March 15, 2023

Honorable Michael Regan
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue NW
Washington DC 20460

Re: The Role of NAMs and Rodent Studies in Protecting Against Unsafe Chemicals

Dear Administrator Regan:

We are writing on behalf of the 38 environmental, health, and justice organizations to convey our deep concern regarding EPA's efforts to prematurely reduce or eliminate whole rodent testing of chemicals. We are concerned that on its current trajectory, this trend will lead to weakened protection of human health and the environment under the Toxic Substances Control Act (TSCA) and other laws. These efforts are also undermining the Biden Administration's commitment to advancing environmental justice and protecting susceptible populations.

In the last several years, EPA has been heavily focused on the development of New Approach Methodologies (NAMs) for assessing the risks of chemicals. These new and unproven NAMs, which are the focus of this letter, include many *in vitro* biochemical, molecular, and cell-based assays and computational-based models.[1] In recent years, EPA has committed substantial resources to the development and promotion of such NAMs, with the goal of near-term deployment and a corresponding decrease in the number of rodent studies it conducts itself or requires industry to perform.

While TSCA encourages EPA to reduce testing on vertebrate animals, the law requires EPA to assure that non-animal studies will produce information of equal or greater relevance and quality for the assessment and management of chemical risks. As described below, NAMs are not currently capable of replacing rodent studies for many key health effects. While limiting the use of rodents in laboratory testing continues to be an aspirational goal of many toxicologists, the science is not yet developed to the point where we can rely on NAMs as the primary basis for risk assessment and management under our chemical laws and regulations. Reliance on NAMs to the exclusion of rodent studies will therefore prevent us from developing critical data on the impacts of chemical exposures on human health, further exacerbating existing health inequities and adding to the disproportionate burdens that toxic chemicals place on communities of color and disadvantaged populations. Environmental justice communities and farmworkers already suffer disproportionate harms from the manufacturing, use, and disposal of chemicals that were inadequately reviewed or approved despite their known risks. EPA must not allow the development or use of NAMs to perpetuate or worsen these unequal and harmful impacts.

We are not anti-NAM or pro-NAM. We are, however, opposed to any uses of NAMs that could understate chemical risks and reduce, prevent, or delay needed public health protections. To ensure that NAMs will not be misused to undermine health protections, we ask EPA to take the following actions:

- Reaffirm the critical value of rodent tests conducted in accordance with animal welfare protections to inform chemical evaluations, and health protective policies and practices;
- Do not use NAMs to exempt chemicals from further review and study.
- Commit to an open process that includes fenceline communities, farmworkers, and other impacted stakeholders in the development of policies surrounding the regulatory use of NAMs;

In addition, our groups have long advocated that EPA take prudent, scientifically sound steps to reduce rodent testing, including:

- Regulate chemical classes;
- Use established methods to fill data gaps, including uncertainty factors, read-across and category-based approaches;
- Reduce known or suspected toxicants by promoting the elimination of unnecessary chemicals and supporting the development and use of safer substitutes.
- Make better use of existing data including from epidemiologic studies, academic research, medical case reports, workplace incident reports, and spill and release information.

The above measures are consistent with EPA's responsibility under section 4(h) of TSCA to encourage and facilitate "the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of a chemical substance would provide scientifically valid and useful information on other chemical substances in the category."[2]

Below we describe in more detail our concerns and recommendations. We plan to meet with Assistant Administrators Michal Freedhoff and Christopher Frey as soon as possible to discuss the issues raised in this letter.

Problems with Relying on NAMs For Assessing Chemical Hazards and Making Safety Determinations

EPA's ability to regulate chemicals and to protect public health requires reliable data about chemical hazards and exposures. Chemical assessment tools must leverage the best available science to develop high-quality information to support health protective policies and practices. At this time, rodent tests should continue to be a prioritized method for chemical evaluations for both industrial chemicals and pesticides.

TSCA Requires That NAMs Provide Scientifically Valid Data Equivalent in Quality to Rodent Studies

If fully validated through an open and transparent process, new NAMs can contribute useful data to understanding the health impacts of chemicals. However, the 2016 TSCA amendments direct EPA to encourage the "use of scientifically valid test methods and strategies that reduce or replace the use of vertebrate animals while providing information of equivalent or

better scientific quality and relevance that will support regulatory decisions under this title."[3] Thus, before rodent testing can be reduced, EPA must assure that the replacement test systems meet at least three criteria:

- they are "scientifically valid;"
- they will "provid[e] information of equivalent or better scientific quality" than the tests they replace;
- they will "support regulatory decisions" under this subchapter.

Unfortunately, EPA has not met this burden. Except for a limited number of acute toxicity endpoints (for example, skin and eye irritation), most NAMs remain unvalidated for determining health effects.[4] Moreover, scientists agree that the scientific quality of NAMs is critically compromised due to inadequate coverage of important biological targets, lack of metabolism, failure to predict effects in complex systems like reproduction and neurobehavior, and failure to address health effects across different life stages.[5] EPA's own 2021 New Approach Methods Work Plan ("Work Plan") confirms these concerns: "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)".[6] Put simply, NAMs cannot reliably measure key health effects including cancer and birth defects for which there are established rodent tests. And, finally, EPA also lacks any guidelines or policies to assure that NAMs will support regulatory decisions to limit or eliminate hazardous chemicals, as noted in the Work Plan.[7]

Prematurely curtailing rodent testing will deprive EPA of the tools it needs to protect the health of individuals and communities – particularly those overburdened by harmful environmental pollutants – and will deepen health disparities. Coupled with the absence of rodent data, the limitations of NAMs mean chemicals could also be unjustifiably deemed safe based on NAMs data alone, allowing toxic chemicals to be approved or to remain in use. That is not what is required or intended by the revised TSCA.

EPA Should Continue to Rely on Proven Tools for Chemical Assessment and Regulation

For decades, hazard and risk determinations have relied primarily on rodent tests to assess chemicals for carcinogenicity, developmental and reproductive toxicity, neurotoxicity, immunotoxicity, and other serious and complex human health endpoints. Over time, scientists and Agency officials developed a comprehensive peer-reviewed framework for using rodent studies to make judgments about the effects of chemicals on human health – including workers and communities – and determine the magnitude and severity of these effects under likely conditions of exposure. EPA notes this in its NAMs Work Plan: "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."[8]

Based on a broadly accepted set of guidelines for interpreting animal data, EPA has largely relied on findings from whole rodent studies for nearly all significant restrictions on unsafe chemicals. For example, the determinations of unreasonable risk to human health in EPA's first ten TSCA risk evaluations are predominantly based on findings of carcinogenicity, reproductive and developmental toxicity, neurotoxicity, and immune effects in rodent studies, often coupled with toxicokinetic information to extrapolate the results of these studies to humans and wildlife species. Similarly, recent toxicity assessments on per- and polyfluoroalkyl substances (PFAS) conducted by the Office of Water have made extensive use of rodent and epidemiological data, as have IRIS assessments on formaldehyde, ethylene oxide, hexavalent chromium, methylene chloride, trichloroethylene, phthalate esters, and many other substances. There have been substantial reductions in mortality and disease due to the use of rodent tests. [9]

While EPA has not done enough to address the burdens facing frontline communities, its response should be to issue stronger regulations using existing data, and to fill relevant data gaps with rodent studies, use of uncertainty factors and the promotion of safer substitutes. EPA must not weaken the scientific foundation for such regulations by prematurely halting or curtailing rodent testing.

EPA is Already Reducing Critical Toxicity Testing

Despite the limitations associated with NAMs, EPA is already curtailing rodent testing that is currently needed to assess chemical toxicity.[10] In 2019, then-Administrator Andrew Wheeler issued a directive to end reliance on animal testing by EPA.[11] That directive states that TSCA "requires the EPA to reduce reliance on animal testing,"[12] but makes no mention of the TSCA provisions that expressly condition such reduction on evidence that NAMs "provid[e] information of equivalent or better scientific quality and relevance" than rodent studies.[13] Although the status of the Wheeler directive is uncertain, EPA continues to sharply reduce the animal testing it conducts itself or requires industry to perform. A senior EPA scientist recently announced "progress and summary metrics on reducing vertebrate animal testing requests and use" as part of the EPA "workplan" for advancing NAMs.[14] According to the scientist, animals used in studies conducted by the EPA Office of Research and Development declined by two-thirds between FY2018 and FY2021.[15] In addition, an Environmental Defense Fund ("EDF") analysis shows that EPA has virtually stopped requiring rodent testing in TSCA section 5(e) consent orders. After excluding legacy Premanufacture Notices ("PMNs"), only ~1.5% of the PMNs subject to orders had testing requirements in FY 2021, as compared to over two thirds of the orders for FY 2016 PMNs.[16] Finally, despite the absence of important health effects data, TSCA section 4 testing orders for high-priority chemicals subject to ongoing risk evaluations failed to require any long-term rodent studies that would address these data gaps.[17]

A Sound Framework for Use of NAMs Data in Regulatory Decision-Making is Needed

In contrast to its reliance on rodent studies, EPA has limited experience using NAMs for risk evaluation and management and no established Agency-wide legal or scientific framework for incorporating NAMs in regulatory decision-making. EPA acknowledges this as an outstanding concern in its NAMs Work Plan: "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."[18] Under TSCA, ensuring that the use of NAMs will "support regulatory decisions" is a prerequisite for their use. In the absence of such a framework, NAMs could be used to prematurely exonerate chemicals, not because those chemicals are safe for use, but because the NAMs are not able to reliably measure all of the chemical's health effects. In addition, halting rodent testing in pursuit of NAMs will bring the chemical risk evaluation process to a standstill by greatly limiting EPA's ability to address the data gaps that prevent health-protective risk determinations for many chemicals.

The 2016 TSCA amendments were intended to accelerate the pace of chemical testing, risk evaluation, and risk management. But EPA's failure to develop actionable information on chemical risks will make it difficult, if not impossible, to achieve the improvements in chemical safety that Congress called for.

EPA Must Not Undermine Established Environmental Health Science

EPA must not use NAMs to discredit existing *in vivo* data – either from whole rodent tests or epidemiologic studies – and cause regulatory delays at the expense of workers and overburdened communities. For example, it is of great concern to us that EPA recently delayed finalizing its registration reviews of organophosphate pesticides – a class of chemicals with decades of developmental neurotoxicity evidence from rodent tests and epidemiologic studies – in part, to unnecessarily promote and create a developmental neurotoxicity NAMs battery. [19] These delays leave farmworkers and their families and pregnant people at continued risk of severe and irreversible health harms.[20]

Workers and communities facing disproportionate harm from chemical exposures cannot sustain such delays. EPA must make regulatory decisions by combining the strengths of various tools, including epidemiologic, mammalian, non-mammalian, read-across, and other class-based approaches and methods to evaluate large numbers of chemicals and support regulatory actions to protect the health of populations for generations to come. When EPA identifies hazardous chemicals, it should also investigate and promote the elimination of unnecessary chemical uses, and the development and use of safer alternatives.

Public Health Progress May Be Lost

It is disappointing but not surprising that many of the same industry voices that have long opposed strong chemical regulation also seek to undermine the predictive value of rodent studies and encourage the use of NAMs. We are concerned that the regulated industry is attempting to undermine rodent testing in order to challenge EPA's public health accomplishments and attempt to block long-overdue action against the many chemical threats not yet addressed, shielding companies from future regulation. These criticisms of rodent testing are not scientifically supported, and they do not serve EPA's mission of protecting public health and the environment.

The Public Must Be Meaningfully Engaged on New Methods Development and Application

EPA must not reduce rodent testing at the expense of farmworkers and other environmental justice communities—often low-wealth and communities of color—who breathe, drink, and ingest toxic chemical pollution every day. But if EPA approves or fails to regulate chemicals without adequate testing, based on new and unproven NAMs, these communities suffer the greatest harm.

EPA has acknowledged that "vibrant stakeholder engagement and partnerships are the backbone of" EPA's environmental justice work and are "essential to achieving meaningful outcomes for overburdened communities."[21] But despite this commitment to "early, ongoing and meaningful stakeholder engagement,"[22] thus far the discussions of NAMs development have been skewed in favor of a small number of organizations promoting NAMs, most prominently the chemical industry and animal welfare organizations. In contrast, groups that speak for broader environmental justice and public health concerns have only rarely been included. As a result, representatives of the most exposed and overburdened communities have not been able to voice concerns about the limitations of many NAMs and their disturbing implications for regulatory decisions. Moreover, in our experience, federal agencies are ill-prepared to engage in scientific discussions of whether and how NAMs can address social determinants of health or population variability and susceptibility. This puts already vulnerable communities at greater risk and deepens distrust between the Agency and the communities it must serve.

Our recommendations are informed by the Louisville Charter for Safer Chemicals, which has been signed by more than 100 organizations representing environmental justice and grassroots communities, environmental and health nonprofits, and leaders in the medical, public health, business, science and research communities across the country.[23] The Louisville Charter calls for a new chemical policy that "use[s] scientific data to support health-protective policies and practices," "ensure[s] the public and workers fully have the right-to-know, participate and decide in the decisions that impact their health because of the potential harm from toxic chemicals," and emphasizes "urgent action to stop production … of chemicals that are unsafe and/or accumulate in the environment and people."[24] EPA's current use of new NAMs and precipitous elimination of rodent testing to identify chemical hazards is inconsistent with those foundational principles.

Before making decisions related to the use of new NAMs and eliminating the use of rodent studies that have proven to be effective in identifying chemical hazards, EPA must reach out to those communities and provide the information and resources required for meaningful participation and engagement. In so doing, we urge EPA to align its work with the Louisville Charter for Safer Chemicals to better ensure that TSCA will advance health and safety for communities and workers as Congress intended.

Recommended Next Steps for EPA

As EPA transitions from testing strategies based largely upon the analysis of apical endpoints in whole rodent systems to one that relies heavily upon molecular pathways that reside upstream of disease outcomes, the Agency must continue to rely on rodent tests conducted according to strict animal welfare protection rules. At this point in time, abandoning rodent

testing will jeopardize the protection of at-risk populations, including overburdened communities that EPA must safeguard under our environmental laws.

We urge you to reaffirm EPA's commitment to protecting workers, communities, susceptible populations, and the environment under TSCA and other laws by relying on the "best available science," including rodent testing, to protect disproportionately burdened communities. EPA must:

- Fully and unambiguously rescind the 2019 directive of former Administrator Wheeler to eliminate rodent testing.
- Confirm that the Agency has no across-the-board policy of eliminating rodent studies, has not set any numerical target for reducing the number of rodent studies it conducts or requires, and will no longer benchmark the number of rodents used in chemical testing under EPA-administered laws unless EPA also benchmarks the number of people harmed by chemical exposures.
- Reaffirm that EPA will continue to perform rodent tests conducted in accordance with animal welfare protection rules and will mandate whole rodent testing by chemical manufacturers where needed to fill critical data gaps on the potential hazards of new and existing substances.
- Recommend that the National Toxicology Program (NTP) continue to conduct rodent tests to address the urgent concerns of environmental justice communities. This should include testing of community-relevant mixtures.
- Establish a legally defensible framework that meets scientific best practices to assess whether NAMs provide adequate and reliable data for chemical hazard assessments and achieve the same or greater level of health protection as rodent studies.
- Reject any presumption of low priority or concern for chemicals that don't elicit responses in NAMs tests (null or negative results).
- Leverage opportunities to reduce rodent testing by employing accepted read-across methods and category-based approaches that use available data on structurally related chemicals as the basis for risk determinations on untested substances, as well as making better use of existing data including from epidemiologic studies, academic research, medical case reports, poisoning incident data, etc.
- Require consideration of and transition to safer chemical substitutes in chemical assessments.

In addition to these actions, EPA and other agencies must assure full transparency and conduct meaningful outreach to susceptible communities, whose interests in enhanced protection against pollution and chemical exposure will be directly impacted by the development and use of NAMs and who deserve a strong voice in how agencies use these assays to address chemical risks.

The ultimate usefulness of new NAMs assays resides in their potential ability to be protective of the health of workers, communities, and ecosystems. However, reliability, relevance, and providing equal or better information than rodent toxicity tests represent independent criteria that have not been sufficiently met at this time. Therefore, the use of NAMs in lieu of well-conducted rodent tests is not consistent with the law and the best available science.

Thank you for your consideration. We are requesting a meeting with Assistant Administrators Frey and Freedhoff to discuss these important issues in the near future, and we will follow up with their respective offices to arrange that meeting.

Respectfully,

Alliance of Nurses for Healthy Environments
Alaska Community Action on Toxics
Black Women for Wellness
Breast Cancer Prevention Partners
Center for Biological Diversity
Center for Environmental Health
Clean+Healthy
Clean Power Lake County
Clean Water Action
Coming Clean
Community to Community
CRLA Foundation
Delaware Concerned Residents for Environmental Justice
Earthjustice
Environmental Defense Fund
Environmental Justice Health Alliance
Family Farm Defenders
Farmworker Association of Florida
Farmworker Justice
Farmworker Self-Help
Friends of the Earth
Healthy Building Network
International Center For Technology Assessment
Los Jardines Institute
Locust Point Community Garden
Made Safe
Moms for a Nontoxic New York
Natural Resources Defense Council
Northwest Center for Alternatives to Pesticides
Organizacion en California de Lideres Campesinas, Inc.
Science and Environmental Health Network
Sierra Club
t.e.j.a.s.
Toxic Free Future
Toxic Free North Carolina
Until Justice Data Partners
Women's Voices for the Earth
7 Directions of Service

cc: Dr. Michal Freedhoff, Assistant Administrator, Office of Chemical Safety and Pollution Prevention

Dr. Christopher Frey, Assistant Administrator, Office of Research and Development

Marianne Engelman-Lado, Acting Principal Deputy Assistant Administrator, Office of Environmental Justice and External Civil Rights

Dr. Na'Taki Osborne Jelks and Sylvia Orduño, Co-Chairs, National Environmental Justice Advisory Committee

Richard Moore and Peggy Shephard, Co-Chairs, White House Environmental Justice Advisory Committee

Dr. Amelia Nguyen, Children's Health Protection Advisory Committee

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[1] As used in this letter, the term NAMs refers only to these newer NAMs, and not to older and more established practices, like read across, that have long been used to evaluate and regulate chemicals.

[2] 15 U.S.C. § 2603(h)(1)(B)(2).

[3] 15 U.S.C. § 2603(h)(1)(A).

[4] EPA, *New Approach Methods: Efforts to Reduce Use of Vertebrate Animals in Chemical Testing*, www.epa.gov/research/epa-new-approach-methods-efforts-reduce-use-vertebrate-animals-chemical-testing (last updated Nov. 17, 2022)

[5] Chartres N, Sass JB, Gee D, Bălan SA, Birnbaum L, Cogliano VJ, Cooper C, Fedinick KP, Harrison RM, Kolossa-Gehring M, Mandrioli D, Mitchell MA, Norris SL, Portier CJ, Straif K, and Vermeire T. *Conducting Evaluations Of Evidence That Are Transparent, Timely And Can Lead To Health-Protective Actions.* Environ Health. 2022 Dec 5;21(1):123. doi: 10.1186/s12940-022-00926-z;

Ginsberg GL, Pullen Fedinick K, Solomon GM, Elliott KC, Vandenberg JJ, Barone S Jr, and Bucher JR. *New Toxicology Tools and the Emerging Paradigm Shift in Environmental Health Decision-Making*. Environ Health Perspect. 2019 Dec;127(12):125002. doi: 10.1289/EHP4745;

[6] EPA, *New Approach Methods Work Plan: Section IV. Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps*, at 16 (Dec. 2021), https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

[7] EPA, *New Approach Methods Work Plan: Section III. Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions*, at 12 (Dec. 2021), https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

[8] EPA, *New Approach Methods Work Plan: Section III. Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions*, at 12 (Dec. 2021), https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

[9] EPA, *Drinking Water Health Advisories (HAs)*, https://www.epa.gov/sdwa/drinking-water-health-advisories-has#published (last updated June 15, 2022).

[10] Sharon Lerner, *The Department of Yes: How Pesticide Companies Corrupted the EPA and Poisoned America*, The Intercept (June 30, 202), https://theintercept.com/2021/06/30/epa-pesticides-exposure-opp/.

[11] https://www.epa.gov/sites/default/files/2019-09/image2019-09-09-231249.txt

[12] Memorandum from Andrew Wheeler, Administrator, EPA to Associate Deputy Administrator, General Counsel, Assistant Administrators, Inspector General, Chief Financial Officer, Chief of Staff, Associate Administrators and

Regional Administrators regarding Directive to Prioritize Efforts to Reduce Animal Testing (Sept. 10, 2019), https://www.epa.gov/sites/default/files/2019-09/image2019-09-09-231249.txt.

[13] 15 U.S.C. § 2603(h)(1)(A).

[14] EPA, *Updated NAM Work Plan Identified Objectives, Strategies and Deliverables for Applying NAMs* (2022), https://www.epa.gov/system/files/documents/2022-11/NAMS%20Conference%202022%20Slides.pdf.

[15] *Id.*

[16] Less than 10% of the section 5(e) Orders for FY 2021 premanufacture notices (PMNs) available on Chemview (https://chemview.epa.gov/chemview/) require toxicity, environmental fate or physical-chemical testing. Of the Orders that required testing, all but one were for related legacy PMNs with a testing strategy initiated in 2016. If these legacy PMNs are excluded, this leaves only ~1.5% of the PMNs subject to Orders for which any testing was required. This contrasts with the testing requirements included in section 5(e) Orders for FY 2016 PMNs. More than two-thirds of those Orders included requirements for toxicity, environmental fate and/or physical-chemical testing.

[17] EPA Issues Additional Test Orders to Support Risk Evaluations of Eight Chemicals under TSCA. March 24, 2022. https://www.epa.gov/chemicals-under-tsca/epa-issues-additional-test-orders-support-risk-evaluations-eight-chemicals

[18] EPA, *New Approach Methods Work Plan: Section III. Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions*, at 12 (Dec. 2021), https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf.

[19] Letter to Patti Goldman, Earthjustice, from Dr. Michal Freedhoff, EPA Assistant Administrator (May 25, 2022).

[20] Earthjustice, *Organophosphate Pesticides in the United States: High Risk Exposure Routes – Farmworkers* (Aug. 4, 2021), https://earthjustice.org/features/organophosphate-pesticides-united-states.

[21] EPA, *EJ 2020 Action Agenda*, at 10 (Oct. 2016), https://www.epa.gov/sites/default/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf.

[22] *Id.*

[23] Coming Clean, *The Louisville Charter for Safer Chemicals: A Platform for Creating a Safe and Healthy Environment through Innovation*, https://ej4all.org/about/louisville-charter (last updated in 2021).

[24] *Id.*