COMMENTS

# NEW APPROACH METHODOLOGIES IN U.S. CHEMICAL REGULATION

by Adam Bettmann

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For most of the 20th century, predicting chemical safety relied upon testing in animals. Today, a new generation of tools is redefining how we assess the risks that chemicals pose, offering a future of chemical risk evaluation that is more efficient, more human-relevant, and doesn't depend on animals.

New approach methodologies (NAMs) are modern testing strategies in the field of toxicology that offer a way to meet regulatory data requirements more efficiently and with more direct relevance to human health, while reducing or replacing the use of animals. NAMs is an umbrella term that covers multiple types of testing strategies to assess the potential risk a chemical may pose to human health or the environment. Examples include *in vitro* (or cell-based) assays, *in silico* (or computational) modeling, and read-across or grouping methods, which use known hazards from previously tested and structurally similar chemistries to infer the potential hazards of the chemical in question.

The field of NAMs is ever-expanding, and they are being applied for regulatory purposes across many different classes and categories of chemicals. This Comment will focus on the application of NAMs for the regulatory testing requirements of industrial chemicals and agrochemicals. Note that in the United States, the U.S. Environmental Protection Agency (EPA) oversees the safety of these chemicals under two key statutes—the Toxic Substances Control Act[1] (TSCA; industrial chemicals) and the Federal Insecticide, Fungicide, and Rodenticide Act[2] (FIFRA; agrochemicals)—which require companies to demonstrate that their products do not pose an unreasonable risk to human health and the environment before they can be sold.

The Comment first examines the historical reliance on animal testing to assess chemical safety. It then explores the global push to develop non-animal methods, now coined NAMs, in light of scientific advancements. Not only have these advancements made it possible to address the growing ethical implications of animal testing, they allow for the design of test methods that are more biologically relevant to humans; provide insights into biochemical mechanisms; allow for the objective, transparent, and reproducible measurement of toxicological outcomes; and can efficiently generate results for regulatory decisionmaking. Highlights include breakthroughs in both *in vitro* assays, with the improvement of cell culture science, and computational toxicology models, with the improvement of computer processing.

These advancements lead us to the present, where EPA continues to incorporate NAMs to meet the regulatory needs of both TSCA and FIFRA. Examples of collaborative case studies then illustrate how joint efforts can bring NAMs from conception to regulatory acceptance. Finally, the Comment looks at the remaining gaps and future needs to help ensure that NAMs can continue to fully deliver on their potential to replace testing in animals while providing equivalent or better chemical safety evaluation.

## I. Historical Reliance on Animal Testing

The 20th century was one of chemical innovations, and for the majority of the 1900s, testing in animals was used to attempt to predict the hazards to human health and the environment that these newly developed chemistries posed. In the United States, as the agriculture industry transformed from small-scale, labor-intensive farms into sprawling fields where machinery could do most of the planting, watering, and harvesting, so with it came the need to protect these high-yield crops from unwanted insects, fungi, weeds, and so forth. This led to an explosion of innovation and product application in the agrochemical sector.

By the mid-1900s, after growing reports of pesticides impacting human health and the environment, regulations were enacted. The first attempt at regulation in the agrochemical space came in the form of the 1947 FIFRA statute that empowered the U.S. Department of Agriculture (USDA) with oversight of pesticide *efficacy*. However, public alarm regarding pesticide *safety* reached a tipping point in 1962 with the publication of Rachel Carson's *Silent Spring*,[3] which highlighted the persistence and ecological harm of pesticides, most notably DDT. Thus, in 1972, the U.S. Congress overhauled FIFRA, transferring authority of FIFRA oversight to the newly formed EPA, and included a greater focus on chemical safety by mandating that toxicity testing be performed on both new and

1. 15 U.S.C. §§2601-2692, ELR Stat. TSCA §§2-412.
2. 7 U.S.C. §§136-136y, ELR Stat. FIFRA §§2-35.
3. Rachel Carson, Silent Spring (Houghton Mifflin 1962).

existing agrochemicals before they could be sold or remain on the market.

Another area of explosive innovation in the 20th century was in the industrial chemical space. There was an increase in efforts to bring revolutionary new chemistries to market that promised to make life easier. By the 1960s and 1970s, concerns about potential adverse health effects began to mount. These included the discoveries that asbestos use in construction was leading to increased lung disease and cancers in those who worked closely with it, that factory workers using vinyl chloride in polyvinyl chloride manufacturing were developing rare forms of liver cancer, and that a key industrial solvent used in a variety of applications, benzene, seemed to be causing blood disorders and leukemia in those regularly exposed.

Environmental concerns were also becoming more prevalent and publicized as areas of chemical disposal were shown to be causing environmental contamination. For example, the discovery of the persistence of polychlorinated biphenyls and their accumulation in fish and wildlife along the Hudson River raised questions as to how far these chemicals may travel and how they may be affecting human health. Similar to the agrochemical space, public pressure and scrutiny led Congress to act, resulting in the passage of TSCA in 1976. As with FIFRA, EPA was given the authority to oversee TSCA, which, while not as prescriptive as FIFRA, still established a regulatory framework to help ensure that industrial chemicals either entering or already present in the United States did not pose "unreasonable risks" to human health or the environment. This required manufacturers to report information such as chemical identity, production volume, intended uses, and any available health and safety data. EPA was then tasked with reviewing this information and ultimately granting approval for the chemical in question to be produced or imported.

For most of the 20th century, under both statutes, regulators would either require or request tests in animals. These types of tests—such as acute lethality studies, 90-day studies, two-year cancer bioassays, and reproductive and developmental studies—have conventionally been used to predict potential chemical toxicity, and as many of their names suggest, vary widely in length and complexity. An acute toxicity test might last only a few weeks, while subchronic feeding studies typically take 90 days of daily dosing plus a post-study observation period. Chronic cancer bioassays in rodents are exceptionally time- and labor-intensive, extending up to two years of continuous exposure, followed by necropsy and histopathology analysis. Reproductive and developmental studies have the added complexity of requiring multiple generations of breeding pairs to complete the testing protocols.

Depending on how many of these tests were required for chemical risk assessment, it could take years to generate and deliver all the required data for a chemical's hazard profile. The financial burden of tests on animals is also significant. Shorter-term tests often cost in the tens of thousands of dollars, and it is not uncommon for the two-year cancer and chronic-toxicity bioassays to run into the $2-million to $5-million range (per chemical). The extensive time, cost, animal use, and interest in increased reliability and human relevance has led to the development of more cost-effective solutions that could more efficiently and reliably predict the potential toxicity of new or existing chemicals. At the same time, there was another public movement of animal welfare concerns gaining traction.

## II. Public Awareness and the Rise of Animal Welfare Concerns

In 1975, Peter Singer published the book *Animal Liberation*,[4] which is widely considered to be a cornerstone of the modern animal rights movement. Not long after, in 1980, Ingrid Newkirk and Alex Pacheco would found People for the Ethical Treatment of Animals (PETA). PETA quickly gained global attention in 1981 by bringing to light the unethical treatment of macaques used for research purposes in Silver Spring, Maryland, prompting the first-ever police raid on an animal laboratory facility. This eventually led to a 1985 amendment to the federal Animal Welfare Act[5] (AWA). Ever since, there has also been a global push from the general public, scientists, and regulators to reduce and replace the use of animals in testing.

This is with good reason. The number of animals used in testing is staggering. The field of regulatory toxicology alone has been estimated to consume hundreds of millions of vertebrate animals globally per year. Within EPA's TSCA and FIFRA programs alone, tens to hundreds of thousands of rodents, rabbits, and dogs were used annually to satisfy chemical testing requirements. Over time, concerns about animal welfare, coupled with growing knowledge of the lack of reproducibility of animal data and gaps in how well these tests predicted human outcomes, would spark calls for more efficient, humane, and human-relevant alternatives. During the past four decades, the field of NAMs has expanded significantly to meet these needs, and an understanding of this progress can be used to identify where efforts should be focused for further advancement.

## III. NAMs: An Overview

While each NAM could be a multi-day course in itself, briefly touching on what types of NAMs are currently being used helps illustrate the technological and scientific advancements that have been, and continue to be, made in the field. *In vitro* assays are a key component of NAMs designed to assess specific toxicological endpoints, often by using human cells that are grown in either a monolayer or a three-dimensional matrix. These assays mimic how chemicals might affect cellular function and viability in humans, typically using quantifiable measurements of specific biomarkers to predict hazardous outcomes. Microphysiological systems, often called "organs-on-chips," take these *in*

4. Peter Singer. Animal Liberation: A New Ethics for Our Treatment of Animals (HarperCollins 1975).
5. 7 U.S.C. §§2131-2160.

*vitro* assays a step further by integrating tiny channels and cell layers to mimic organ functions to better understand how exposure to a chemical may affect single organs or multiple organ systems, as would be expected in a real-world human exposure. These cell-based tools can reliably reveal signs of toxicity in a fraction of the time of traditional animal testing.

Alongside cell-based assays, computational or *in silico* models predict chemical behavior using the chemical's molecular structure and its physicochemical properties. Quantitative Structure Activity Relationships can take information on a new chemical's structure and properties and use mathematical algorithms to link these features with known adverse toxicological effects of chemicals that have been previously entered into the system. Similarly, read-across approaches compare a new chemical to its structural "neighbors," inferring toxicological effects from data on similar, already-tested substances. Both approaches are useful in the assessment of new chemicals, including helping to flag high-risk candidates early and prioritize them for further testing if needed, thereby streamlining decisionmaking shortly after the chemical is developed.

Leveraging *in vitro* and *in silico* technologies, including high-throughput screening platforms (e.g., ToxCast and Tox21), makes it possible to evaluate many chemicals rapidly and reproducibly. EPA's Toxicity Forecaster[6] (ToxCast) program, launched in 2007 by the National Center for Computational Toxicology, now houses data from more than 1,000 *in vitro* assays and covers nearly 10,000 unique chemicals. Tox21[7] was then developed in 2008 by a federal partnership between EPA, the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS), and the Food and Drug Administration, and uses quantitative high-throughput screening (qHTS) to generate concentration-response data across a 10,000-compound library using hundreds of assays.

Together, these efforts produce rapid profiles of potential toxicological hazards for a chemical of interest in a single run. In addition, when integrated with "omics" assays that are designed to identify whole-organism shifts in gene activity, protein levels, or metabolic byproducts (e.g., transcriptomics, proteomics, or metabolomics), researchers are able to gain a robust view of how a chemical may impact biological processes.

With many types of NAMs now available, multiple NAMs are often used within Integrated Approaches to Testing and Assessment (IATAs). These frameworks bring diverse weight-of-evidence data analysis together and are designed to balance results from *in vitro* testing, *in silico* modeling, and exposure data to arrive at robust safety conclusions. Adverse Outcome Pathways often play important roles within an IATA, as they map the chain of events from a chemical binding to a molecular target to disease-relevant outcomes, thus providing a transparent and reproducible flow of biological events that explain, biochemically and mechanistically, how toxicity occurs. These integrated strategies guide regulators on when data suffice for risk assessment and when further investigation is needed.

## IV. Global Policy Shifts in Chemical Regulation

The global push to implement more reliable and human-relevant testing approaches that do not use animals continues to fuel the regulatory adoption of many types of NAMs, and has inspired international commitments to develop and validate these non-animal methods. In the United States, the 2016 Frank R. Lautenberg Chemical Safety for the 21st Century Act[8] amended the original TSCA, and explicitly directs EPA to "reduce and replace, to the extent practicable and scientifically justified, the use of vertebrate animals in the testing of chemical substances or mixtures; and promote the development and timely incorporation of alternative test methods or strategies that do not require new vertebrate animal testing."[9] It also requires the development of a "Strategic Plan to Promote the Development and Implementation of Alternative Test Methods within the TSCA program."[10]

EPA published this Strategic Plan in 2018,[11] followed by a broader "New Approach Methods Work Plan" that was released in 2020 and updated in 2021.[12] The Work Plan lays out specific near-term, mid-term, and long-term actions the Agency will take to integrate *in vitro, in silico*, and other NAMs into its decisionmaking process under TSCA, FIFRA, and other statutes. It further set firm milestones for expanding the use of reliable and relevant NAMs, enhancing validation pathways, and building the data management infrastructure needed to support this plan. Both the Lautenberg Act and the NAMs Work Plan underscore a shift toward these methods at EPA, and they continue to play a role in advancing the use of reliable and relevant NAMs.

Beyond statutes and plans, another critical piece to the development and regulatory uptake of NAMs is collaboration. EPA, other governmental organizations, industrial partners and consortia, contract research organizations, and nonprofit organizations, among others, have shown a willingness and ability to work together toward a common goal of advancing the field of NAMs. These types of col-

6. U.S. EPA, *Toxicity Forecasting (ToxCast)*, https://www.epa.gov/comptox-tools/toxicity-forecasting-toxcast (last updated Sept. 17, 2025).
7. National Institute of Environmental Health Sciences, *Tox21*, https://www.niehs.nih.gov/research/programs/tox21 (last updated July 7, 2025).
8. Pub. L. No. 114-182, 130 Stat. 448 (2016).
9. U.S. EPA, *Alternative Test Methods and Strategies to Reduce Vertebrate Animal Testing*, https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce (last updated Nov. 10, 2025).
10. U.S. EPA, *Strategic Plan to Reduce the Use of Vertebrate Animals in Chemical Testing*, https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/strategic-plan-reduce-use-vertebrate-animals-chemical (last updated Jan. 30, 2025).
11. EPA Doc. No. EPA-740-R1-8004 (June 22, 2018), https://www.epa.gov/sites/default/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf.
12. U.S. EPA, *New Approach Methods Work Plan*, https://www.epa.gov/chemical-research/new-approach-methods-work-plan (last updated Oct. 14, 2025).

laborations have led to many validated NAMs in the form of Organisation for Economic Co-operation and Development (OECD) test guidelines, and collaborative efforts continue to aid the development of new test guidelines, along with the expansion of existing test guidelines in broadening applicability domains. And when an OECD test guideline doesn't yet exist for a proposed method, there is value in collaborating to develop and use reliable and relevant non-guideline NAMs that are fit for their intended purpose.

An example of this comes from the use of a fit-for-purpose assessment of a pesticide (chlorothalonil) for re-registration under FIFRA. A weight-of-evidence NAM approach for evaluating the inhalation toxicity of this pesticide was developed by the manufacturer in discussions with EPA. The approach and generated data were then presented to the FIFRA Scientific Advisory Panel (SAP) in 2018, after which EPA's Office of Pesticide Programs (OPP) continued to work with the manufacturer to address recommendations from the SAP. In 2021, OPP published a draft risk assessment for chlorothalonil[13] with the first-ever regulatory application of this NAM, and in 2022, the OECD published a case study[14] on further application of this approach. This example illustrates the willingness of EPA to collaborate with the regulated community to advance and apply the best science and to accept the use of non-guideline studies that have demonstrated reliability, relevance, and fitness for purpose.

## V. Establishing Scientific Confidence in NAMs

The key components of developing a successful NAM have been summarized in recent years. Publications of note include *A Framework for Establishing Scientific Confidence in New Approach Methodologies*,[15] by collaborating authors from EPA, PETA Science Consortium International, the European Centre for the Validation of Alternative Methods, the OECD, the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and the U.S. Consumer Product Safety Commission. And in 2024, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) published a report titled *Validation, Qualification and Regulatory Acceptance of New Approach Methodologies,*[16] which included similar components and findings.

Both publications highlight five elements for establishing scientific confidence in a NAM: fitness for purpose (or context of use); biological relevance; technical characterization; data integrity and transparency; and independent review. Using these key elements provides transparent and standardized guidance for NAM developers, allowing for the advancement of science to best protect human health and the environment. These publications build on various other documents and the long-standing principles of validation, including those described in OECD Guidance Document 34 on the validation and international acceptance of new or updated test methods for hazard assessment (which is currently being updated).[17]

## VI. The Path Forward

In the years ahead, the successful integration of NAMs into chemical safety assessment will depend on strategic investments in research, infrastructure, education, and policy reform. A top research priority has been expanding our knowledge of complex toxicological endpoints. This includes developmental neurotoxicity and endocrine disruption, where traditional tests in animals have been demonstrated to be unreliable predictors of human outcomes. New approaches in these areas provide an opportunity to improve our ability to identify and reliably predict these outcomes using human-relevant methods.

Public databases must also be expanded to house raw data in standardized, machine-readable formats. Databases that span federal agencies, international bodies, and industry consortia would reduce duplication, promote interoperability, and help to accelerate validation of new methods. Initiatives like EPA's CompTox Chemicals Dashboard,[18] the European Chemicals Agency's ECHA CHEM database,[19] and OECD's eChemPortal[20] are valuable resources that would benefit from broader coordination. Additionally, this year, the NICEATM released its Collection of Alternative Methods for Regulatory Application (CAMERA).[21] CAMERA is an interactive public database that serves as a central resource of information on NAMs to enhance access to validation study reports, data, protocols, and information related to regulatory acceptance, and will continue to be expanded to include additional endpoints and methods.

With artificial intelligence (AI) expanding across many facets of our lives, data transparency will be critical for enabling emerging machine-learning applications in the field of regulatory toxicology. These models rely on large,

13. U.S. EPA, Chlorothalonil: Revised Human Health Draft Risk Assessment for Registration Review (May 21, 2021), https://www.regulations.gov/document/EPA-HQ-OPP-2011-0840-0080.
14. OECD, Case Study on the Use of an Integrated Approach for Testing and Assessment (IATA) for New Approach Methodology (NAM) for Refining Inhalation Risk Assessment From Point of Contact Toxicity of the Pesticide, Chlorothalonil (Sept. 1, 2022), https://one.oecd.org/document/ENV/CBC/MONO(2022)31/en/pdf.
15. Anna J. van der Zalm et al., *A Framework for Establishing Scientific Confidence in New Approach Methodologies,* 96 Archives of Toxicology 2865-79 (2022), https://doi.org/10.1007/s00204-022-03365-4.
16. ICCVAM, Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies (March 2024), https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf.
17. OECD, Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (Aug. 18, 2005), https://ntp.niehs.nih.gov/sites/default/files/iccvam/suppdocs/feddocs/oecd/oecd-gd34.pdf.
18. U.S. EPA, *CompTox Chemicals Dashboard*, https://comptox.epa.gov/dashboard (last updated Oct. 29, 2024).
19. European Chemicals Agency (ECHA). *ECHA CHEM,* https://chem.echa.europa.eu/ (last visited Dec. 2, 2015).
20. OECD, *eChemPortal: The Global Portal to Information on Chemical Substances,* https://www.echemportal.org (last visited Dec. 2, 2015).
21. NTP, *Alternative Methods Accepted by U.S. Agencies*, https://ntp.niehs.nih.gov/whatwestudy/niceatm/accept-methods (last updated Aug. 26, 2025).

well-defined datasets to detect patterns, predict toxicity, and refine chemical risk assessments. AI-driven models could enhance existing *in silico* tools if the underlying data are clean, transparent, and interoperable. Investing in open data infrastructure today lays the groundwork for future regulatory systems that may be faster, more predictive, and capable of continuous learning and refinement as new chemicals and endpoints emerge.

Policy will continue to be essential in institutionalizing NAMs. Clear guidance from regulatory agencies, including EPA, that details the desire for reliable, relevant, and fit-for-purpose NAMs, as well as information on how EPA uses NAM data to make decisions, will help remove regulatory barriers. More on this topic, specifically pertaining to pesticides, can be found in the paper *Enhancing Pesticide Risk Assessment Processes at the US Environmental Protection Agency*.[22] Additionally, federal grants, continued collaboration between the public and private sectors, and streamlined processes could incentivize innovation and reduce the time and cost of validating new methods.

Finally, education is essential. The field of NAMs is complex and continuously advancing. Therefore, regulators, risk assessors, and industry scientists need targeted training programs to keep pace with the development of new methods and how to interpret and apply NAM data effectively. Academic institutions can assist in this effort by developing cross-disciplinary curricula that blend toxicology, computational modeling, bioinformatics, and regulatory science to prepare the next generation of professionals to navigate a rapidly evolving landscape. Professionals must stay current through publications, conferences, and webinars. One such option is a free webinar series co-organized by EPA, PETA Science Consortium International, the Institute for In Vitro Sciences, and the California Department of Pesticide Regulation, known as the EPIC Webinar Series.[23]

Together, these actions will embed NAMs into the core of chemical safety decisionmaking, delivering faster, more ethical, and scientifically robust assessments that protect human health and the environment.

22. Gina M. Hilton et al., *Enhancing Pesticide Risk Assessment Processes at the US Environmental Protection Agency*, 164 Reg. Toxicology & Pharmacology 105959 (Jan. 2026), https://doi.org/10.1016/j.yrtph.2025.105959.

23. PETA Science Consortium International, *EPIC Webinar Series on the Use of NAMs,* https://www.thepsci.eu/epicwebinars/ (last visited Dec. 2, 2025).