Science Advancement & Outreach
A DIVISION OF PETA

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NIEHS FY 2025–2029 Final Draft Strategic Plan

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We are writing on behalf of People for the Ethical Treatment of Animals—PETA entities have more than 9 million members and supporters globally—regarding the National Institute of Environmental Health Sciences (NIEHS) draft strategic plan framework. Recognizing the failure of animal-based research results translating into human-relevant knowledge, PETA supports NIEHS's goals and priorities on advancing environmental health sciences via the implementation of the many modern, human-based approaches presented in this five-year strategic plan. In this regard, we expand on recommendations for most of the areas of emphasis listed in this request for public comment. **Our key recommendation for the NIEHS is to conduct and fund research using only human biology-based systems and not those that use other species**.

We also take this opportunity to share our Research Modernization Deal, a plan of action with detailed recommendations for advancing biomedical research in the U.S. through non-animal methods, applicable across various research domains. This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf. We are happy to meet and discuss with NIEHS any questions related to this response or the topics covered in the Research Modernization Deal.

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Exposomics

Exposomics is a burgeoning research field focused on understanding the environmental exposures that can affect an individual's health over their lifetime. According to the NIEHS, exposomics serves as the "environmental counterpart to genomics." Longitudinal studies are particularly valuable for exposomics research, as they enable the tracking of individuals over extended periods, which is unfeasible with animals who are confined to laboratories. A 2023 meta-analysis, which included over 400 publications and was published in *Nature Medicine* by Flor and colleagues, found that secondhand smoke exposure was linked to nine health outcomes, including an 8% increased risk of heart disease and a 5% increased risk of stroke. [1] Most of these studies were case-control studies. When combined with other study modalities, such as retrospective clinical cohorts, exposomics can significantly contribute to the future human exposome atlas, a key goal of the NIEHS.

Environmental exposure significantly contributes to various illnesses. For instance, in 2022, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) recognized the link between charcuterie consumption and an increased risk of colon cancer, recommending reduced dietary exposure.[2] This recommendation was later endorsed by the Canadian Cancer Society[3] and extended to other cancer types.[4] Similarly, air pollution has long

[1] Flor, L.S., Anderson, J.A., Ahmad, N. et al. Health effects associated with exposure to secondhand smoke: a Burden of Proof study. *Nat Med*. 2024:30, 149–167.
[2]Reducing dietary exposure to nitrites and nitrates. *ANSES*. Published July 12, 2022. Assess July 1, 2024. https://www.anses.fr/en/content/reducing-dietary-exposure-nitrites-and-nitrates
[3] Reducing your risk for colorectal cancer. *Canadian Cancer Society*. Assess July 1, 2024. https://cancer.ca/fr/cancer-information/cancer-types/colorectal/risks/reducing-your-risk.
[4]Le lien entre le cancer colorectal et les nitrites se confirme. Émilie Bilodeau. *La Presse*. Published July 13, 2024. Assess July 1, 2024. https://www.lapresse.ca/actualites/sante/2022-07-13/le-lien-entre-le-cancer-colorectal-et-les-nitrites-se-confirme.php

been associated to respiratory diseases and lung cancer incidence.[5,6] Despite understanding some underlying mechanisms of the biological damage caused by these factors, studying their health impacts and replicating results with the use of other species presents significant challenges and lacks relevance to humans. **Therefore, the "model systems" mentioned in approach (d) of this area must be exclusively non-animal, human-based model systems to facilitate "efficient interpretation and validation of findings" to humans**. For example, human-relevant study models are already showing promising results. A 3D dispersion model tested by a petrochemical company effectively detected health-threatening concentrations of BTEX volatile pollutants up to 2 km from a wastewater plant.[7] Another 3D model calculated the chemical transformation of air in high-pressure aircraft turbines, providing accurate predictive data on aviation's environmental and health impacts.[8]

Given the global interconnectedness of today's world, the NIEHS should collaborate with international institutions to develop a comprehensive exposomics atlas with data from various continents. By establishing international research networks, the NIEHS can improve the understanding and evaluation of how environmental factors affect human health across borders. In parallel, NIEHS should prioritize grants for evidence-based studies that use human-based data and systems and invest in environmental monitoring projects for real-time data assessment that help identify threats and enable timely interventions, such as the studies mentioned above. It is also important to engage in public health initiatives that raise awareness about the health risks associated with environmental exposures and encourage behavioral changes in society.

Precision Environmental Health (PEH)

We applaud NIEHS's interest in developing "human biology-based testing methods that will provide insights into specific biological processes or disease states and represent population diversity" (Priority Approach (e)). Studying humans themselves is the most reliable way to

[5] Turner MC, Andersen ZJ, Baccarelli A, et al. Outdoor air pollution and cancer: An overview of the current evidence and public health recommendations. *CA Cancer J Clin*. 2020:70,6, 460-479.
[6] Paolo Vineis, Kirsti Husgafvel-Pursiainen. Air pollution and cancer: biomarker studies in human populations. *Carcinogenesis*. 2005:26,11, 1846–1855.
[7] Eslami N, Fatehifar E, Kaynejad M.A. A 3D mathematical evaluation of the emission into the air of reactive BTEX compounds: A new approach for mechanism reduction. *Environ Eng Res*. 2022;27(6): 210196:210196-0.
[8] Nguyen TH, Nguyen-Tri P, Garnier F. 3D modeling of transformation of gaseous pollutants in the high-pressure turbine of an aircraft engine. *Propulsion and Power Res*. 2020:9: 1, 1-14.

produce science that benefits humankind. Among the topics described in the strategic plan, integrative research methods are important, but integrative multidisciplinary teams gathering specialists are also necessary to achieve NIEHS goals. In the U.K., the British program Born in Bradford (BIB) is the largest longitudinal program studying different aspects of human life. It includes more than 40 thousand people over many years, involving entire families, communities, and health specialists.[9] The network is a great model, and a good example for the NIEHS, for studying humans in their environment to identify health determinants and develop appropriate healthcare interventions.

Although exposomics can be geography-dependent,[10,11] there are universal environmental factors that affect human health; the COVID-19 pandemic was a prime example. Similarly, the application of geographic information system (GIS) software and AI technologies can contribute to mapping contextual environmental factors, and some companies, such as ESRI, are already working with these systems.[12] Such strategies would likely reduce bias from small cohorts and, at the same time, provide significant information about risk factors for human health and insights to develop more personalized interventions. This is the subject of geomedicine, an emerging field that integrates spatial and health data to improve the quality of care and human health. More details about this area are available in the book *Geomedicine: Geography and Personal Health*, by Bill Davenhall.[13]

Mechanistic Biology and Toxicology

In this area, there are myriad cutting-edge technologies that the NIEHS can explore to obtain reproducible, human-based data for toxicology testing. Patient-derived *in vitro* models, such as organoids and organs-on-chip (OoC), have the potential for high-throughput application and mechanistic-driven studies. Multi-OoCs have been developed to study the relationship between

[9] Born in Bradford. About Bradford. BorninBradford.nhs.uk. Copyright 2024. Access June 13, 2024. https://borninbradford.nhs.uk/.
[10] Campbell M, Marek L, Hobbs M. Reconsidering movement and exposure: Towards a more dynamic health geography. *Geo Compass*. 2021:15,6, e12566.
[11]Michael Blanding. Project uses geographic data to show that where a person lives matters to their health. Harvard School of Public Health. Published November 10, 2022. Assess July 2, 2024. https://www.hsph.harvard.edu/news/features/project-uses-geographic-data-to-show-that-where-a-person-lives-matters-to-their-health/
[12] About ESRI: Overview. *ESRI*. Assess July 2, 2024. https://www.esri.com/en-us/about/about-esri/overview
[13]Bill Davenhall. Geomedicine: Geography and Personal Health. ESRI. Published August 2012. Assess July 2, 2024. https://www.esri.com/content/dam/esrisites/sitecore-archive/Files/Pdfs/library/ebooks/geomedicine.pdf

responses to drugs and off-target effects or biodistribution,[14,15] conditions that are both physiologically and technically difficult and misleading when tested using animal models.[19]

Recently, a promising mini human colon organoid was developed to emulate human gut physiology and function in real-time, providing an interesting platform for the investigation of toxicity and understanding multifactorial diseases.[16] Similarly, an emerging area of interest is the development of models to investigate obesity in humans, which is now an epidemic affecting 43% of adults 18 years and older,[17] and which has been linked to environmental factors such as pesticide and microplastic contamination.[18,19,20,21,22,23]

Experiments on animals that attempt to replicate human metabolic alterations have consistently failed to provide translational data. As discussed by Suleiman and colleagues in a review published in 2019, "till now, no animal model of obesity can replicate models of the human condition."[24] In recent years, adipose tissue has been recognized for its endocrine role and implication in the development of multiple diseases. Microfluidic models using human adipose tissue-derived stem cells (hASCs) provide a new venue to investigate the molecular mechanisms and environmental factors implicated in obesity in humans. Three-dimensional culture enhances the differentiation of hASCs into the functional and mature cells that are observed *in vivo* in

[14] McAleer CW, Long CJ, Elbrecht D, et al. Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics. *Sci Transl Med*. 2019;11(497):eaav1386.
[15] Zhu J, Ji L, Chen Y, et al. Organoids and organs-on-chips: insights into predicting the efficacy of systemic treatment in colorectal cancer. *Cell Death Discov*. 2023;9(1):72.
[16] Mitrofanova O, Nikolaev M, Xu Q, et al. Bioengineered human colon organoids with in vivo-like cellular complexity and function. *Cell Stem Cell*. 2024;9:S1934-5909(24)00184-X.
[17] Obesity and overweight. World Health Organization. Published March 1, 2024. Assess July 9, 2024. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
[18] Amato AA, Wheeler HB, Blumberg B. Obesity and endocrine-disrupting chemicals. *Endocr Connect*. 2021;10(2):R87-R105.
[19] Pesticide Exposure Linked to Obesity, Type 2 Diabetes, and Metabolic Disease in Seniors. Beyond Pesticides. Published February 27th, 2024. Assess July 16, 2024.
[20] Kannan K, Vimalkumar K. A Review of Human Exposure to Microplastics and Insights Into Microplastics as Obesogens. *Front Endocrinol* (Lausanne). 2021;12:724989.
[21] Egusquiza RJ, Blumberg B. Environmental Obesogens and Their Impact on Susceptibility to Obesity: New Mechanisms and Chemicals. *Endocrinology*. 2020;161(3):bqaa024.
[22] Narduzzi S, Fantini F, Blasetti F, et al. Predictors of Beta-Hexachlorocyclohexane blood levels among people living close to a chemical plant and an illegal dumping site. *Environ Health*. 2020;19(1):9.
[23] Chen T, Liu X, Zhang J, et al. Associations of chronic exposure to a mixture of pesticides and type 2 diabetes mellitus in a Chinese elderly population. *Chemosphere*. 2024;351:141194.
[24] Suleiman JB, Mohamed M, Bakar ABA. A systematic review on different models of inducing obesity in animals: Advantages and limitations. *J Adv Vet Anim Res*. 2019;7(1):103-114.

humans.[25] A recent study using a 3D printed chamber introduced an ASC-on-a-chip that allowed for a multiplex platform of up to 32 culture chambers to further analyses of metabolism and proteomics.[26] These human-derived approaches can help to identify environmental factors contributing to obesity in humans and can be used to explore biological mechanisms in other areas of the NIEHS's interest. Moreover, they provide accurate knowledge on biological responses to environmental factors in a human physiological context, which experiments on animals are not able to do.

For these reasons, research supported by the NIEHS to "Elucidate the mechanisms and systems underlying tissue, cell, and genetic abnormalities that occur in the face of known and emerging environmental exposures, and develop approaches to better understand the molecular mechanisms through which some environmental exposures can promote health and potentially mitigate adverse physical/chemical exposures" (Priority Approach (a)) and "Develop mechanistically driven approaches to understanding the toxicology of emerging contaminants to provide more timely knowledge that can help avoid adverse health impacts" (Priority Approach (h)), should be conducted using only non-animal, human-relevant systems.

Data Science and Computational Biology

Here, the NIEHS' focus is to translate the knowledge derived from these tools into action. Computational biology and artificial intelligence will continue to evolve and play key roles in different fields of science.[19] To improve clinical care and outcomes, NIEHS can invest in observational and retrospective studies in regions of interest that allow for the application of knowledge extracted from data science into specific contexts. Concomitantly, this will open the opportunity to explore interventions and monitor outcomes.

An interesting example of monitoring is HBM4EU, a five-year project involving 30 European countries that monitors citizens' exposure to chemicals and the possible health consequences of

[25] Yang F, Carmona A, Stojkova K, et al. A 3D human adipose tissue model within a microfluidic device. *Lab Chip*. 2021;21(2):435-446.
[26] Compera N, Atwell S, Wirth J, et al. Adipose microtissue-on-chip: a 3D cell culture platform for differentiation, stimulation, and proteomic analysis of human adipocytes. *Lab Chip*. 2022;22(17):3172-3186.

those exposures by collecting human samples.[27] Since the conclusion of the initiative in 2021, a platform developed by the Flemish Institute for Technological Research and managed by the Partnership for the Assessment of Risk from Chemicals (PARC) has been sharing data to inform decision-makers, enabling more precise health interventions across Europe.[28] Such strategies can leverage the impact of fundamental science to the benefit of humans by using humans as models, not other animals that lack human relevance. **Therefore, all cross-system *in vivo* models supported by the NIEHS should be of human origin (either through wearable devices, epidemiology, health records, or *ex vivo* samples).**

Spatial biology, which investigates the spatial distribution of molecules or cells within a tissue, is another growing field for which NIEHS can increase funding. When integrated into -omics technologies and algorithms, it can generate data on human biological function in a range of complex conditions, such as metabolic dysfunction. [19] These approaches relying on patients' data can be combined with AI/ML tools to simulate the human response to chemicals and better correlate phenotype and environmental factors. Therefore, NIEHS can significantly boost data science and computational biology through a series of strategic initiatives in the coming years. First, the NIEHS should create collaborative grants that encourage partnerships between computational biologists and environmental health scientists and should invest in cutting-edge computing resources to support complex computational needs. Second, the NIEHS can establish interdisciplinary research centers, taking as an example the MILA Quebec Artificial Intelligence Institute, which opened in 2018 in Canada and is today the world's largest academic research center for deep learning.[29] MILA connects universities, industry, and startups, fostering public-private partnerships in different research areas. Third, we also encourage the NIEHS to promote training and education by offering fellowships and scholarships for young scientists to develop expertise in these new *in silico* tools that can accelerate the translation of fundamental biology into actionable plans for the benefit of all.

[27] About HBM4E. HBM4EU. Assess July 16, 2024. https://www.hbm4eu.eu/about-us/about-hbm4eu/
[28] Human biomonitoring data services. VITO. Assess July 16, 2024. https://hbm.vito.be/human-biomonitoring-data-services
[29] About Mila. Mila. Assess July 10, 2024. https://mila.quebec/en/about-mila

Environmental Health Disparities, Environmental Justice, and Health Equity

Community engagement in research is essential to facilitate the collection of much-needed human samples and data. To achieve the priorities described in Area 5, it is crucial to build trust within communities. The NIEHS must organize campaigns and discussions that disseminate scientific knowledge in ways that the public can understand and that are responsive to their needs. These efforts can encourage communities to enroll in studies. For example, New York City launched the Plant-Based Lifestyle Medicine Programme (PBLM) in 2019, the first of its kind initiative to mitigate cardiometabolic risk by adopting a healthier lifestyle.[30] The multidisciplinary study was funded by the New York City Health + Hospitals (NYC H+H) system to serve an initial 200 participants from different races. The project resulted in a significant reduction in the consumption of health-risk foods such as sweet beverages, meat, and dairy, as well as a drop in media and screen time with improvement in physical activity during the initial six months of the study.[31]

The PBLM is currently expanded to more hospitals within the NYC H+H, which is the largest municipal public health care system in the United States, serving over 1 million patients annually.[32] Although the lifestyle changes resulted in weight loss and a reduction in medication for chronic conditions among the cohort, the program reported "challenges faced delivering the program or navigating participation" because of insufficient administrative support.[33] The NIEHS should partner with municipalities engaged in identifying health determinants to pursue its goal of major investments in human studies, providing the necessary support for an effective program implementation and management of collected data, which will also benefit its goals of increasing "Public Trust in Science."

Crosscutting Themes

The NIEHS' priorities of investing in infrastructure and professional capacity in both health care and research centers are laudable. **In this vein, new infrastructure and professional training should focus on non-animal, human-relevant research to best prepare teams for the future**

[30] New York City, USA: Plant-Based Lifestyle Medicine Programme. AIPH. Access July 9, 2024. https://aiph.org/green-city-case-studies/new-york-usa/.
[31] Massar RE, McMacken M, Kwok L, et al. Patient-Reported Outcomes from a Pilot Plant-Based Lifestyle Medicine Program in a Safety-Net Setting. *Nutrients*. 2023;15(13):2857.
[32] Babich JS, McMacken M, Correa L, et al. Advancing Lifestyle Medicine in New York City's Public Health Care System. *Mayo Clin Proc Innov Qual Outcomes*. 2024;8(3):279-292.
[33] Albert SL, Massar RE, Kwok L, et al. Pilot Plant-Based Lifestyle Medicine Program in an Urban Public Healthcare System: Evaluating Demand and Implementation. *Am J Lifestyle Med*. 2022;18(3):403-419.

of science. As the fields of animal-free research and testing continue to expand, increased education and hands-on training will accelerate the transition to these methods. Students and early-career scientists, especially, must be provided with opportunities to develop the skills necessary to contribute to this research field so that the U.S. can compete with international developments. Curriculum for professionals should include mandatory courses on new approach methodologies, *in vitro* to *in vivo* extrapolation, systematic reviews, and adverse outcome pathways. Furthermore, established researchers and regulators using animal-based methods should be provided with retraining opportunities and encouraged to forge multidisciplinary collaborations to evolve their skills and establish new and innovative ways of asking research questions and methods for answering them. Building a trained team with the proper resources is important to promote health care with scientific-based interventions that have a real chance of benefiting human health.

Importantly, NIEHS should engage in implementing animal-free research methods across themes and phasing out experiments on animals for research that uses only human-relevant technologies, following the example of the international scientific community. Please see our Research Modernization Deal for more detail on how this can be achieved: https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf.