientific quality and relevance for assessing risks of injury to health or the environment" as compared to vertebrate animal testing, consistent with Section 4(h)(2)(A). Section 4(h)(2) requires the EPA identify criteria "for considering scientific reliability and relevance" of NAMs. The following paragraphs describe international efforts to update and refine the relevance and reliability of NAMs. EPA is building on these efforts to meet the TSCA requirements identified above.

Multiple entities and individuals have proposed frameworks for building confidence and accelerating the use of NAMs (e.g., ICCVAM, 2018; Patlewicz et al., 2015; Cox et al., 2014; Patlewicz et al., 2013). The OECD *Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (OECD, 2005)* 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."

The first component is *relevance*. The OECD Guidance Document (OECD, 2005) defines relevance as the ability of a test method to measure or predict an effect/target of interest as well as the regulatory need, usefulness of the alternative method(s) and associated limitations of the test method. 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 the 2005 OECD Guidance Document as the extent of reproducibility of results from a test within (intra-) and among (inter-) laboratories over time, when performed using the same standardized protocol. Some *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. It is also important to include performance-based considerations to describe the reliability of NAMs. As the science moves in the direction of NAM use and development, it is critical to understand specificity (low false positive rate) and sensitivity (low false negative rate) to assess reliability.

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 of the computer code or explicitly define the computational models. However, release of the complete data may not be possible in some cases since OPPT uses information claimed as CBI to update and refine some of its NAM. This information, although not public, increases the robustness and domain of applicability of the NAM and is critical to the Agency's mission of evaluating TSCA chemicals.

Between 2005 and 2017, a number of collaborators under the OECD umbrella began to work through some cases studies with NAMs for skin sensitization. This resulted in some suggested refinements of the concepts in the 2005 OECD document. As part of this effort, Casati et al. (2017) have proposed a framework for performance-based approaches in the evaluation of defined approaches 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, 2017b)*. 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) serve as a basis for an evaluation framework to be applied to defined approaches.

Based on the framework outlined above, EPA is providing the following criteria as a starting point for considering scientific reliability and relevance of NAMs within the TSCA program:

1. The decision context should be clearly defined.
2. Where possible, the NAMs should be mechanistically and/or biologically relevant to the hazard being assessed. The chemical domain of applicability of the NAMs should also be defined to determine relevance to the TSCA chemical landscape.
3. Criteria for selecting reference or training chemicals should be defined and supporting information should be adequately referenced.
4. The reliability of the NAM should be considered within the context of intended use and accepted best practices within the given field and the variability of the existing animal model.
5. The NAMs should be transparently described and information made available to the public (e.g., any datasets are publicly available and its known limitations are clearly described). Information claimed as TSCA CBI may not allow public accessibility of all information in some cases.
6. Uncertainty should be described to the fullest extent possible; both independently and compared to the existing animal model (if possible).
7. The NAMs should undergo an independent review in order to raise confidence in the approach.
8. Access and use by third parties should be possible (i.e., the alternative approach must be readily accessible commercially and/or the relevant protocols should be available).

These criteria are important as a rubric for EPA and others to consider as NAMs are being developed and evaluated. However, EPA often receives information from new chemical submitters (and others) that may include NAMs that are new or different than what the Agency uses. For example, in some cases, EPA receives [Q]SAR estimates as outputs from proprietary programs in the new chemicals program with which the Agency does not have first-hand knowledge or experience. Another example is when a submitter submits a novel *in vitro* assay for a new chemical submission (i.e., one that is proprietary or new). In such cases, all available information provided is evaluated and, in addition to the TSCA decision context, is used to determine whether the NAM may be useful for a particular application or decision. 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 (to the extent consistent with available resources and the Administrator's other responsibilities under TSCA). EPA views its domestic collaborations with ICCVAM and NICEATM, its international engagement with OECD, and its working with stakeholders and the public as helping to meet this requirement. Recently, OPPT 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 EPA scientists and managers, the regulated community, and interested stakeholders are properly trained to understand and use NAMs is critical as EPA moves forward in its implementation of TSCA. Learning the new advancements in science (biology, chemistry, exposure science, computational toxicology, non-vertebrate animal test methods) are necessary to use the NAMs effectively and confidently under TSCA.

EPA is undertaking and plans to continue 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. EPA specifically envisions internal training/education of EPA staff and managers. Finally, similar to the *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 identifies 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 TSCA.

7. Implementation of NAMs Under TSCA

EPA has published NAM implementation strategies for pesticides and the endocrine program under FIFRA (U.S. EPA, 2018d) and EDSP (U.S. EPA, 2015, 2011) respectively. In this Strategic Plan, EPA builds on those strategies, as well as the *ICCVAM Strategic Roadmap*, the U.S. Food and Drug Administration (FDA) Predictive Toxicology Roadmap (U.S. FDA, 2017), and the Tox21 Strategy and Operational Plan (Thomas et al., 2018) - but with a focus on 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 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 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.

This chapter further describes the activities that EPA expects to undertake to implement this Strategic Plan. The activities are centered around three core components as presented in Figure 1, and for which timelines are provided that are sensitive to the requirements in the law. 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, risk evaluation, and other risk-based decisions). 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, needs and activities provide the basis for identifying and 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. EPA's long-term goal is to continue to protect public health and the environment by moving towards making TSCA decisions with NAMs in order to reduce and eventually eliminate vertebrate animal testing for TSCA "to the extent practicable, scientifically justified, and consistent with" the policies of TSCA. Achieving this goal will require 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.

To ensure success of this Plan, EPA has established a TSCA NAM Team (TNT) to take advantage of experts/resources within the Agency. The members of the team include experts from OPPT, OPP, OSCP and ORD. EPA understands the desire of multiple stakeholders to widen the membership of the TNT beyond EPA. At this point in time EPA is limiting the TNT to EPA personnel. This is largely due to the need for CBI clearance of members and to establish a

system and process for the internal information. The TNT will engage with stakeholders – including ICCVAM, OECD and other entities and individuals – for insight and advice on the milestones in this Strategic Plan. EPA intends to continually engage all stakeholders throughout implementation of this Strategic Plan. Table 1 provides specific information on the TNT. The role of the TNT will likely evolve with the science of NAM development and use.

Table 1 – Implementation of the Strategic Plan Through the TSCA NAM Team (TNT)	
Team Members	
The TNT will consist of EPA staff/managers from across OCSPP and ORD. The TNT will be chaired by OPPT and the team will report to the OPPT Office Director	
Brief Description of Likely Tasks May Include	
Logistical	Hold regularly scheduled meetings, seek advice from stakeholders and the public, and provide status reports.
Communication, Training, Outreach	Oversee launch of dedicated TSCA NAM website, develop education/training schedules for EPA staff/managers, stakeholders and end-users.
Technical	Refine criteria in Chapter 5 of the Strategic Plan, maintain and update the TSCA Section 4(h) List [including developing a mechanism to monitor development of new NAMs], review/analyze results of retrospective analyses and TSCA in-house information, oversee development of TSCA-specific case studies, identify research needs/gaps for NAMs.
Collaboration	Maintain and expand EPA collaborations with domestic and international partners with all sectors (public, private, academic).

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

In identifying near-term needs and activities, EPA envisions these next few years as modernizing its knowledge base on NAMs for regulatory use under TSCA and to identify potential NAMs for development which would be specific for TSCA needs for the review and evaluation of both new and existing chemicals in the US.

These next few years EPA plans to continue and expand its collaborative efforts inside and outside the government pertaining to the identification and possible use of NAMs within the TSCA program, and to put more effort into the important process of training and educating regulatory users (i.e., EPA staff and managers) and industry end-users (i.e., submitters of TSCA-related information to EPA).

There are eight near-term activities identified:

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

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 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). EPA plans to build upon these and identify other NAMs that meet the criteria outlined in Chapter 5. EPA will continue to evaluate and consider any/all information submitted (by industry and others) to determine whether a particular NAM has scientific merit or basis to support a TSCA decision context. Also, as mentioned earlier, recently EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) released a draft policy to reduce animal testing for skin sensitization. Implementation of this policy in recent months shows the commitment of EPA to the principles of reducing testing in vertebrate animals with a methodology that is relevant and reliable.

TIMELINE: ***Ongoing***

ii. Maintain and Regularly Update a List of NAMs per Section 4(h)(2)(C)

Section 4(h)(2)(C) requires EPA develop a list of particular 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., EURL-ECVAM in Europe and the OECD.[19] The PETA International Science Consortium has put all three lists on one website.[20]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 at that time.

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[19] List of alternative methods accepted by US agencies through ICCVAM - https://ntp.niehs.nih.gov/pubhealth/evalatm/accept-methods/index.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

[20] https://www.piscltd.org.uk/alternatives-approved-by-regulators/

The TSCA Section 4(h) List[21] is the current list called for in TSCA Section 4(h)(2)(C) (U.S. EPA, 2017a). It includes NAMs currently used by EPA in TSCA and ones identified as being accepted under the OECD. EPA believes these NAMs 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. EPA will also evaluate information submitted/available for a given TSCA decision context (i.e., prioritization, hazard, exposure or environmental fate characterization).

Chapter 5 in this Strategic Plan provides initial criteria for considering scientific reliability and relevance of NAMs to be eligible for placement on the TSCA Section 4(h) List. In considering both Section 26(h) and Section 4(h)(2) (C) and (D), EPA provides the TSCA Section 4(h) List as available and currently used NAMs for use under TSCA. EPA further understands there are many NAMs in various stages of evolution which may have value for TSCA decisions but have not been thoroughly evaluated under criteria such as those presented in Chapter 5. For example, there are other NAMs available (ToxCast (U.S. EPA, 2016), Tox21 (Thomas et al., 2018)) that may fit TSCA needs. It is envisioned that one of the central functions of the newly formed TNT will be to establish a transparent process to update and maintain the list.

TIMELINE:

1. *With this Strategic Plan, EPA is publishing a list of NAMs per Section 4(h)(2)(C). The TSCA Section 4(h) List[21] currently posted is the original list. Future updates will be posted on the EPA website. EPA plans to update this list at least once a year.*
2. *In the near term, the EPA TNT will conduct its first review of other existing NAMs according to the initial criteria provided in Chapter 5. There will be opportunities for engagement with stakeholders during this process.* ***(First Quarter 2019)***

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

EPA reviews approximately 800-900 new chemical submissions (premanufacture notifications, PMNs) and various types of exemption requests per year. EPA requests information for a variety of human health and environmental endpoints for new chemicals.

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

[21] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

TIMELINE: *Retrospective analysis **(Second Quarter 2019)**, with plans to continue the analysis on an ongoing basis*

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

The TNT plans 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. EPA plans to make this analysis publicly available, to the extent possible with information claimed as CBI, to advance the development and implementation of NAMs. EPA will continue to explore approaches to maintain confidentiality but make key scientific information publicly available.

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 (U.S. EPA, 2017c). A rule was published in June, 2017 to establish a process for prioritizing chemicals and a public meeting was held on December 11, 2017 to discuss approaches to inform candidates for prioritization. At the public meeting, EPA presented a document *(Discussion Document: Possible Approaches and Tools Identifying Potential Candidate Chemicals for Prioritization)(U.S. EPA, 2017d)* which contains a section on the use of NAMs for identifying potential candidates for prioritization purposes. EPA is required to prioritize at least 20 high, and at least 20 low, priority chemicals by approximately the end of December, 2019. 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. Furthermore, development of this infrastructure will facilitate the ability to monitor and measure the development and use of NAMs to replace vertebrate animal testing under TSCA. Finally, in addition to building the internal IT capacity within OPPT, this effort will include the development and launch of a new public EPA TSCA NAM website (see near-term activity (viii) below).

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 EPA (and others) could work towards identifying and developing appropriate NAMs (e.g., possible test methods and the use of IATA, AOP, and DA frameworks) that need further development to meet TSCA Section 4(h) needs for NAMs.

EPA anticipates that during this near-term time period there may be knowledge gaps identified to focus possible research/testing on NAMs and to prioritize NAMs for performance assessment and translational studies to accelerate the development of appropriate NAMs (per Section 4(h)2) (F) of TSCA).

OPPT will also work closely with ORD and others inside and outside EPA to enhance collaborative efforts for identifying research needs for NAMs specifically for TSCA. Since the passage of the TSCA amendments, EPA has become an active member of several ICCVAM technical workgroups (skin sensitization, developmental and reproductive toxicity, acute toxicity, ecotox, 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. One recent example of the networking/collaboration within the federal government is the development of the Integrated Chemical Environment (ICE).[22] Another is the new Tox21 strategy and cross-partner projects (i.e., reference chemicals, adoption of existing OECD methods to HTS) (Thomas et al., 2018). 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

[22] https://ice.ntp.niehs.nih.gov/

Screening, Validate EpiAirway™, EpiAlveolar™ and macrophage models as alternatives for OECD TGs 403 and 436 (acute inhalation toxicity).

EPA's TNT will be active participants in collaborations with partners and stakeholders to ensure that NAMs are developed to fit the needs of TSCA. For example, 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, 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. *Increase EPA participation in collaborative efforts* ***(Ongoing)***
    a. *Develop a regular series of webinars (both for internal education/training and with stakeholders)*
    b. *Become more active in ICCVAM and OECD activities/workgroups*
    c. *Actively seek out and visit academic, industry and stakeholder experts/facilities*
    d. *EPA will host academic, industry and stakeholder experts to exchange ideas*
2. *Increase in the development and publicizing of TSCA-specific Case Studies through TNT* ***(Ongoing)***

viii. Launch TSCA NAM Website

EPA will launch a new website dedicated to NAMs within the TSCA program. It will be a focal point for information pertaining to education, training, outreach, the TSCA Section 4(h)(2)(C) List and more.

TIMELINE: ***(Third Quarter, 2018)***

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

In 2021, EPA is required to submit a report to Congress on the progress made on implementation of this Strategic Plan. 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, 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) is important in directing future development and integration of NAMs. Also, EPA will continue to receive new information submitted under TSCA including voluntarily testing which may include testing using NAMs. As this information is collected, EPA will be able to more systematically and strategically develop and implement NAMs.

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

i. Review Retrospective and In-House Analyses to Identify Appropriate NAM Research Needs of Importance to TSCA

The TNT will review the information collected from both the retrospective (near-term activity (iii)) and TSCA in-house (near term activity (iv)) projects to determine the most appropriate TSCA-specific research needs/gaps. This will involve engagement and dialog with stakeholders, and particularly the research community, to guide the development of future NAMs

ii. Progress Towards Use of NAMs for Prioritization, Risk Evaluation, and Other Risk-Based Decisions

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, use of NAMs could improve the process of identifying candidates for prioritization. Similarly, the NAMs could be used to make hazard, exposure, environmental fate characterization decisions for risk evaluation under Section 6 and risk-based decisions under Section 5.

TIMELINE: *3-5 Years*

iii. Maintaining the Continual Expansion of the TSCA Section 4(h) List[23]

The process to identify, develop, and integrate NAMs for implementation will continue in this timeframe as new technologies are developed. As noted earlier, the TNT will be active in reviewing and developing criteria and the list will be updated at least once per year.

TIMELINE: *3-5 Years*

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

EPA plans 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 educational institutions.

TIMELINE: *3-5 Years*

[23] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical

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

EPA believes the development of NAMs for regulatory use will continue to be important and as the science improves. EPA will continue to work with partners and stakeholders to keep abreast of NAM research, as well as the regulatory implementation of their use under TSCA. Importantly, the near-term activities will identify NAMs for TSCA-specific needs; which will be publicly available to partners and stakeholders to help inform research agendas. Possible examples include developing NAMs for complex endpoints such as developmental toxicity, reproductive toxicity, and others as areas of targeted research needs.

TIMELINE: *3-5 Years*

c. Long-Term Goal: Reduce and Eventually Eliminate Vertebrate Animal Testing

The overall mission of EPA is to protect human health and the environment. OPPT views the long-term goal of this Strategic Plan as reducing, and eventually eliminating, vertebrate animal testing under TSCA in a way that fully implements this mission. Achieving this goal will require 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:

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

The newly established TSCA NAM Team (TNT) will be overseeing the implementation of the Strategic Plan. The TNT will consist of EPA staff and managers from across OCSPP and ORD and will report to the OPPT Office Director. Some of the likely tasks the TNT may be charged with are listed in Table 1.

EPA will implement this Strategic Plan in a manner that advances the Agency's mission 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 evolving science-based methods and approaches. With this Strategic Plan, EPA is focusing on improving the science and increasing confidence in regulating new and existing chemicals in US commerce through the development and use of NAMs.

Table 2: 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 and existing chemicals (**Ongoing)**
	Identify requested information (Retrospective Analysis) **(2nd Qtr., 2019)**	Maintaining Database of Requested Information (**Ongoing)**	Launching a TSCA NAM Website (3rd Qtr, 2018)
	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 enhance 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 (e.g., identifying candidates for prioritization, prioritization, risk evaluations and other risk-based decisions) with NAMs 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 has been established to ensure the successful implementation of this Strategic Plan.

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Appendix: 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).