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New Approach Methods Work Plan

Reducing use of animals in chemical testing

U.S. Environmental Protection Agency
Office of Research and Development
Office of Chemical Safety and Pollution Prevention

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Executive Summary

In September 2019, EPA Administrator Andrew Wheeler signed a directive to prioritize EPA's efforts to reduce animal testing including reducing mammal study requests and funding 30 percent by 2025 and eliminating them by 2035. In accomplishing these ambitious goals, the Agency will continue to rely on the development and application of new approach methodologies (NAMs), which refer to any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing.

In this document, EPA describes its roadmap and identifies tangible steps to pursuing and achieving these reduction goals while ensuring that the Agency's regulatory, compliance, and enforcement activities, including chemical and pesticide approvals and Agency research, remain fully protective of human health and the environment. In doing so, EPA will have to ensure its regulatory framework is robust and flexible enough to accommodate the development and the use of NAMs; establish baselines, measurements and reporting mechanisms to track progress in meeting its goals; establish scientific confidence in NAMs and demonstrate application to regulatory decisions; develop NAMs that fill critical information gaps; and continue to engage and communicate with stakeholders to incorporate their knowledge and address concerns as EPA moves away from mammalian testing. In this work plan, EPA discusses the short- and long-term strategies it will deploy to accomplish these five objectives, working across offices and with stakeholders, and the different deliverables on which the Agency will focus, so the public can track EPA's progress towards meeting the 2025 and 2035 goals.

Abbreviations

APCRA	Accelerating Progress in Chemical Risk Assessment
ATAEPI	Analysis of TSCA Available, Expected, and Potentially Useful Information
CAA	Clean Air Act
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
CFR	Code of Federal Regulations
CWA	Clean Water Act
EDSP	Endocrine Disruptor Screening Program
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-Know Act
ESA	Endangered Species Act
FFDCA	Federal Food, Drug, Cosmetic Act
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FQPA	Food Quality Protection Act
GAO	Government Accountability Office
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
NAM	New Approach Method
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organisation for Economic Co-operation 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
PFAS	Per- and Polyfluoroalkyl Substances
RCRA	Resource Conservation and Recovery Act
SDWA	Safe Drinking Water Act
SNAP	Significant New Alternatives Policy
STAR	Science to Achieve Results
TSCA	Toxic Substances Control Act

Introduction

The Environmental Protection Agency (EPA) uses information from a broad range of animal tests when evaluating the potential risks of chemicals, assessing potential impacts on the environment, and approving chemicals for certain uses, consistent with its statutory obligations. Given the large number of chemicals that EPA regulates, the number of animals used to generate information is substantial. In September 2019, Administrator Wheeler directed the Agency, and specifically the Office of Chemical Safety and Pollution Prevention (OCSPP)[1] and the Office of Research and Development (ORD), to prioritize efforts and resources towards activities that will demonstrate measurable impacts in the reduction of animal testing while ensuring protection of human health and the environment.[2]

In summary, the goals laid out in the Administrator's directive for the Agency are to:

- Reduce its requests for, and funding of, mammalian studies by 30 percent by 2025;
- Eliminate all mammalian study requests and funding by 2035; and
- Come as close as possible to excluding from its approval processes any reliance on mammalian studies conducted after January 1, 2035, including those performed by third parties.[3]

As part of this directive, ORD and OCSPP were tasked with developing this work plan focused on the development, testing, and application of New Approach Methods (NAMs).[4] NAMs have the potential to provide more rapid, cost-effective, and human-relevant information on potential chemical risks compared with traditional animal testing. To develop the work plan, both offices convened and coordinated with experts across the Agency to identify tangible steps to ensure that the Agency's regulatory, compliance, and enforcement activities, including chemical and pesticide approvals and Agency research, remain fully protective of human health and the environment while pursuing these goals.

In this work plan, the Agency is laying out the objectives and strategies to achieve these ambitious goals. The objectives are: I) evaluate regulatory flexibility for accommodating the use of NAMs; II) develop baselines and metrics for assessing progress; III) establish scientific confidence in NAMs and demonstrate application to regulatory decisions; IV) develop NAMs

[1] Includes Office of Pesticide Programs (OPP), Office of Pollution Prevention and Toxics (OPPT), and Office of Science Coordination and Policy (OSCP).
[2] EPA. Directive to Prioritize Efforts to Reduce Animal Testing (Sept. 10, 2019).
[3] Subject to applicable legal requirements, including the Administrative Procedure Act.
[4] As defined in the Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program (June 22, 2018) (hereinafter referred to as "TSCA Strategic Plan"), a NAM is 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.

that fill critical information gaps; and V) engage and communicate with stakeholders to incorporate their knowledge and address concerns as EPA moves away from mammalian testing (Figure 1). This work plan represents a snapshot in time, and it will evolve as EPA's knowledge and experience grows, and as outside experts offer their perspectives and contributions to our work. As such, the Agency intends to regularly review the work plan to ensure the efforts involved provide the best path to success.

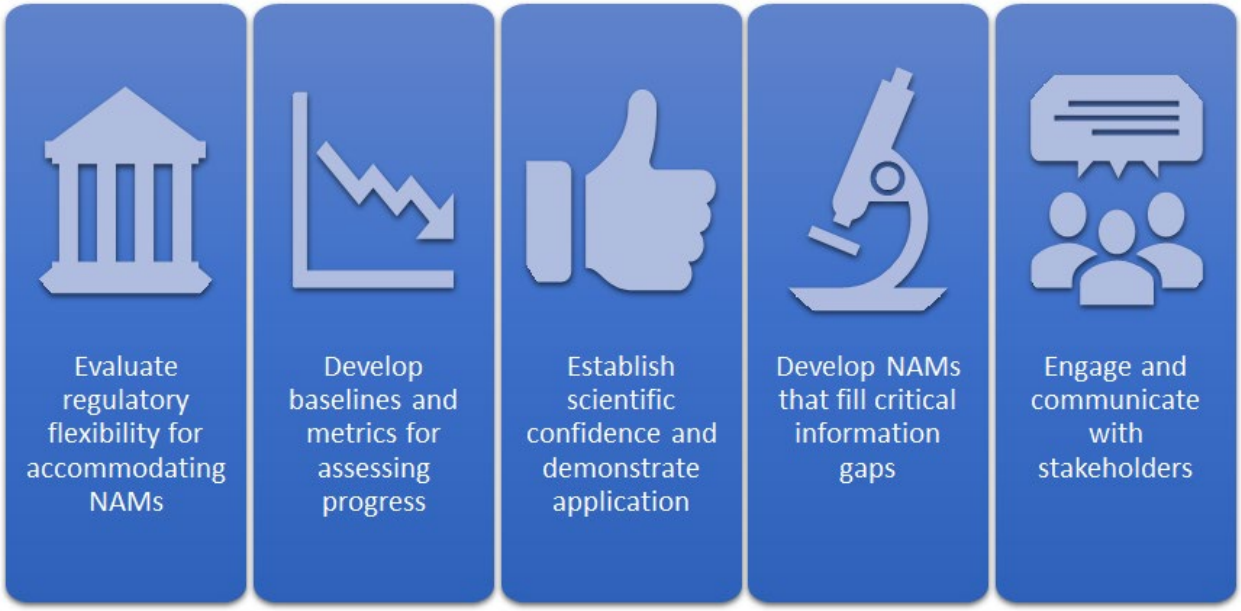

Figure 1. Five work plan objectives towards achieving the EPA mammalian testing reduction goals.

I. Evaluate regulatory flexibility for accommodating the use of NAMs

EPA operates under laws and regulations which provide the authority and framework for the Agency's regulatory and research programs. EPA implements and enforces these laws and regulations to protect human and ecological health; maintain the integrity of the nation's air, water and land; manage emergency response, spills and waste; and regulate pesticides and chemicals throughout the United States. In certain cases, that authority needs to be further refined or explained to accommodate the implementation of NAMs, requiring the development of rules, policies, and written guidance that represent the Agency's interpretation or view of specific issues.

An initial review of the major environmental statutes reveals that these statutes do not prevent EPA from considering information from NAMs when carrying out its responsibilities (Table 1). Most of the statutes and regulations surveyed include statements such as the necessity of upholding scientific standards and using "the best available science," which may include NAMs.[5] Similarly, the authority for EPA's research programs arising from these statutes is broadly written and does not constrain the Agency from developing or advancing the use of NAMs. For those regulations that have specific testing requirements, the Agency has been successful in using its authority to increase flexibility in some cases (e.g., using science policy changes).

[5] Three examples are: (1) Per section 26 of the Toxic Substances Control Act (TSCA), the Administrator must use the "best available science" and consider "reasonably available information" when carrying out TSCA sections 4, 5, and 6. 15 U.S.C. § 2625. (2) When setting drinking water standards under the Safe Drinking Water Act (SDWA), EPA is required to use "(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices; and (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data)." 42 U.S.C. § 300g-1(b)(3)(A). (3) Section 304(a) of the Clean Water Act (CWA) requires EPA to develop and publish criteria for water quality that accurately reflect the "latest scientific knowledge" and does not specify the type of toxicity data the Agency must consider. 33 U.S.C. § 1314(a).

Table 1. Initial Survey Results of Mammalian Testing Requirements in Major Environmental Statutes

Major Environmental Statute	Statutory Requirements for Mammalian Testing	Regulatory Requirements for Mammalian Testing
Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and Federal Food, Drug, Cosmetic Act (FFDCA)	None	40 CFR Part 158 specifies FIFRA and FFDCA data requirements that include use of animals (pesticide registration, registration review, and tolerance or exemptions from the requirements of a tolerance for a pesticide chemical residue).
Endangered Species Act (ESA)	None	None
Food Quality Protection Act (FQPA) amendments to the FFDCA and the Safe Drinking Water Act (SDWA) amendments	None	None[6]
Toxic Substances Control Act (TSCA)	None, but TSCA Section 4(h) requires reducing use of vertebrate animals in testing.[7]	40 CFR Parts 790 through 799 apply to TSCA Section 4 test rules.
Clean Air Act (CAA)	None	Fuel and Fuel Additive Registration;[8] Significant New Alternatives Policy (SNAP) programs.[9]
Clean Water Act (CWA)	None	None
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)	None	None
Emergency Planning and Community Right-to-Know Act (EPCRA)	None	None
Resource Conservation and Recovery Act (RCRA)	None	None
Safe Drinking Water Act (SDWA)	None	None

[6] Visit EPA's Endocrine Disruptor Screening Program webpage. Also, see the EDSP Workplan for using NAMs.
[7] See TSCA § 4(h)(1) (stating "to the extent practicable, scientifically justified, and consistent with the policies of TSCA.").
[8] Visit EPA's Fuels Registration, Reporting, and Compliance Help webpage.
[9] Visit EPA's Significant New Alternatives Policy (SNAP) Program webpage.

Strategy, Deliverables, and Timeline

To ensure a robust regulatory framework that accommodates the development and use of NAMs, EPA will expand on the initial survey and perform a thorough review of existing statutes and programmatic regulations, policies and guidance to identify mammalian testing requirements that may not allow flexibility for the Agency to apply NAMs. Following the review, EPA will consider options for introducing flexibility on implementing and/or using appropriate NAMs for regulatory purposes.

Deliverable: *EPA report containing a review of existing statutes, programmatic regulations, policies, and guidance that relate to mammalian testing and the potential implementation and use of appropriate NAMs for regulatory purposes. The EPA report will be delivered in 2021.*

II. Develop Baselines and Metrics for Assessing Progress

The Administrator directed EPA to develop baselines and metrics to track the Agency's progress towards its goal of reducing its request for, and funding of, mammalian studies. Shortly after the Administrator's directive, the United States Government Accountability Office (GAO) completed its review on issues related to alternatives to animal research at multiple federal agencies, including EPA.[10] GAO concluded that, while agencies have facilitated the development and use of alternatives to animal research, they have not "routinely developed or reported metrics that demonstrate how their efforts to encourage the use of alternative methods affect animal use." As such, GAO recommended that EPA and the other agencies better monitor and report on their efforts to develop and promote alternative methods and decreases in animal use.

Existing efforts to establish mammalian use baselines across the Agency

EPA requires substantial toxicology testing to support pesticide registration. Toxicological studies in laboratory animals are generally used to provide information on a wide range of adverse health outcomes, routes of exposure, exposure durations, species, and lifestages. The number of animals used varies widely depending on the pesticide type and use pattern; but, between 100 and 9,000 animals, most of them mammals, may be used for human health and ecological toxicology testing for a single pesticide.

[10] GAO. Animal Use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives (Sep. 2019), GAO-19-629.

EPA has flexibility in implementing Part 158 data requirements, with FIFRA allowing for waivers to be granted and alternative methods to be accepted on a case by case basis. The number of waivers granted, and animals saved from not needing to perform repeated-dose toxicity studies have been tracked by the OPP's Hazard and Science Policy Council since 2012 and constitutes an important metric for animal use reduction for EPA. Similarly, OPP has started tracking information on the waiving of acute toxicity studies.

The Endocrine Disruptor Screening Program (EDSP) established a two-tier approach to screen (Tier I) and test (Tier II) substances for perturbations to the estrogen, androgen, and thyroid systems. The Tier 1 battery of tests uses mammals but also includes non-mammal species and *in vitro* assays. The Office of Science Coordination and Policy (OSCP) compiles the number of substances and associated tests ordered under EDSP, which allows the number of mammals used to be tracked.

Under TSCA, the 2016 amendments added an explicit requirement under section 4(h)(2) for the Agency to promote the development and incorporation of methods that reduce or replace the use of vertebrate animals, to publish a strategic plan for reducing, refining, or replacing vertebrate animal testing, and to publish a list of alternative test methods or strategies that do not require new vertebrate animals. In accordance with two elements of the TSCA Strategic Plan, OPPT has embarked on the Analysis of TSCA Available, Expected, and Potentially Useful Information (ATAEPI). This analysis will allow EPA to determine the extent of animal testing that the Agency has explicitly required companies to perform using its authority under TSCA sections 4 and 5. Once the ATAEPI project is complete, EPA will have a single database of all TSCA-related animal studies, including mammals, that were conducted or made available as a result of the Agency exercising its authorities and will be able to publish metrics consisting of the number of mammals that were required for those tests, by year.

ORD performs mammalian research to support the Agency's mission of protecting human health and the environment. While research performed by ORD includes studies to establish the risk parameters of various classes of compounds, ORD is also active in the development and validation of alternative methods and models that refine, reduce, and replace animals test. For example, ORD is evaluating the use of zebrafish embryos as a replacement for mammalian developmental toxicity studies and the use of integrated high-throughput *in vitro* assays and computational modeling to identify endocrine-active compounds. ORD has tracked the number of animals, including mammals, used at its research sites since 2015. Overall, the shift towards developing these new methods is expected to reduce the use of mammals in toxicology research over time.

Strategy, Deliverables, and Timeline

Due to their regulatory roles and/or programmatic missions, OCSPP and ORD account for a significant portion of EPA's requests for and use of mammals for toxicity testing and research. Thus, baselines and metrics for animal use will be further developed for programs within OCSPP and ORD that regularly rely on animal studies. As other EPA offices determine their contribution to animal use, their baselines and metrics will be incorporated into the overall reporting mechanisms. Due to the differences in statutory requirements and the wide range of research uses, EPA will most likely need to establish baselines and metrics that are specific to each program, building on the existing efforts and current data gathering initiatives outlined above. EPA will communicate the results and progress towards the 2025 and 2035 goals through its website. Additionally, updates will be provided during EPA's annual NAMs conferences and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) biannual reports. In the past, EPA has also reported metrics for animal use reduction via peer-reviewed publications.[11]

Initial Baseline Calculations and Metrics

Within OCSPP, EPA will initially use the number of animals required for testing under the 40 C.F.R. Part 158 as a baseline to measure and track mammalian use for pesticide actions. As guideline requirements vary based on the type of pesticide, specific baselines are as follows: 510 animals for biochemical pesticides, 3430 animals for microbials, 4920 animals for antimicrobials and 6260 animals for conventional pesticides. EPA will also establish a specific baseline for chemicals that fall under TSCA once the ATAEPI analysis is completed. For EDSP, the baseline is 1,800 animals based on the number required to complete the Tier I battery of assays. Within ORD, the average number of mammals used for research purposes between

Deliverable: *Progress and summary metrics on reducing mammalian animal testing requests and use. The metrics will be reported annually through its website starting in the fourth quarter (Q4) of 2021 (associated with the 2021 NAMs conference).*

2016 and 2018 was 8,600 per year. The average number during these years will be used as a baseline to provide both a stable and relatively recent estimate of use. OCSPP and ORD will work with the other EPA's offices to establish specific baselines and calculation methods. As additional baselines and metrics are established, EPA will distribute these estimates through the established communication mechanisms.

[11] E. Craig et al. *Reducing the need for animal testing while increasing efficiency in a pesticide regulatory setting: Lessons from the EPA Office of Pesticide Programs' Hazard and Science Policy Council* (Nov. 2019). Regulatory Toxicology and Pharmacology, 108:104481. https://doi.org/10.1016/j.yrtph.2019.104481

III. Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions

As described above, EPA's statutes and regulations regarding chemicals span a wide range of decision contexts. Examples of these decisions include prioritization, classification and labeling, alternatives assessment, and risk assessment. In many cases, mammalian tests, directly and indirectly, provide the information by which many of these decisions are made. The scientific confidence associated with the mammalian tests comes from the decades of experience in their development and application. In the transition from the reliance on the traditional mammalian tests to the application of the NAMs across the range of decisions, EPA needs to continually build more scientific confidence in information from NAMs while also establishing the appropriate expectations for their performance and demonstrating their application to regulatory decisions.

Strategy, Deliverables, and Timeline

In order to establish scientific confidence in NAMs and demonstrate application to regulatory decisions, a three-part strategy was developed that characterizes the scientific quality and relevance of existing animal tests, develops recommended reporting requirements, and demonstrates application of the NAMs to regulatory decisions through case studies. The strategy establishes appropriate expectations for NAMs while ensuring transparency and consistency and the education of staff and stakeholders through a process of 'learning by doing'.

Characterize scientific quality and relevance of existing mammalian tests

The Administrator's directive and similar text in section 4(h)(1) of TSCA note the need for information of "equivalent or better" scientific quality and relevance to animal test-based results. These requirements imply that the scientific quality and relevance of the existing animal tests should be considered in order to understand the strengths and limitations of the existing models, as well as the developing NAMs. The amount and type of analyses needed will be dependent on the NAM being developed, the adverse outcome of interest, and information available. For example, human data from pharmaceutical clinical trials may be utilized to

Deliverable: *U.S. National Academies of Sciences report that reviews the uncertainties and utility of existing information from mammalian toxicity tests in the context of NAM development. The report will be completed by the fourth quarter (Q4) 2022.*

evaluate human to animal concordance; however, human data are not available for many chemicals and these analyses might not be appropriate for certain NAMs being developed. Furthermore, differences between animals and humans can impact the ability of animal tests to predict human health effects. As such, it may not always be appropriate to compare NAMs to animal studies. EPA will need to focus on the mechanistic and/or biological relevance of the NAM for the hazard being assessed and potential uncertainties both with respect to and independent of the existing animal model. Although existing studies have evaluated important components associated with characterizing scientific quality and relevance, such as variability and human concordance, no authoritative report has been developed that can inform expectations for NAMs.

Develop a scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs

Historically, test methods have been validated according to principles described in guidance from the Organisation for Economic Co-operation and Development (OECD).[12] The OECD guidance document defines validation as a process that establishes the reliability and relevance of a particular test, approach, method, or process for a specific regulatory purpose. Although OECD guidance states that the validation process should be "flexible and adaptable," implementation has been relatively uncompromising, requiring significant investment of time and resources. To more flexibly accommodate the range of decision contexts and rapid pace of NAM development, multiple entities and individuals have proposed frameworks for building confidence and accelerating the use of NAMs.[13,14,15,16]

[12] OECD. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (GD34) (Aug. 18, 2005).
[13] NICEATM. A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States (Jan. 2018).
[14] G Patlewicz et al. (2013). *Use and validation of HT/HC assays to support 21st century toxicity evaluations.* 65(2):259-68. doi: 10.1016/j.yrtph.2012.12.008.
[15] G Patlewicz et al. (2015). *Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes*. Regul Toxicol Pharmacol. 71(3):463-77. doi: 10.1016/j.yrtph.2015.02.01.
[16] S Casati et al. (2018). *Standardization of defined approaches for skin sensitization testing to support regulatory use and international adoption: position of the International Cooperation on Alternative Test Methods*. Arch Toxicol. 92(2):611-617. doi: 10.1007/s00204-017-2097-4

Based on these frameworks, EPA developed a set of criteria for evaluating the scientific reliability and relevance of NAMs within TSCA and presented these criteria in the TSCA Strategic Plan.[17] While many of the criteria in the TSCA Strategic Plan are fundamental to evaluating the quality, reliability, and relevance of NAMs, a generic framework that is applicable across EPA's myriad of statutes and regulations is also needed.

Deliverable: *Scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs. The framework will be released as an EPA report in the third quarter (Q3) of 2022.*

Develop robust reporting templates for NAMs

Studies are submitted to regulatory programs with specific reporting requirements to aid in evaluation and interpretation. To promote consistency, the OECD has general reporting templates that may be used by different regulatory jurisdictions. The templates include standard elements that should be included in methods descriptions for individual test assays, batteries of assays, and algorithms for evaluating sets of assay results. Although the reporting templates for NAMs are still evolving, the OECD has developed guidance to help standardize *in vitro* methods suitable for regulatory purposes[18] as well as a reporting template for *in vitro* tests describing molecular and cellular observations that can be relevant to the hazard assessment.[19] To accommodate mutual acceptance of data, the EPA will build off these established templates while providing additional templates that capture the range of specific NAMs used for Agency decisions.

Deliverable: *Reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions. The reporting templates will be delivered in the fourth quarter (Q4) of 2022.*

Case studies for evaluating application to regulatory decision making for near-term and long-term application

To build on success in developing and using NAMs to date, EPA will continue to identify case studies focusing on specific questions and regulatory contexts to develop and evaluate NAMs. An initial selection of on-going case studies in EPA were identified for potential incorporation into the work plan (Table 2). Other case studies will be developed on a rolling schedule to address specific data gaps and regulatory needs. Case studies will be critical for building

[17] TSCA Strategic Plan at p. 19.
[18] OECD. Guidance Document on Good In Vitro Method Practice (Dec 2018).
[19] OECD. OECD Harmonised Template 201: Intermediate effects (Dec 2018).

scientific confidence in the NAMs as well as understanding their strengths and limitations across different decision contexts. The case studies will provide educational opportunities that will also help build capacity and confidence within EPA.

Table 2. Initial Selection of On-Going EPA Case Studies for Potential Incorporation into Work Plan

Title	Description
Refining Inhalation Risk Assessment with NAMs	Refine inhalation risk assessment for point of contact toxicity using a three-dimensional *in vitro* test system of human respiratory tissues to derive a point of departure, in conjunction with computational fluid dynamic modeling.
Integrating *In Vitro* Assay and Toxicokinetic Data in Read Across	Use of *in vitro* toxicity and toxicokinetic testing to refine/support read across categories for per- and polyfluoroalkyl substances (PFAS).
Application of *In Vitro* Bioactivity for Screening-Level Risk Decisions	Use of bioactivity from *in vitro* assays and *in vitro* toxicokinetics to prioritize chemical contaminants in biosolids.
Application of NAMs for Chronic and Carcinogenicity Testing	Integration of NAMs to identify chronic toxicity and non-genotoxic carcinogenicity modes-of-action and quantitative points-of-departure for regulatory decisions

Deliverable: *Case studies for evaluating application of NAMs to risk assessment and demonstrating protection of human health and the environment. Approximately one case study will be developed and communicated through the peer-reviewed scientific literature every other year beginning in 2022.*

IV. Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps

While considerable progress is being made in developing NAMs, there are still scientific challenges and information gaps that limit a complete reliance on NAMs for Agency decisions related to the assessment of a chemical's potential risk to human health and the environment. Examples of these scientific challenges and gaps include inadequate coverage of potential biological targets and pathways, reduced or distinct xenobiotic metabolism in *in vitro* test systems, limited capabilities to represent the complex cellular, tissue, organ, and organism-level interactions, and a lack of robust integrated approaches to testing and assessment (IATAs)[20] for higher tier endpoints of concern (e.g., development and reproductive toxicity). Although all

[20] OECD. *Guidance Document on the Reporting of Defined Approaches to be Used Within Integrated Approaches to Testing and Assessment* (April 2017).

these challenges do not apply to every situation and may not need to be addressed in order to apply NAMs to regulatory decisions, continued refinement and development of NAMs will be required to meet the Agency's animal testing goals.

Strategy, Deliverables, and Timeline

In order to refine and develop NAMs that address both the myriad of Agency decisions and ways that chemicals can impact human health and the environment, a two part strategy was developed that facilitates joint planning of NAM development by EPA research scientists and regulators as well as encourages development of NAMs by external parties. The strategy ensures that the NAMs being developed will meet the needs of end users for a specific context of use and an acceptable level of uncertainty, while also opening opportunities for innovation by scientists from academia and industry.

NAM development through EPA research planning and implementation

As part of the ORD research planning process, NAM refinement and development should begin with problem formulation and include teams of EPA research scientists and regulators (Figure 2). Well-constructed problem formulation is an important component of determining the appropriate use of NAMs by helping to identify research questions, ultimate goals for NAM use, and define levels of uncertainty that may be acceptable within the context of use. For integration into Agency decisions, matching the type and certainty of information provided by a NAM (or set of NAMs) with the type and certainty of information needed for a given decision is an important consideration. This concept ensures that data and information associated with the research are 'fit-for-purpose.' Initial development of a NAM focuses primarily on data collection and data integration where it may be combined with other NAMs as part of a weight of evidence approach, such as an IATA or defined approach.[21] Once developed, the NAM or combination of NAMs can be applied in case studies to evaluate their performance, define their applicability domain, and identify data gaps within the scientific confidence framework. This process may be iterative as additional information and lessons learned in the case studies are incorporated. When sufficiently mature, these NAM or combination of NAMs may then be applied to regulatory decision making. The ORD research associated with the planning process are outlined at a high level in the Strategic Research Action Plans.[22] Research products such as peer reviewed publications, tools, or data sets that communicate the methods and results or facilitate application of the NAMs are an integral part of the process.

[21] OECD. *Guidance Document on the Reporting of Defined Approaches to be Used Within Integrated Approaches to Testing and Assessment* (April 2017).
[22] EPA. Strategic Research Action Plans 2019-2022.

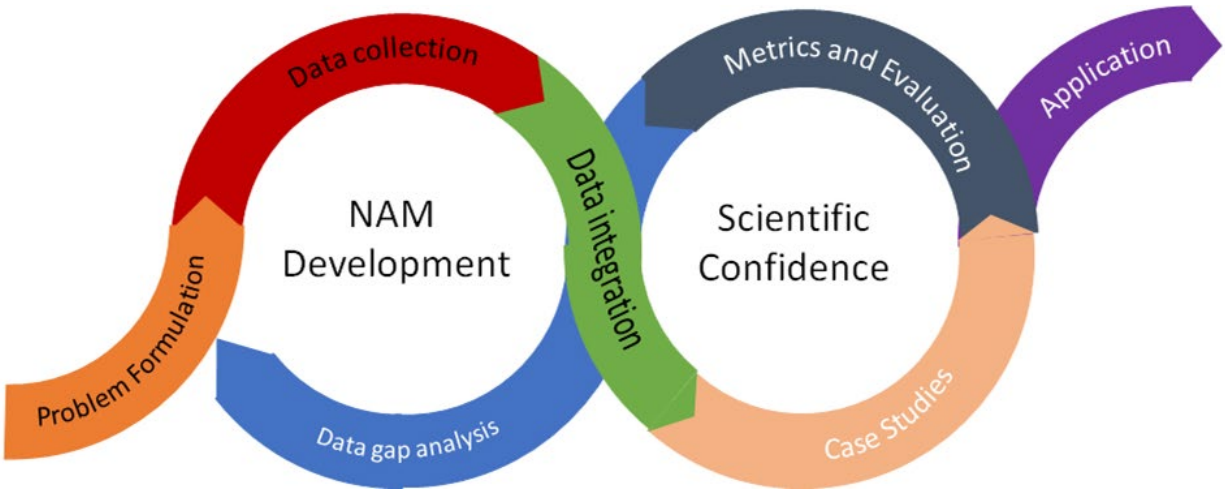

Figure 2. Problem-focused research planning and implementation process at EPA.

Deliverable: *EPA research planning process that involves teams of research scientists and regulators and provides research products that communicate the methods and results of studies and facilitate application of the NAMs. The EPA Strategic Research Action Plans will be delivered on a regular 4-year planning cycle.*

Encourage NAM development and evaluation by external entities

NAM development and evaluation by external entities leverages a large pool of resources, experience, and expertise that is not directly available to the Agency. Tapping into this pool more rapidly closes important information gaps and accelerates movement toward achieving the overall animal reduction goals. EPA has been working actively with numerous external groups, including other U.S. government agencies, animal welfare groups, industry representatives, academia, and international organizations, to encourage the development and evaluation of NAMs. One example of EPA encouraging the development of NAMs by external entities is the award of $4.25 million to five universities through its Science to Achieve Results (STAR) Program to reduce, refine, and/or replace vertebrate animal testing in chemical hazard assessment.

Deliverable: *Encourage development of NAMs through mechanisms such as the STAR program and facilitate partnerships with organizations focused on establishing scientific confidence in alternative methods. This is an ongoing deliverable.*

V. Engage and Communicate with Stakeholders

The information and data resulting from NAMs have the capacity to replace animal testing, while still protecting public health and the environment. However, the wide-spread use and reliance on NAMs in Agency decisions requires a fundamental change in thinking for regulators, the regulated community, and other stakeholders. Changes of this magnitude are difficult as traditional approaches have been used for decades in both national and international regulatory decisions. Effective engagement and communication with stakeholders are essential to increase acceptance, obtain constructive feedback, and improve the acceptance of using NAMs to inform Agency decisions.

Strategy, Deliverables, and Timeline

The strategy involves communicating and engaging with internal Agency partners as well as external stakeholders throughout the development and implementation of the NAMs work plan. The strategy ensures that important information on EPA's NAMs efforts is available and stakeholders are engaged in each step of EPA's NAMs efforts. EPA will place an emphasis on communications and engagement as important milestones of EPA's NAMs efforts are reached and how the work plan evolves as EPA's knowledge and experience grows. For example, milestones will be communicated as the work plan deliverables progress or evolve, and annually during the EPA NAMs conference. The communication and engagement activities will be tailored to reach a wide variety of stakeholder groups and provide numerous opportunities for engagement.

EPA Central Website for NAMs Information

EPA will make communication and other informational materials available through a central EPA NAMs website. This online resource will provide a mechanism for EPA to distribute NAM information including the baselines and metrics on how the effort is progressing; a portal to access informational materials such as fact sheets, conference reports, webinars; and a mechanism for stakeholders to provide feedback. The communication materials and other informational resources on the website will clearly communicate findings and progress to a diverse group of stakeholders.

Deliverable: *EPA website to house information about EPA's NAM efforts and progress being upon release of the work plan. The website will be delivered in Q3 2020.*

Solicit comment and feedback associated with deliverables

Public feedback and expert scientific review are essential to the development of this work plan and associated deliverables. EPA will request stakeholder and public feedback on deliverables associated with the work plan through public webinars. In addition, EPA will also solicit expert review and input, where appropriate, through groups such as the National Academies of Science, EPA's Science Advisory Board, EPA's Board of Scientific Counselors, and other EPA scientific advisory groups.

Deliverables: *Public webinars and, peer-review when planned, on deliverables from the work plan. This is an ongoing deliverable.*

Develop training courses, workshops, and conferences for stakeholders on NAMs

Training courses, workshops, and conferences are a vital component of reducing the use of animals in assessing the potential risks of a chemical. Stakeholders want to understand how to use NAMs and their knowledge is needed to inform how NAMs can be applied. As more stakeholders learn how to use NAMs, they will become more comfortable with using them to inform regulatory decisions. EPA will organize its own efforts to train and inform stakeholders through sessions at regularly scheduled conferences and EPA hosted workshops such as EPA's NAMs conference which will occur annually to provide progress updates and solicit stakeholder feedback. In addition, there are numerous ongoing training efforts already offered by other organizations (e.g., professional societies, universities, other federal agencies). Since these ongoing training efforts already have training in place, EPA may partner with these organizations to be able to offer trainings to a wide range of stakeholder groups. Feedback received from stakeholders and collaborations with external entities demonstrating how information from NAMs can be applied will be used to refine and improve communication and engagement with stakeholders as EPA's NAMs efforts progress.

Deliverables: *Training, opportunities for scientific exchange, and progress updates through Agency sponsored events as well as partner with organizations already offering courses. This is an ongoing deliverable.*

Summary and Next Steps

The September 2019 directive built upon progress the Agency has been making to reduce its reliance on animal testing. Over the next 15 years, EPA will continue to improve the science it uses and relies on for Agency decisions and work towards eliminating the use of mammals in testing where scientifically proven alternatives are available. This work plan is an important

milestone in this endeavor and the objectives, strategies, and deliverables provide a roadmap towards accomplishing the ambitious goals. However, like any roadmap, the work plan represents a snapshot in time. This document will need to continue to evolve as EPA's knowledge and experience grows. The Agency is committed to regularly reviewing the work plan to ensure that the objectives, strategies, and deliverables provide the best possible path to success.

Although the directive and the work plan are inherently confined to the Agency's authority and associated activities, achieving the goals will not be possible without the involvement of external partners, stakeholders and the broader scientific community. EPA has been heavily involved in multiple domestic and international organizations developing, evaluating, and applying NAMs such as the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), Tox21, Accelerating the Pace of Chemical Risk Assessment (APCRA) inter-governmental workshops, and OECD. EPA will continue to engage in these efforts. Other U.S. federal agencies and international regulatory bodies are undertaking similar initiatives and the private sector continues to apply new methods and technologies to product development. The sharing of experience, information, and approaches will accelerate efforts to use the best available science in assessing the potential risks of a chemical.

Through this work plan, the Agency is creating a new paradigm for chemical risk assessment while ensuring transparency and accountability. Federal partners, stakeholders and the public at large will be able to track EPA's progress in meeting each of the objectives identified in this work plan and ensure that the methods being applied remain fully protective of human health and the environment. As the Agency embarks on implementing the work plan it is important to remember that a plan is meaningless without action.

Appendix

Milestones/Deliverables	Proposed Dates
Evaluate regulatory flexibility for accommodating the use of NAMs	
EPA report on a review of existing statutes, programmatic regulations, policies, and guidance that relate to mammalian testing and the implementation and use of appropriate NAMs for regulatory purposes	2021
Develop Baselines and Metrics for Assessing Progress	
Progress and summary metrics on reducing mammalian animal testing requests and use	Annually starting in Q4 2021
Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions	
U.S. National Academies of Sciences report that reviews the uncertainties and utility of existing information from mammalian toxicity tests in the context of NAM development	Q4 2022
A scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs	Q3 2022
Reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions	Q4 2022
Case studies for evaluating application to risk assessment and demonstrating protection of human health and the environment	Approximately one every other year starting in 2022
Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps	
EPA research planning process that involves teams of research scientists and regulators and provides research products that communicate the methods and results of studies and facilitate application of the NAMs.	Every 4 years
Encourage development of NAMs through mechanisms such as the STAR program and facilitate partnerships with organizations focused on establishing scientific confidence in alternative methods	Ongoing
Engage and Communicate with Stakeholders	
EPA website to house information about NAM efforts and progress being upon release of the Work Plan	Q3 2020
Public webinars and, where appropriate, peer-review on deliverables from this work plan	Timing dependent on deliverable dates
Training, opportunities for scientific exchange, and progress updates through Agency sponsored events as well as partner with organizations already offering courses	Ongoing