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Office of Chemical Safety and
Pollution Prevention

Response to Comments on the Draft Strategic Plan to Promote the Development and Implementation of Alternative Test Methods

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Introduction

Purpose:
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 (Section 4(h), *Reduction of Testing on Vertebrates*).

EPA has instituted a transparent and public process for the development of 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.[1] This same docket was used to post a March 7, 2018 draft of the Strategic Plan, with a public comment period that closed May 11, 2018. A public meeting to solicit comments was also held on April 10, 2018 in Washington, DC. This Strategic Plan is available both on the OPPT website (https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical) as well as the public docket.[2] EPA is publishing this document to respond to comments received associated with the March 7, 2018 draft.

The draft Strategic Plan and materials from the public meeting are available in a docket.[3] EPA received over 900 comments from April 23, 2018 through May 11, 2018 and the vast majority of the comments (>850) were form letters supporting the concept of moving away from the use of animals in toxicity testing. There were 32 non-form letter comments received from 30 individuals/organizations (see list in Appendix).

EPA received a number of public comments on the Strategic Plan, including questions, comments and recommendations on general principles and approaches pertaining to the development and use of New Approach Methodologies (NAMs)[4], on specific processes, procedures and projects in the field of NAMs, as well as editorial comments. All public comments provided were taken into consideration in revising the Strategic Plan. The complete set of public comments can be found on the docket (see link in footnote 1).

[1] https://www.regulations.gov/docketBrowser?rpp=25&so=DESC&sb=commentDueDate&po=0&dct=SR&D=EPA-HQ-OPPT-2017-0559
[2] *Ibid* at 1
[3] *Ibid* at 1
[4] 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."

Comments and responses are grouped in this document into the following 11 major themes:[5]

- Terminology
- Identification of NAMs
- Development of NAMs
- Integration of NAMs
- Confidence
- Criteria and Section 4(h) List
- Collaboration
- Communication
- Implementation of NAMs
- Timeframe
- Other

There were other comments which were incorporated into the Strategic Plan and/or expressed support for the Strategic Plan and are not highlighted here. For example, some commenters recommended the education and training of EPA staff and managers as well as end-users on the development and use of NAMs. Virtually all commenters, and EPA, agree with this recommendation and the concept has been incorporated into the Strategic Plan.

EPA also received many detailed and specific comments about individual NAM endpoints (e.g., specific endocrine pathways), specific questions/comments requesting details for implementing the Strategic Plan and a variety of approaches to inform developing the criteria for the Section 4(h)(2)(C) list of NAMs. EPA notes that the newly established TSCA NAM Team (TNT) will be overseeing the implementation of the Strategic Plan. As such, some specifics are not spelled out in the Strategic Plan or this Response to Comments as the TNT needs to devote time and resources towards the implementation plan; including interacting and collaborating with the general public and stakeholders before some of these comments can be further addressed. In addition, some of the suggestions received, while they are being considered by EPA, were not deemed appropriate for incorporation into this higher-level Strategic Plan because they were more detailed than what is in this Plan.

The TNT will consist of EPA staff and managers from across the Office of Chemical Safety and Pollution Prevention (OCSPP) - the Office of Pesticide Programs (OPP), the Office of Science Coordination and Policy (OSCP) and OPPT, as well as the Office of Research and Development (ORD).[6] The TNT will be chaired by OPPT and the team will report to the OPPT Office Director. Table 1 provides specific information on the TNT. The role of the TNT will likely evolve with the science of NAM development and use.

[5] General and editorial comments that were not substantive are not included in this Response to Comments.
[6] Including representatives from the National Center of Computational Toxicology (NCCT), National Exposure Research Laboratory (NERL), and the Immediate Office of ORD.

Table 1 – Implementation of the Strategic Plan Through the TSCA NAM Team (TNT)	
Team Members	
The TNT will consist of EPA staff and 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, develop 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).

1. Terminology

Terminology Comment 1:
Commenters asked that EPA clarify or better articulate plans around specific terms including: NAMs and phylogenetically lower species.

Response to Terminology Comment 1:

> In the final Strategic Plan, EPA provided more clarity around the term "NAM"[7] and, upon further research, replaced "phylogenetically lower species" as the descriptor for replacement of animals with "non-vertebrate animals".[8]

2. Identification of NAMs

Identification of NAMs Comment 1:
Some comments supported an increasing emphasis on exposure-NAM development including advancing dosimetry and metabolism, noting their important role in focusing testing only for

[7] NAM was defined in the Strategic Plan as "…a phrase that has been adopted as a broadly descriptive reference to any technology, methodology, approach, or combination thereof that…. avoids the use of intact animals."
[8] For the definition of "replacement", EPA went back to the original Russell and Burch (1959) definition (which does not use the term phylogenetically lower species).

those substances that truly merit it due to potential biological activity at relevant exposure levels. Others stated that the Strategic Plan should focus only on approaches that directly replaced vertebrate animal testing, highlighting the potential limitations of exposure-NAM approaches.

Response to Identification of NAMs Comment 1:

> EPA has included exposure as an important part of the weight of scientific evidence (WoE) in determining whether there may need to be testing for hazard to determine risk. Although some commenters felt this was not warranted, EPA does see an important connection here and believes that not considering or evaluating exposure (whether it is a NAM or not) may lead to testing for hazard when it may not be necessary. Exposure is a key component of the TSCA requirement for risk-based decision making.

Identification of NAMs Comment 2:

EPA received a comment that this Strategic Plan should encompass all of OCSPP regulatory decision-making.

Response to Identification of NAMs Comment 2:

> The Strategic Plan draws on other plans from EPA, including OPP and OSCP. The recent OPP/OPPT skin sensitization policy exemplifies cooperation within OCSPP. Section 4(h)(2)(A) states that the Plan is to promote the development and implementation of alternative test methods and strategies related to assessing risks of injury to health or the environment of chemical substances and mixtures. Chemical substances and mixtures are terms defined in TSCA; therefore, the Strategic Plan necessarily is focused on testing related to such chemicals. Furthermore, section 4(h)(1) states that the "Administrator shall reduce and replace, . . . the use of vertebrate animals in the testing of chemical substances or mixtures *under this title*", referring to TSCA. However, OPPT, as part of OCSPP, works closely with both OPP and OSCP on NAMs. For example, both offices are represented on the TNT.

3. Development of NAMs

Development of NAMs Comment 1:
Specific ideas to enhance NAM development include (but are not limited to) various methods/approaches:

a. Mining literature and providing incentives to publish negative results
b. Utilizing NAMs to probe mixtures and unknown, variable composition, or biologics (UVCBs)
c. Developing and validating NAMs specifically designed to address Potentially Exposed or Susceptible Subpopulations (PESS)
d. Expand the species that are considered
e. Giving NAM derived results/notices preferential/more rapid regulatory review
f. Invest in NAMs to cover all endocrine pathways

Response to Development of NAMs Comment 1:

EPA received many comments describing how to enhance NAM development. They range from relatively simple (e.g., encourage journals/researchers to publish negative results) to the complex (e.g., developing NAMs to specifically address Potentially Exposed or Susceptible Subpopulations). As noted in the Introduction to these Response to Comments, many of the details associated with implementing the Strategic Plan will be developed through the newly established TNT. As a Strategic Plan, EPA believes it is appropriate to lay out a framework with objectives (as presented in Chapter 7) and provide a road map (in this case, reliance on the TNT) to achieving the statutory goal of TSCA Section 4(h).

4. Integration of NAMs

Integration of NAMs Comment 1:
EPA received suggestions and comments with respect to various potential NAM integration frameworks including addressing uncertainty in weight-of-evidence approaches and the use of systematic review frameworks.

Response to Integration of NAMs Comment 1:

EPA proposes the use of multiple approaches for the potential integration of NAMs in the Strategic Plan in order to determine if the proposed "scientific information, technical procedures, measures, methods, protocols, methodologies, or models are consistent with the best available science" (TSCA Section 26(h)). As noted in Section 4.b of the Strategic Plan, there are currently a variety of weight-of-evidence approaches for using or integrating NAMs as alternatives for existing in vitro and in vivo studies used in decision making, including (but not limited to), IATAs, DA's, and AOPs.[9] While these approaches may have some uncertainties associated with them, they remain an important way to organize relevant endpoints and biological responses to environmental chemicals. They also may enable more efficient testing for a large number of chemicals, may provide a means for increasing scientific confidence in a chemical response, and can inform fit for purpose application of NAMs.

The TNT will consider the different approaches for the evaluation and integration of NAMs, including the use of systematic review, both in general and in specific cases. EPA appreciates that multiple approaches may be used given the need of a specific TSCA decision context, availability of information, and the uncertainty of the endpoints of concern.

[9] IATA = Integrated Approaches to Testing and Assessment; DA = Defined Approaches and AOPs = Adverse Outcome Pathways.

Integration of NAMs Comment 2:

One commenter believes that pathway-based approaches, such as adverse outcome pathways (AOPs), are limited in their ability to fully describe the biological complexity and variability of whole animal systems. Thus, they do not meet the amended TSCA statutory requirement of protecting potentially exposed or susceptible populations (PESS) under the conditions of use when used to dismiss or downgrade toxicity or exposure.

Response to Integration of NAMs Comment 2:

> Many toxicological test systems and exposure assessments strive to be models of real-world biology and exposures of individual humans and animals to environmental stressors. No model is able to fully recapitulate the biological complexity and variability of whole animal systems just as no whole animal system is able to fully recapitulate the biological complexity and variability of individual humans and diverse species across broad populations.
>
> Regarding the role of NAMs (and the integrative framework such as the AOP) in protecting PESS, there is active EPA (and other) research in this area and the TNT will continue to monitor progress.

5. Confidence

Confidence Comment 1:
EPA received numerous comments supporting the need for clearly articulating issues related to uncertainty of NAMs in relation to existing in vivo assays, specifically:

a. Grounding any uncertainty associated with NAMs (including AOPs) in comparison to the uncertainty of traditional in vivo models
b. Comparing the reliability and reproducibility of NAMs versus in vivo models
c. Prioritizing statutory requirements to "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"
d. Explicitly articulating the domain of applicability for NAMs (and in vivo assays)
e. Highlighting the health, scientific and economic benefits of increasing deployment of NAMs

Response to Confidence Comment 1:

> In developing the retrospective analysis (near-term objective, Chapter 7.a.iii. in the Strategic Plan), and looking at information prospectively, EPA understands the importance of reliability and relevance to describe uncertainty. Based on comments received, EPA enhanced the definitions and descriptions of both relevance and reliability. In addition, although recognizing that *in vivo* animal studies may not be the "gold standard", there is a certain amount of confidence gained by doing comparison/evaluations between NAMs and animal studies. Of course, the best comparison is with human data when available (as was the case with the skin sensitization endpoint).

EPA understands the importance of the phrase in the law: "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" and determining whether NAMs meet this is a component of the Strategic Plan. In the next several years as the TNT matures and interacts with stakeholders and analyzes the results of the retrospective analysis (and case studies as they are developed), EPA will have a better understanding of NAMs in this regard.

The domain of applicability is an important concept in the development and implementation of NAMs and is throughout the final Strategic Plan. Because the TSCA chemical space is so broad, explicitly articulating it is difficult. EPA believes it is important to focus on chemical categories as the organizing principle to identify appropriate applicability domains (by structure and endpoint of concern).

The final point under Confidence Comment 1 relates to the benefits of increasing deployment of NAMs. It is possible that use of NAMs could lead to a lower economic cost compared to vertebrate animal testing as well as a possible increase in the potential scientific and health benefits from their use.

6. Criteria and the TSCA Section 4(h) List

Criteria Comment 1:
Many commenters articulated the need for TSCA decision-contexts and how the criteria of "equivalent or better scientific quality and relevance" relate to these contexts (especially the criteria and presentation for the list of NAMs). Commenters also identified a need to articulate how - and how frequently - the list would be updated, including a public input process.

Response to Criteria Comment 1:

As noted in Figure 1 and throughout the Strategic Plan, EPA specifically points to the importance of "fit-for-purpose" for development and implementation of NAMs for TSCA decisions (i.e., candidates for prioritization, prioritization, risk evaluation and risk-based decisions).

As part of the draft Strategic Plan, EPA provided a list of NAMs and proposed criteria (Chapter 5) for NAMs to be placed on that list. EPA modified some of the wording in six of the eight criteria listed based on comments received. In addition, the agency modified the list of NAMs in the final Strategic Plan and posted it separately (see TSCA Section 4(h) List).[10] Finally, the agency modified the Plan to add flexibility to allow the use of new NAMs even if they are not on the list. This requires a thoughtful approach that will likely change over time and which will be a high priority of the newly established TNT.

A few specific changes/points which are in the final Strategic Plan pertaining to criteria and the list deserve mention. First, EPA often receives information from new chemical

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

submitters (and others) that may include NAMs that are new or different than what the Agency uses – or that may not be on the list. 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. 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. Second, the Plan recognizes the need for a thoughtful approach at establishing a process for the listing of NAMs and public input on this process will be actively sought out. Third, EPA anticipates updating the list on at least an annual basis.

List Comment 1:
EPA received many comments on defining the list of NAMs including: keeping the list up to date, defining specific regulatory purpose or decision-context for which a particular NAM is acceptable, identifying NAMs for ecotoxicology and nanoscale materials, and providing decision-trees for NAM utilization.

Response to List Comment 1:

EPA agrees that at the rate that novel NAMs are developed, any static list of NAMs may not include the most recent methods or strategies. The list of NAMs included in the final Strategic Plan contains four tables. Tables 1 and 2 are some NAMs that have been reviewed and established as acceptable NAMs by different organizations (i.e., OECD, EURL-ECVAM and ICCVAM) and that meet the criteria in section 4(h)(2)(C). Table 3 contains the recent OPP/OPPT policy requiring (in general) NAMs for skin sensitization testing rather than vertebrate animals.[11] Table 4 is a list of some NAMs that have historically been used by OPPT in the new chemicals program. It is envisioned that the list will be updated on at least an annual basis.

This list is not meant to be exhaustive, but more representative of possible NAMs. EPA will consider methods and strategies not included in this list if they meet the criteria (see Chapter 5 of the Strategy for a starting point for considering scientific reliability and relevance of NAMs within the TSCA program starting point), including any on specific topics such as ecotoxicology or for nanoscale materials. For flexibility and ease of review, NAMs on this list will be organized by type of NAM, and not by regulatory or decision context. EPA expects that the decision context for an individual NAM may change over time as confidence in different tests may evolve based on data, experiences, and retrospective analyses.

7. Collaboration

Collaboration Comment 1:
EPA received numerous comments encouraging the Agency on various approaches to increase collaboration with stakeholders, including (but not limited to):

[11] https://www.epa.gov/newsreleases/epa-releases-draft-policy-reduce-animal-testing-skin-sensitization

a. OECD, EPA experts, ICCVAM, CAAT, animal welfare/protections organizations, environmental NGOs, allied chemical industry, ECVAM, pharmaceutical industry, academic community, NAM developers
b. The TSCA NAM Team (TNT) should include experts outside of EPA
c. Acknowledge NAM progress in regulatory bodies in foreign jurisdictions
d. Regularly plan to update and engage the public on status and implementation of the Alternative Testing Strategy implementation
e. Take a leadership role in collaboration around NAMs

Response to Collaboration Comment 1:

EPA has been engaged with many stakeholders regarding NAMs over the years, but since the passage of the 2016 amendments to TSCA, there has been renewed interest and commitment. For example, OPPT has taken a more active role in ICCVAM activities. Furthermore, as stated in the final Strategic Plan, EPA intends to engage a broader audience for NAMs education/training through workshops and webinars. EPA will continue to play a large role in the OECD arena and intends to play a larger role in all of its NAM-related activities (IATA case studies, development of AOPs, etc.). Finally, EPA envisions interacting with more foreign jurisdictions regarding NAMs.

Regarding the make-up of the TSCA NAM Team (TNT), EPA has stated in the final Strategic Plan that the TNT is an internal EPA group and includes representatives from OPPT, OPP, OSCP and ORD. This is by necessity in order to work efficiently to develop and follow the implementation of the Strategic Plan under TSCA, including the importance of considering information claimed as confidential business information (CBI). However, EPA acknowledges the importance of engaging with stakeholders – and intends to do so on a regular basis on TNT-related matters for insight and advice on the milestones in the Strategic Plan. These interactions will be through the collaborations and outreach described above.

Collaboration Comment 2:

EPA received several comments regarding specific actions to enhance collaboration to support implementation and education, including (but not limited to):

a. IATA case studies projects are a good place for collaborative efforts
b. Opportunities for collaborative case studies and low-hanging fruit
c. EPA, companies, and consortia should have frequent one-on-one meetings on NAMs/collaboration/education
d. Explore the use of public-private partnerships and industry consortia
e. Consider a process to identify and pursue key priorities for long-term collaborations.
f. Identify and document funding for collaboration
g. Better utilization of an IT platform to share scientific data relevant to NAMs (potentially ChemView)
h. Clear communication from EPA leadership to staff on the importance of NAM collaboration (such as daily communications or annual review)

Response to Collaboration Comment 2:

As stated in the final Strategic Plan and above in response to Collaboration Comment 1, EPA plans to play a more active role in developing case studies in the OECD IATA program; as well as other fora as possible. EPA understands the importance of the development and use of collaborative case studies to increase confidence in the understanding and use of NAMs in a regulatory decision context.

In terms of meeting with industry stakeholders, EPA/OPPT has always been open to establishing and maintaining a dialogue with companies as needed. Although the door is always open, EPA will attempt to be more proactive about initiating such discussions (see Response to Communication Comments below).

EPA agrees with the comments regarding the need for prioritizing, funding and having the appropriate IT platform as keys to the success of implementing the Strategic Plan. The TNT will be an important part of prioritizing collaborative efforts; including strengthening ones already in place. As presented in the Strategic Plan, development of a state of the art IT platform is critical to the success of the development and use of NAMs.

Finally, EPA leadership is committed to the implementation of this Strategic Plan. In the current re-organization of OPPT, there is the recognition of the need to devote resources and leadership to this area. This includes the move to hire new data scientists with training/experiences in NAM-related fields. There is also a research budget which has been identified and dedicated to NAM development.

8. Communication

Communication Comment 1:
EPA received several comments encouraging the Agency to improve, harmonize, and promote its communications around NAMs, especially as they relate to the EPA website. In a related comment, it was mentioned that when announcing a new NAM-related policy (such as the recent skin sensitization policy), that EPA needs to pro-actively send it out to industry.

Response to Communication Comment 1:

Based on these comments, EPA intends to improve its education/outreach and communication mechanisms, including the launching of a new website dedicated to NAMs within the TSCA program. The List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs]) is here.

In addition, launching a new website dedicated to NAMs is a near term activity with a timeline for completion of the third quarter in 2018. The new website will be a focal point for information pertaining to education, training, outreach, the List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs]) and more.

The recent skin sensitization policy was issued as a joint effort from the Office of Pesticide Programs (OPP) and OPPT. The document and link to the appropriate docket for submitting comments were released using the OPPT list-serve e-mail list on April 10, 2018; which serves as a general announcement and includes many regulated stakeholders.

9. Implementation

Implementation Comment 1:
EPA received numerous comments suggesting an approach to allow for one-off and proprietary methods or approaches that have not yet been accepted by, for example, the OECD, especially in support of prioritization, pre-manufacture notice, or in response to a consent order testing requirement. At the same time, there were numerous comments cautioning against acceptance of these types of methods, highlighting the need for independent review, transparency, and, scientific rigor.

Response to Implementation Comment 1:

Traditionally, industry has petitioned EPA with new information that may include proprietary information, which the Agency considered based on its scientific merits and in the context of the use for which it is proposed. This information may not be verified by a third party prior to EPA's receipt. Examples include the various *in silico* models which are available commercially as well as some models developed by industry for their in-house use. EPA will strive to verify, and make publicly available to the extent possible, results of analyses (internal or external as needed) to determine whether the submitted information would be acceptable for TSCA decisions. In all such situations, EPA consideration is on a case-by-case basis.

Implementation Comment 2:

EPA received many comments advocating both for a rapid process to enhance adoption of NAMs in a regulatory setting and a cautious approach urging adoption of NAMs only once they had been rigorously evaluated and validated.

Response to Implementation Comment 2:

Commenters were divided between using a rapid process to adopt and use NAMs versus a cautious approach in which NAMs are used only after rigorous evaluation/validation. EPA appreciates this dichotomy and has chosen a middle ground in its Strategic Plan by identifying NAMs from various vetting authorities (e.g., OECD), but allowing other NAMs to be brought forward by stakeholders which will be evaluated by EPA based on their scientific merit and TSCA decision context.

Implementation Comment 3:

Commenters supported EPA's plan to conduct retrospective analyses on requested and submitted information for new chemicals. Simultaneously, the commenters identified additional potential analyses or alternative approaches for EPA to consider.

Response to Implementation Comment 3:

EPA appreciates the suggestion to expand the retrospective analysis to include existing chemicals. Although not stated explicitly in the Strategic Plan, because much of the historical information on existing chemical test requests (old Section 4 test rules) and submissions (from Sections 6 and 8) have been compiled and placed in various databases, this information will likely be included in the overall analysis. 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.

Implementation Comment 4:

Commenters suggested re-ordering, advancing, or developing certain implementation priorities including:

a. Expand the focus of this intermediate-term activity to include existing chemicals, not just new chemicals
b. Development of NAMs for TSCA green chemistry programs
c. Using NAMs to ensure coverage of hormonal pathways
d. Developing a list of research needs and focusing resources on those NAMs that were deemed most needed after the retrospective analysis
e. Improve read-across approaches, provide greater emphasis on read-across, and expand to include existing chemicals program

Response to Implementation Comment 4:

EPA considered reordering and adding to implementation priorities. The Agency expects priorities may shift as the TNT begins the work of implementing the Strategic Plan. At the same time, the priorities have been identified based not only on Agency priorities, but feasibility as well. As such, the Agency believes that focusing on TSCA New Chemicals may lead to more experience in developing confidence to use NAMs as compared with the risk evaluations under existing chemicals.

Read-across remains a critical focus of the Strategic Plan, and is regularly deployed as part of the TSCA New Chemicals Program. EPA researchers and other scientists continue to publish approaches that enhance the existing read across approaches (see, for example, Zhu, et al., (2016), Ball, et al (2016) and Shah, et al (2016)). The feasibility of accepting read across approaches under the existing chemicals program has not been explored. This area may be ripe for an early case study.

As part of the research and science translation program, EPA scientists have begun work to identify "minimal assay sets" (see, for example, Judson, et al., (2017)) that may help inform green chemistry approaches. This work is currently undergoing review by OECD partners through the IATA case study project and represents an opportunity for stakeholders to utilize existing minimal assay sets or develop their own to inform green chemistry opportunities.

With respect to coverage of hormonal systems, EPA established the Endocrine Disruptor Screening Program in 1998 based on recommendations from the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC) (U.S. EPA, 1998). The Committee recommended that three primary hormone systems be included in the EDSP - estrogen, androgen, and thyroid -because they are important hormones in both humans and wildlife that also had a relatively large body of available, relevant data. The EDSTAC encouraged EPA to periodically evaluate and, where appropriate, incorporate new screens and tests to expand the EDSP to include additional hormones and endpoints. Given available resources and progress to date, rather than further expanding the battery of EDSP assays, EPA has prioritized developing NAM approaches to screen the existing EDSP Universe of Chemicals (U.S. EPA, 2015, 2012).

Implementation Comment 5:

Several commenters encouraged the Agency to avail itself of all available voluntary and statutory authorities to encourage and collect both NAM and traditional toxicological information, noting that guidance documents may need to be updated or better contextualized. Commenters also suggested that the TNT review regulations and consent orders to ensure these correctly implement the requirements under 15 U.S.C. §2603(h). Commenters also suggested building in consultation requirements or using enforcement provisions to ensure industry compliance with TSCA alternative testing provisions.

Response to Implementation Comment 5:

To the extent possible, the cross-agency TNT group will advocate for the use of NAM, where feasible and appropriate, throughout the Agency.

EPA intends to utilize many different avenues to collect information relevant to TSCA. This includes, but is not limited to: reviews of scientific literature, promoting the formation of industry consortia and public-private partnerships, collaborative research with ORD and other federal research entities, and the issuance of test orders and rules

A key responsibility of the TNT will be to ensure the development and updating of guidance relevant to TSCA NAM deployment. Additionally, the TNT will work to develop and implement ongoing training of TSCA risk assessors and regulators to ensure that NAMs are being assessed and recommended appropriately. Within the new chemicals program, EPA has recently made changes in orders to facilitate greater use of NAMs. EPA encourages dialogue between submitters and EPA and also describes any information needed rather than a specific test. This approach should allow for the broader use of NAMs when they exist and are relevant. Further, proposed regulations (such as significant new use rules or SNURs) provide an opportunity for the public to identify

when EPA has missed an opportunity to replace vertebrate animal testing with an acceptable NAM.

Just as industry already routinely consults EPA regarding TSCA notices, testing, and regulations, EPA anticipates that industry will regularly consult with EPA to foster deployment of NAMs. In addition to requiring fewer animals, NAMs may cost less than existing approaches (see responses to Collaboration Comment 2 above).

As EPA develops metrics for NAM deployment, if utilization of NAMs by the regulated community does not keep pace with the rate with which NAMs are accepted, EPA may consider alternative approaches for encouraging adoption.

Implementation Comment 6:

Regarding the use of NAMs to identify candidates for prioritization, one commenter pointed to a set of comments they made on *EPA's Discussion Document: Possible Approaches and Tools for Identifying Potential Candidate Chemicals for Prioritization.*

Response to Implementation Comment 6:

EPA will address these comments when further information is released on efforts related to identifying candidates for prioritization. (See: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/prioritizing-existing-chemicals-risk-evaluation)

Implementation Comment 7:

Commenters expressed differing views on the implementation of the toxicological threshold of concern (TTC) approach for regulatory decision-making.

Response to Implementation Comment 7:

EPA believes that exploration and potential implementation of the toxicological threshold of concern approach, at least for some chemical structural classes, is an important possible avenue for making some TSCA decisions. EPA is considering this topic as part of collaborative efforts identified above (see responses to Collaboration Comment 2 above).

Implementation Comment 8:

Several commenters identified a need for EPA to develop metrics and tools (especially IT) for monitoring and measuring NAM replacement of traditional vertebrate tests.

Response to Implementation Comment 8:

EPA concurs and is actively exploring approaches for monitoring and measuring NAM replacement of traditional toxicological testing including within its IT systems. Implementation specifics will fall in part to the TNT.

10. Timeframe

Timeframe Comment 1:
Many commenters identified a need for EPA to articulate more specific goals, especially over the short-term. Additionally, commenters expressed that EPA should articulate a concrete timeframe by when animal testing will be eliminated.

Response to Timeframe Comment 1:

EPA appreciates the public's interest in specific information with respect to next steps. Given the broad nature of the substances and uses regulated under TSCA, many next steps beyond those articulated in the Strategic Plan are expected to be derived from the implementation work of the TNT.

The Statute does not include the objective to eliminate vertebrate animal testing nor does it include a timeframe for reducing, refining, or replacing vertebrate animal testing. Rather EPA should make progress to prioritize and, to the extent consistent with available resources, to continuously 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.

11. Other

Other Comment 1:
Several commenters questioned why EPA would expend TSCA resources on K-12 outreach.

Response to Other Comment 1:

The identification of K-12 as a specific age group was removed from the final Strategic Plan.

Other Comment 2:

EPA received some comments relating to the PETA/PCRM analysis posted in the docket on April 23rd, 2018 highlighting the increase in animal test requests under the amended TSCA.

Response to Other Comment 2:

This response to comments is specific to the development of the final Strategic Plan. An official response to the January 2018 PETA/PCRM analysis is being handled separately.

Other Comment 3:

Several commenters asked broad questions whether use of NAMs would lead to changes in EPA's risk assessment or regulatory approaches such as moving away from high-dose testing to focus on real-world exposures.

Response to Other Comment 3:

> As NAMs become more prevalent and integrated into EPA risk assessment processes, it is reasonable to anticipate EPA risk assessment and risk management frameworks and approaches will change with emerging science. EPA is exploring this area, with some examples of research areas[12] and regulatory approaches[13] available on the EPA website. However, it is too early in the implementation process for EPA to provide concrete predictions as to what these changes might look like.

[12] https://www.epa.gov/aboutepa/about-national-center-computational-toxicology-ncct

[13] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science

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APPENDIX

LIST OF INDIVIDUALS/ORGANIZATIONS WITH NON-FORM LETTER COMMENTS

	Commenter/Organization
1	Afton Chemical
2	American Chemistry Council (ACC)
3	American Petroleum Institute (API)
4	Anderson (citizen)
5	Animal Defenders International
6	ARDF
7	Berry (citizen)
8	Biotech Innov Org
9	CAARE
10	Carson (citizen)
11	Cruelty Free International
12	Cullen (citizen)
13	Endocrine Society
14	Environmental Defense Fund (EDF) 1
15	Environmental Defense Fund (EDF) 2
16	Human Society of the US (and International)
17	Locke (Johns Hopkins U)
18	Michael J Fox Foundation
19	NICEATM 1
20	NICEATM 2
21	NAVS
22	NRDC
23	PCRM
24	PEACE
25	PETA
26	PETA/PCRM Combined
27	Ringgard (citizen)
28	Scitovation
29	Silent Spring Institute
30	Speaking of Research
31	Wright (citizen)
32	Wynn (citizen)