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New Approach Methods Work Plan

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

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EPA New Approach Methods Work Plan

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Executive Summary

Reducing the use of vertebrate animals for toxicity testing is a priority for the U.S. Environmental Protection Agency (EPA) and, as such, the Agency is working on the development and application of New Approach Methodologies (NAMs). NAMs are defined as 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 updated roadmap and identifies tangible steps to pursuing and achieving a reduction in the use of vertebrate animals for toxicity testing and related research 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 needs; and continue to engage and communicate with stakeholders to incorporate their knowledge and address concerns as EPA moves away from vertebrate animal testing. In this work plan, EPA discusses the near- and long-term strategies it will deploy through 2024 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.

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
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

Evaluating and applying emerging technologies for assessing risks to human health and the environment is vital to keeping the Agency at the forefront of science and for continuing to achieve its mission. New Approach Methods (NAMs)[1] are included among these emerging technologies and have the potential to increase the rigor and sophistication of Agency assessments while reducing the reliance on vertebrate animals to test chemicals. Reducing the use of vertebrate animals in evaluating the risks of chemicals has been identified as a priority for EPA as well as for other national and international organizations and regulatory agencies. The EPA has multiple statutory requirements and policy initiatives that prioritize reduction of animal testing (e.g., the 2018 TSCA Alternatives Strategic Plan,[2] the Endocrine Disruptor Screening Program for the 21st Century,[3] the Office of Pesticides Program guidance on waiving acute toxicity studies[4]) and for decades the Agency has invested in developing a strong, integrated research program focused on the development and application of NAMs.

The U.S. EPA's Office of Research and Development (ORD) and the Office of Chemical Safety and Pollution Prevention (OCSPP) were tasked with developing a work plan for reducing the use of vertebrate animals in the Agency's regulatory, compliance, enforcement and research activities through the use of NAMs while remaining fully protective of human health and the environment. The original EPA NAMs Work Plan was released in June 2020 and laid out the Agency's objectives and strategies. The objectives are: (1) evaluate regulatory flexibility for accommodating the use of NAMs; (2) develop baselines and metrics for assessing progress; (3) establish scientific confidence in NAMs and demonstrate application to regulatory decisions; (4) develop NAMs that fill critical information gaps; and (5) engage and communicate with stakeholders to incorporate their knowledge and address concerns (Figure 1). The Agency committed to regularly reviewing the work plan and acknowledged that the work plan would evolve as EPA's knowledge and experience grows, and as outside experts offer their perspectives and contributions. In the updated work plan, the main objectives and strategies were left unmodified. The primary changes in the updated work plan include:

- Expansion of the species covered in the work plan to include all vertebrate animals to be consistent with TSCA.

[1] 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.

[2] https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf

[3] https://www.epa.gov/sites/production/files/2015-07/documents/edsp21_work_plan_summary_overview_final.pdf

[4] https://www.epa.gov/pesticide-registration/bridging-or-waiving-data-requirements

- Modified deliverables that provide revised timelines through 2024 that reflect the expansion of covered species and incorporate feedback received over the preceding years.
- Updated scope of the U.S. National Academies of Sciences, Engineering, and Medicine study to include a review of validation and scientific confidence frameworks for NAMs in addition to evaluating the variability and relevance of existing mammalian toxicity tests.
- Two new case studies for building confidence and demonstrating application of NAMs.
- A pilot study to develop NAMs training courses and materials for a broad range of stakeholders.

Figure 1. Five work plan objectives for reducing the use of vertebrate animals in the EPA's regulatory, compliance, enforcement and research activities while remaining fully protective of human health and the environment.

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; to manage emergency response, spills and waste; and regulate pesticides and chemicals throughout the United States. In particular

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).

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

Major Environmental Statute	Statutory Requirements for Vertebrate Animal Testing	Regulatory Requirements for Vertebrate Animal 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 vertebrate 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]

[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).

[6] Visit EPA's Endocrine Disruptor Screening Program webpage. Also, see the EDSP Workplan for using NAMs.

Table 1 (cont). Initial Survey Results of Vertebrate Animal Testing Requirements in Major Environmental Statutes

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

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 vertebrate animal 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 vertebrate animal testing and the potential implementation and use of appropriate NAMs for regulatory purposes. The EPA report will be delivered in 2022.*

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[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.

II. Develop Baselines and Metrics for Assessing Progress

EPA has started developing baselines and metrics to track the Agency's progress towards its goal of reducing its use of vertebrate animals. In 2019, the United States Government Accountability Office (GAO) completed its review on issues related to alternatives to laboratory animal research at multiple federal agencies.[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 laboratory animal use. In response to the report, an Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) workgroup found that no one set of metrics is appropriate and that metrics should be relevant, practical, and tailored to the specific needs of the organization.[11]

Existing efforts to establish vertebrate animal use baselines across the Agency

EPA requires substantial toxicology testing to support pesticide registration. Toxicological studies in vertebrate 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 vertebrate animals used varies widely depending on the pesticide type and use pattern; but, between 100 and 9,000 animals are typically used for human health and ecological toxicology testing for a single pesticide.

EPA has flexibility in implementing 40 CFR Part 158 data requirements, with FIFRA allowing for waivers to be granted and alternative methods to be accepted on a case-by-case basis. By using waivers, EPA can avoid the generation of data that does not influence the scientific certainty of a regulatory decision. 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 vertebrate animal use reduction for EPA. Similarly, OPP has started tracking the use of waivers for acute toxicity studies.

[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.
[11] ICCVAM. Measuring U.S. Federal Agency Progress Toward Implementation of Alternative Methods in Toxicity Testing (Feb 2021).

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 vertebrate animals and *in vitro* assays. Following a reorganization of OCSPP, the EDSP is now managed by OPP. The EDSP compiles the number of substances and associated tests ordered under the EDSP, which allows the number of vertebrate animals used to be tracked.

Under TSCA, the 2016 amendments added explicit requirements 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 laboratory 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 database of all TSCA-related studies 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 vertebrate animal tests that were required for those tests, by year.

ORD performs research using vertebrate animals 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 vertebrate animal tests. For example, ORD is evaluating the use of integrated high-throughput *in vitro* assays and computational modeling to identify endocrine-active compounds. Overall, the shift towards developing these new methods is expected to reduce the use of vertebrate animals 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 vertebrate animals for toxicity testing and research. Thus, baselines and metrics for the use of vertebrate animals will be initially developed for programs within OCSPP and ORD. As other EPA offices determine their contribution to the use of vertebrate animals, 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 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 through its website and the ICCVAM biannual reports. In the past, EPA has also reported metrics for the reduction in the use of vertebrate animals via peer-reviewed publications.[12]

Initial Baseline Calculations and Metrics

Within OCSPP, EPA will initially use the number of animals required for testing under the 40 CFR Part 158 as a baseline to measure and track use for pesticide actions. EPA will also establish a specific baseline for vertebrate animal use under TSCA once the ATAEPI analysis is completed. For the EDSP, the baseline is 1,800 animals based on the number required to complete the Tier I battery of assays. Within ORD, EPA will use the average number of mammals used for research purposes between 2016 and 2018 (8,600 per year) as an initial baseline to provide both a stable and relatively recent estimate of use. More recent estimates have been impacted by the reductions in studies during the pandemic. Over time, ORD will transition to extend the baseline to include all vertebrate animal use. OCSPP and ORD will work with other EPA offices to establish baselines and calculation methods. As additional baselines and metrics are established, EPA will distribute these estimates through the established communication mechanisms.

Deliverable: *Progress and summary metrics on reducing vertebrate animal testing requests and use. The metrics will be reported annually through its website starting in the fourth quarter (Q4) of 2022.*

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, vertebrate animal tests, directly and indirectly, provide the information by which many of these decisions are made. The scientific confidence associated with the traditional toxicity tests comes from the decades of experience in their development and application. In the transition from the reliance on the vertebrate animal tests to the application of the NAMs across the range of decisions, EPA needs to continually build more scientific confidence in

[12] 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

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 (1) characterizes the scientific quality and relevance of existing vertebrate animal tests; (2) develops recommended reporting requirements; and (3) 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 traditional toxicity tests

Section 4(h)(2) of TSCA notes the need for information of "equivalent or better" scientific quality and relevance to vertebrate animal test-based results. This requirement implies that the scientific quality and relevance of the existing toxicity tests should be considered to understand the strengths and limitations of the existing models, as well as NAMs under development. The amount and type of analyses needed will depend on the NAM being developed, the adverse outcome of interest, and information available. For example, the inherent variability in traditional toxicity tests may limit the predictivity that could be achieved in any comparison. Furthermore, differences between laboratory animals and humans can impact the ability of these models to predict human health effects. As such, it may not always be appropriate to compare NAMs to traditional toxicity tests. 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 toxicity testing model. Although existing studies have evaluated important components associated with characterizing scientific quality and relevance, such as variability and human concordance, no authoritative study has been developed that can inform expectations for NAMs. The expectations will be incorporated into the scientific confidence framework in the subsequent deliverable.

Deliverable: *U.S. National Academies of Sciences, Engineering, and Medicine study that evaluates the variability and relevance of existing mammalian toxicity tests and reviews frameworks for validation and establishing scientific confidence in testing methods. The study is funded by the EPA, but the timing is determined by the National Academies and is currently scheduled for 2023.*

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).[13] 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 and should be flexible and adaptable. To increase flexibility to 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.[14,15,16,17]

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.[18] 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. The generic framework may be informed by the U.S. National Academies of Sciences, Engineering, and Medicine review of the frameworks for validation and establishing scientific confidence in testing methods and recent ICCVAM activities to revise its report on validation and regulatory acceptance of toxicological methods.

Deliverable: *Scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs. The framework will be released as an EPA report in the fourth quarter (Q4) of 2024.*

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

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[13] OECD. Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (GD34) (Aug. 18, 2005).
[14] NICEATM. A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States (Jan. 2018).
[15] 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.
[16] 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.
[17] 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
[18] TSCA Strategic Plan at p. 19.

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[19] as well as a reporting template for *in vitro, ex vivo, or in silico* tests describing molecular and cellular observations that can be relevant to the hazard assessment.[20] To accommodate mutual acceptance of data, the EPA will build on these established templates while providing additional templates that capture the range of specific NAMs used for Agency decisions. Further, elements of the scientific confidence framework described above will be important to capture in robust reporting templates for NAMs. As such, the deliverable for the reporting templates will coincide with that for the generic framework.

Deliverable: *Reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions. An initial set of reporting templates will be delivered in the fourth quarter (Q4) of 2024.*

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 as needed to address specific data gaps and regulatory needs. Case studies will be critical for building 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 points of departure.
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.

[19] OECD. Guidance Document on Good In Vitro Method Practice (Dec 2018).
[20] OECD. OECD Harmonised Template 201: Intermediate effects (Dec 2018).

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

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
Utilization of a NAM Battery for Evaluation of Developmental Neurotoxicity (DNT) Potential	Incorporation of a battery of *in vitro* assays that assess processes critical to the development of the nervous system into the weight of evidence evaluation of DNT potential for a chemical
Evaluating *In Vitro* and *In Silico* Toxicokinetic Approach	Evaluating the uncertainties and predictivity of i*n vitro* and *in silico* toxicokinetic data and computational models

Deliverable: *Case studies for evaluating application of NAMs to risk assessment and demonstrating protection of human health and the environment. Case studies will be developed and communicated through the peer-reviewed scientific literature.*

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)[21] for higher tier endpoints of concern (e.g., development and reproductive toxicity). Although all these challenges do not apply to every situation and may not need to be addressed in order to apply NAMs to particular regulatory decisions, continued refinement and development of NAMs will be required for the Agency to continue making progress on reducing vertebrate animal testing.

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

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

developed that facilitates joint planning of NAM development by EPA research scientists and regulators as well as encourages development and dissemination of NAMs by external parties. The strategy ensures the NAMs being developed will meet the needs of end users for a specific context of use and provide an acceptable level of uncertainty, while also opening opportunities for innovation by scientists from academia, industry, and public interest organizations.

NAM development through EPA research planning and implementation

As part of the ORD research planning process, NAM refinement and development will 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.[22] 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 is outlined at a high level in the Strategic Research Action Plans.[23] 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.

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

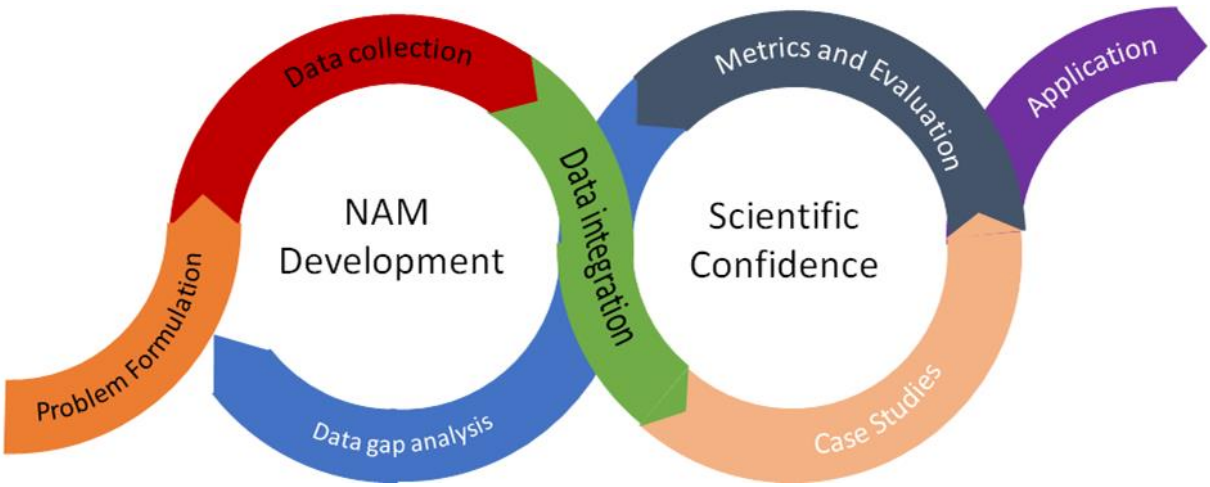

Figure 2. Problem-focused research planning and implementation process at EPA.

Deliverable: *EPA Strategic Research Action Plans outlining research products to develop and apply NAMs. The next EPA Strategic Research Action Plans will be delivered in the first quarter (Q1) of 2023.*

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 an overall reduction in the use of vertebrate animals in testing. 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 vertebrate 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, the scientific and technical 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. 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 during the EPA NAMs conferences. 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 continue to release NAMs informational materials and updates through the EPA NAMs website (https://www.epa.gov/nam). This online resource provides 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.

Deliverable: *EPA website to house information about NAM efforts and progress being upon release of the work plan*

Solicit comment and feedback associated with deliverables

Public feedback and expert scientific review are essential to this work plan and associated deliverables. EPA will request stakeholder and public feedback on deliverables associated with the work plan through public webinars and other mechanisms. In addition, EPA will 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.

Deliverable: *Public webinars and, peer-review where appropriate, 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 vital to help reduce the use of vertebrate 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 is performing a pilot study to develop NAMs training courses and materials. Based on the results of the pilot study, EPA will develop and organize regular training opportunities on NAMs across a broad range of stakeholder communities as well as continue efforts to inform stakeholders through sessions at regularly scheduled conferences and EPA hosted workshops, such as EPA's NAMs conference, which will 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 efforts already have existing 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.

Deliverable: *Complete NAMs pilot training program in the fourth quarter (Q4) of 2023 and provide regular scientific exchanges and progress updates through Agency-sponsored and partner organized events.*

Summary and Next Steps

EPA will continue its leadership role to develop the science and policies necessary to reduce its reliance on vertebrate animal testing as expeditiously as possible while remaining true to the Agency's mission of protecting public health and the environment. This updated work plan is an important milestone in this endeavor and the objectives, strategies, and

deliverables provide a roadmap towards accomplishing the goal. 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 work plan is confined to the Agency's authority and associated activities, success 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 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 continues to implement 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 vertebrate animal testing and the implementation and use of appropriate NAMs for regulatory purposes.	2022
Develop Baselines and Metrics for Assessing Progress	
Progress and summary metrics on reducing vertebrate animal testing requests and use.	Annually starting in Q4 2022
Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions	
U.S. National Academies of Sciences, Engineering, and Medicine study that evaluates the variability and relevance of existing mammalian toxicity tests and reviews frameworks for validation and establishing scientific confidence in testing methods. The study is funded by the EPA, but the timing is determined by the National Academies.	2023
A scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs.	Q4 2024
An initial set of reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions.	Q4 2024
Case studies for evaluating application to risk assessment and demonstrating protection of human health and the environment.	Ongoing
Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps	
EPA Strategic Research Action Plans outlining research products to develop and apply NAMs.	Q1 2023
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.	Complete
Public webinars and, where appropriate, peer-review on deliverables from this work plan.	Ongoing
Complete NAMs pilot training program in the fourth quarter (Q4) of 2023 and provide regular scientific exchanges and progress updates through Agency sponsored and partner organized events.	Q4 2023 and Ongoing