The National Toxicology Program: A Reimagined Partnership to Enhance Its Impact and Further Safeguard Public Health

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For more than 40 years, the National Toxicology Program (NTP) has been renowned for its rigorous scientific approach to identifying and evaluating potential hazards to human health. This long-standing and successful federal partnership of the Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH) has supported the advancement of toxicology and environmental health. As we enter the second quarter of the 21st century, we are pleased to lay out NTP's most recent organizational evolution, which will ensure its continued key role as a collaborative and trusted leader in tackling the world's most pressing toxicological and environmental health challenges.

The NTP exists to develop the information and tools that both agencies of government and industry need so we can all live together safely in the same world.
– David P. Rall, M.D., Ph.D.
(first NTP director, 1978–1990)

The NTP was established in 1978 by Secretary Joseph A. Califano, Jr. as a federal interagency partnership within the U.S. Public Health Service of the U.S. Department of Health, Education, and Welfare (now the U.S. Department of Health and Human Services [HHS]) (Califano 1978; Califano 1979) and was granted permanent status as an HHS activity in October 1981 (Hawkins 1987). The need for a program like the NTP arose because of increasing scientific, regulatory, and congressional concerns in the 1960s–1970s about the human health effects of exposure to chemical agents. Many human diseases were then, and continue to be, directly or indirectly related to certain chemical exposures. Therefore, it was correctly reasoned that decreasing or eliminating human exposures to those chemicals would help prevent human disease and disability (Bucher and Birnbaum 2016; Walker and Wolfe 2023). Through partnership, we and prior stewards of the NTP have strived to ensure that its research on the toxicity of chemicals, environmental exposures, and biological agents continues to be informative for public health decisions and provides a strong science base for other programs and policies that protect human health and the environment.

The early days of the NTP were focused on achieving the intent of its establishment—to implement defined and rigorous toxicological approaches and identify chemical hazards to which humans are exposed. The NTP has made great progress toward achieving its vision for toxicology in the service of public health. We are proud of this progress and remain committed to advancing toxicological sciences and predictive toxicology. We also recognize that the

February 2026

toxicological issues facing the NTP today are more complex than when the program was conceived—such as a shift from single-agent to multiple-agent exposures across the lifespan, the impacts of endocrine disruptors, the underappreciated additional effects of nonchemical and social stressors, and the unknown toxicology of emerging contaminants such as micro- and nano-plastics and purportedly sustainable alternatives. Additionally, smart phones, artificial intelligence, social media, and other technologies can transform the scientific understanding and public awareness of the chemical landscape. The methods for conducting toxicological research have also evolved, shifting away from reliance on traditional, prescriptive in vivo rodent-based studies assessing primarily apical endpoints to more fit-for-purpose in vivo studies in a greater diversity of species and rodent strains, and new approach methodologies, such as in vitro and in silico systems, which engender cautious optimism regarding their utility in health-protective decision-making in the face of incomplete data and knowledge. Our reimagined partnership ensures the NTP can meet these challenges by making it more adaptable, crosscutting, and responsive to rapidly shifting needs and emerging public concerns.

The NTP's three core partners—the National Institute of Environmental Health Sciences (NIEHS) of NIH, the National Institute for Occupational Safety and Health (NIOSH) of CDC, and the National Center for Toxicological Research (NCTR) of FDA, shown in Figure 1—have guided the program's activities since its inception. The NIEHS has provided the program's research and operational infrastructure, supplemented by research contributions from the other two core partners. The NTP is advised by its Executive Committee (Figure 1), the composition of which has evolved over time. The National Cancer Institute (NCI) of the NIH was a charter member of the NTP until 1981, when the NCI carcinogenesis bioassay program was transferred to the NIEHS by the Secretary and formed the cornerstone of the NTP's chemical toxicology characterization program (Bucher and Birnbaum 2016; Walker and Wolfe 2023). The NCI has remained an active member of the NTP Executive Committee, reaffirming its commitment to the NTP. Other federal entities have joined the committee, including the Agency for Toxic Substances and Disease Registry in 1987 (NTP 1988), the National Center for Environmental Health in 1997 (NTP 1999), and the Department of Defense in 2011 (NTP 2012), recognizing its value as a forum for discussion, exchange, and coordination around national toxicological issues.

The NIEHS director, who also serves as the director of the NTP, maintains an enduring commitment to the NTP and its leadership in toxicology testing and research. Honoring this commitment, the latest organizational evolution of the NTP, outlined herein, reaffirms and strengthens its core values of partnership, collaboration, and federal coordination. These values will enhance responsive federal action in the service of addressing public concerns and foster greater participation by other federal partners committed to public health.

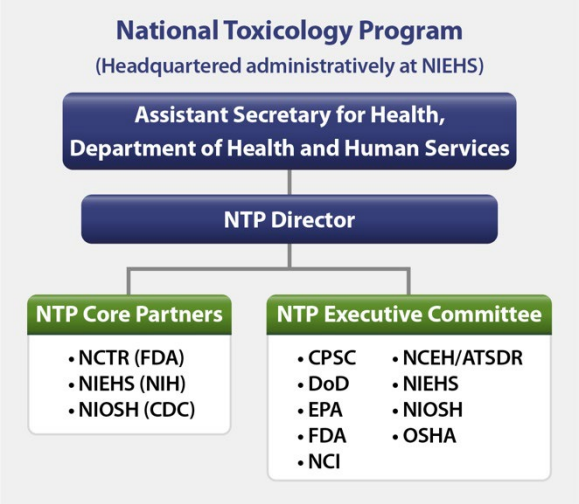

Figure 1. The NTP encompasses specific activities within the three core partners: NCTR, NIEHS, and NIOSH. The NTP is headquartered administratively at NIEHS in Research Triangle Park, North Carolina.

ATSDR = Agency for Toxic Substances and Disease Registry; CDC = Centers for Disease Control and Prevention; CPSC = Consumer Product Safety Commission; DoD = Department of Defense; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NCEH = National Center for Environmental Health; NCI = National Cancer Institute; NCTR = National Center for Toxicological Research; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.

The NTP's activities encompass a broad range of human exposures, reflective of its multiagency partnership. More than 2,800 substances have been studied under the auspices of the NTP via nomination by the public, federal agencies, nongovernmental organizations, and regulators, making it one of the primary programs responsive to pressing public health concerns. Studied substances include industrial chemicals, botanicals, occupational exposures, environmental pollutants, endocrine disruptors, food additives and contaminants, nanoscale materials, water-disinfection by-products, metals, electromagnetic fields, and pharmaceuticals. These agents have been assessed for a variety of health-related effects, including general toxicity, carcinogenicity, genotoxicity, and effects on reproduction, development, and the immune, nervous, and cardiovascular systems (Bucher and Birnbaum 2016; Walker and Wolfe 2023). This research has provided, directly or indirectly, a large component of the fundamental research used by federal and state agencies, as well as private sector organizations and international groups, to address issues relevant to understanding the effects of chemical and physical agents on human health and the environment. The quality, rigor, and independence of the NTP's work make it the preeminent resource for toxicology research aimed at the independent testing of chemicals and the development and validation of new and better-integrated toxicology methods, with conscious intent to strengthen the science base in toxicology and provide information about potentially toxic substances to regulatory and research agencies, scientific and medical communities, and the public (Califano 1978; Califano 1979; Walker and Wolfe 2023).

Additionally, the NTP has developed and implemented new toxicological approaches and models focused on better predicting the potential effects of environmental exposures on human health, while aiming to reduce reliance on the use of animals in toxicity testing. Responding to the growing interest in using mechanistic data for predicting potential human health hazards, and with guiding input from leading researchers in academia, industry, government, and nongovernmental organizations, the NTP developed and laid out a roadmap in 2004 to achieve a new vision for toxicology in the 21st century (NTP 2004). This vision called for the NTP to provide data and leadership to advance the *evolution of toxicology from a science largely based on the observation of disease to a science focused on the prediction of disease through collection of mechanism-based, biological observations*. In carrying out its roadmap, the NTP focused on increasing knowledge of the physiological, biochemical, and molecular basis of disease and the development of mechanistic toxicology tools for targeting key pathways, molecular events, or

processes linked to disease or injury to allow transition from predominately mammalian in vivo models toward in vitro systems and nonmammalian models (Bucher and Portier 2004; NTP 2004). This initiative led to the collaborative interagency effort known as Tox21 (Toxicology in the 21st Century), which has provided the conceptual and molecular basis for integrating and understanding toxicity in the broader context of environmentally induced disease and dysfunction (Bucher and Birnbaum 2016; Collins et al. 2008; Tice 2013). The current reimagining is aligned to this evolution of toxicology and should position the NTP to be more *responsive* to emerging toxicological research needs and enable timely *preventative* health decisions.

In addition to its focus on identifying potentially hazardous substances through research and testing, the NTP has been a cornerstone for identifying substances that may cause cancer or noncancer health effects through evaluations of the published literature. We were early adopters of applying systematic review methodology to literature-based assessments that address environmental health questions because systematic review enhances transparency and consistency by documenting the steps, inputs, and decisions made (Birnbaum et al. 2013). Notably, the NTP was given responsibility for preparing the congressionally mandated Report on Carcinogens (RoC) (NTP 1979), one of the world's leading compilations of data on agents, substances, mixtures, and exposure circumstances (collectively called "substances") that pose a cancer risk to humans. Through rigorous processes—including systematic review approaches, which provide opportunity for input from the public, NTP Executive Committee agencies, and external experts—a comprehensive report is prepared for the HHS Secretary; the 15th edition of the RoC was published in December 2021 (NTP 2021). Incorporating the most cutting-edge systematic review tools and other leading approaches, a new handbook for the RoC was released in June 2025 (NTP 2025). The RoC serves as an authoritative source for decision-making and hazard communication by several federal and state agencies (Birnbaum and Bucher 2016; Lunn et al. 2022).

NTP leadership strives to distinguish the NTP through a commitment to open exchange, public scrutiny, impartiality, rigorous peer review, and public access to the knowledge generated by the program, distributed through its website, databases, and scientific publications. As a result, the past 47 years have clearly demonstrated that public health is strengthened by steady NTP leadership in practice and knowledge generation. Its expertise in toxicology and commitment to global leadership have provided innovative approaches to identifying and controlling hazardous substances in our environment to safeguard public health. The NTP has become a trusted global resource, addressing pressing and emerging toxicological needs while adhering to the fundamental principles of independence, transparency, rigor, and quality. The Program has played a critical role in toxicology and regulatory science, adapting and shifting focus and approach as toxicological issues facing public health have evolved (Bucher and Birnbaum 2016).

The Reimagined NTP: The Nucleus of Collaborative Toxicology

Over the past 5 years, partnerships have been strengthened and teamwork enhanced to ensure the NTP remains relevant and impactful. As part of this self-assessment, a new NTP mission statement was crafted—partnering to build knowledge and advance toxicological sciences to protect and promote human health—targeted toward activities that will fulfill an NTP vision of innovative and trusted toxicological science protecting human health (Walker and Wolfe 2023). We have worked to reimagine an "NTP in the 21st century" that can promote a national agenda for toxicological sciences with greater coordination, federal participation, and public engagement. The NTP has a unique opportunity to convene and facilitate dialogue around that agenda both within and outside the federal government. We propose to use the NTP's role as a federal interagency partnership that leverages expertise from across the U.S. Government to credibly focus attention on national and international concerns and, to engage the NTP Executive Committee in dialogue to reach strategic decisions about which initiatives the NTP should pursue.

For the NTP to be successful in addressing contemporary toxicological challenges and emerging public health issues, each of its components—core partners, advisory groups, and operational infrastructure—is essential. Its framework (see Figure 2) includes compartmentalization as well as interconnectedness of NTP operations and oversight. At the highest level, both external and internal groups will advise the NTP director. The NTP Board of Scientific Counselors, a federally chartered group of scientific and public health leaders, will provide external guidance on NTP activities including scientific program content and the scientific merit of NTP's interagency and collaborative programs. The NTP Executive Committee, working together with the NTP Steering Committee (NTP core partners, Figure 1), will identify areas of need or concern and recommend initiatives for decision by the NTP director. Established in 2022, the Office of NTP Scientific Operations and Coordination (ONSOC), with responsibility for the management and coordination of NTP's scientific operations, will provide centralized oversight. ONSOC will work on behalf of the NTP to:

- Foster identification of new NTP initiatives.
- Implement a transparent and comprehensive communication model.
- Establish interagency work groups.
- Develop research strategies and implementation plans.
- Ensure responsive, public-facing communications about the NTP.

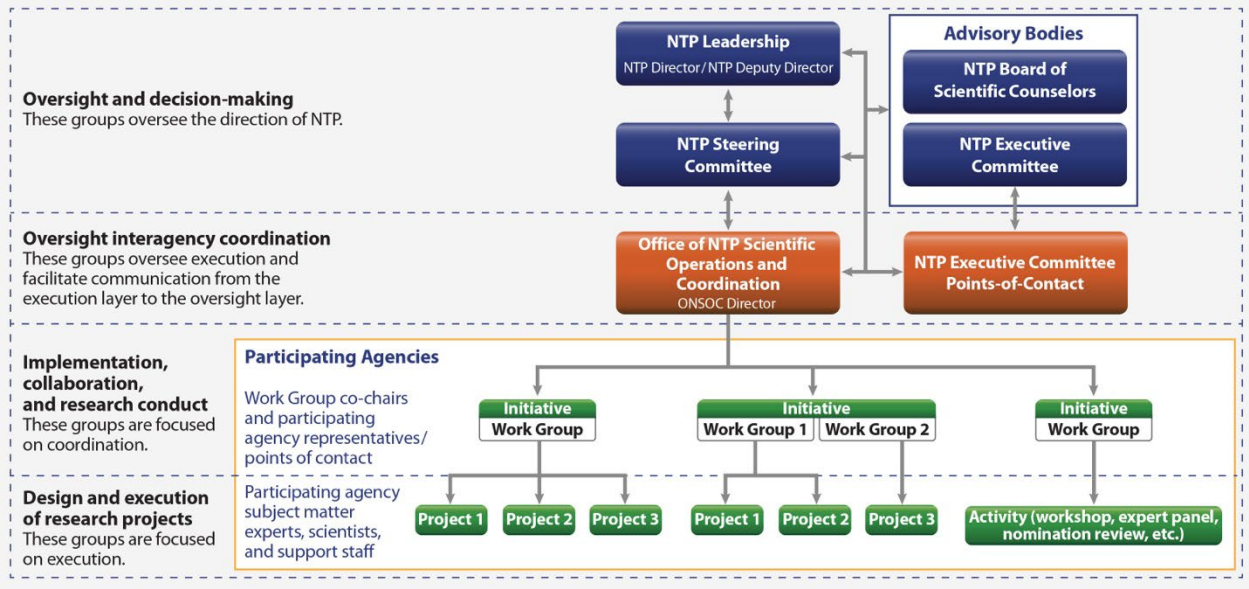

Figure 2. NTP oversight and operations are managed and implemented at different levels. Both internal and external advisory bodies inform NTP decision-making by the NTP director. The newly formed ONSOC plays a central role in implementing, coordinating, and managing NTP's scientific operations. ONSOC is creating a communication network of staff at agencies represented on the NTP Executive Committee, and through focused work groups staffed by subject matter experts, scientists, and support staff, ONSOC will implement NTP initiatives.

The NTP Moving Forward

To effectively carry out those initiatives, we will leverage partnerships and coordinate broadly across the interconnected governmental network and beyond to ensure that NTP initiatives, research investments, and knowledge generation are trusted, innovative, and not duplicative. We have implemented a new holistic operational model for the NTP called 4Cs—Conduct, Collaborate, Coordinate, and Communicate—to guide its engagement as an interagency program (see Figure 3). For example, *Communicate*, the largest and outer sphere, encompasses many past, current, and future activities, including the NTP website, exhibitor-hosted sessions at scientific meetings, public forums, and workshops to bring together scientists to share information and address issues of importance in environmental health sciences. The NTP believes in transparent and clear communication through open dialogue, discussion, and dissemination of information. We also understand the value of stakeholder trust in the NTP and will continue to seek input widely from stakeholders while ensuring independence from undue influence by those affected, positively or negatively, by the outcome of NTP's work.

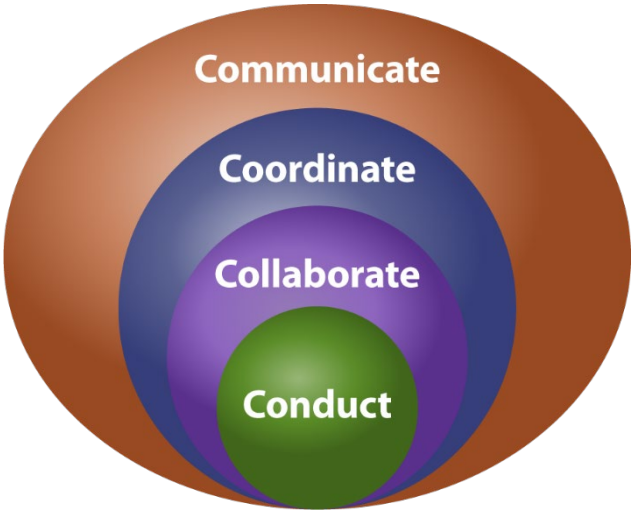

Figure 3. The NTP 4Cs model guides programmatic engagement. The four interconnected spheres provide NTP flexibility in its approach to addressing toxicological challenges and public health issues.

The next sphere in the 4Cs model, *Coordinate*, is exemplified through recent engagement of the NTP with the White House Office of Science and Technology Policy's Subcommittee on Environment, Innovation, and Public Health. As an outcome of this dialogue, the NTP established a multi-agency work group to coordinate federal efforts and share information on 6PPD-quinone. 6PPD-quinone is a degradation product of tire wear associated with acute mortality among some aquatic species, but its potential human health effects are still being assessed. Information exchange among the work group's members is highly effective for identifying where collaboration and additional research might strengthen the science base. We envision the NTP will actively use the work group model to organize and manage other future initiatives.

Historically, the other two components of the 4Cs model—*Collaborate* and *Conduct*—have been central to NTP's culture as part of its 1978 establishment to strengthen HHS activities in testing chemicals of public health concern and developing and validating new and better integrated test methods. Notable past examples include the NTP collaboration with academic partners in the CLARITY-BPA research program, the NTP Nanotechnology Safety Initiative in support of the National Nanotechnology Initiative, and the NTP collaboration on hazards associated with mold exposure in water-damaged buildings. The NIEHS has principally managed and conducted the broad portfolio of previous and ongoing NTP studies evaluating a wide array of environmental substances for a variety of health-related effects. Those efforts include NTP health hazard assessments of chemical, physical, and biological agents for noncancer and cancer health effects. NIEHS in partnership with NCTR and NIOSH will continue to be critical conductors of this work.

For future key activities, we envision through this operational 4Cs model that participation in NTP initiatives will extend beyond the three core partners. New NTP initiatives will be actively coordinated through establishment of work groups that include other federal agencies to share information and identify data needs. Through planning and coordination, the NTP partners will develop collaborations that enable identification of thoughtful, synergistic approaches for tackling the most pressing issues in toxicology science. We envision that opportunities will arise to collaborate on or conduct new toxicology research or health hazard assessments, and those

efforts may involve one or more of NTP's core partners and possibly others within and outside the federal government. We will look for agencies interested in collaborating or conducting projects in support of NTP initiatives to voluntarily use their own resources.

Communication is a core value of the NTP, and as such we will continue to coordinate messages and communicate findings through agency and departmental briefings, NTP Board of Scientific Counselors meetings, the Chemical Effects in Biological Systems database, NTP reports and monographs, and journal publications. Implementation of this operational model will help maximize NTP's potential as an interagency program as its core partners work simultaneously in multiple spheres to address contemporary toxicological problems and public health issues and inform decision-making within the public and private sectors. Additionally, regular review by the NTP Board of Scientific Counselors provides important external advice on the scientific merit and overall quality of the NTP's interagency and collaborative activities. Its input helps ensure that NTP's activities are relevant, scientifically rigorous, and aligned to its mission. Finally, as the media landscape rapidly evolves and moves more online, we will look toward leveraging additional communication platforms as appropriate, including platforms accessed by lay audiences.

We are committed to carrying out the NTP's mission through responsible partnership, management, and planning, underpinned by its values of transparency, openness, and scientific rigor. Moving into 2026 and beyond, the NTP will continue to focus on identifying emerging toxicological challenges and important public health issues and making strategic decisions about what projects to pursue. Implementation of the 4Cs model will provide the NTP flexibility in its approach to addressing those concerns and broaden its positive effect on public health. We look forward to continuing the NTP partnership, building knowledge, and advancing toxicological science that safeguards human health.

Acknowledgments

The authors wish to thank Rick Woychik, Matthew Dahm, Gonçalo Gamboa da Costa, John Piacentino, Dana van Bemmel, Gayle Bernabe, Kelly Shipkowski, and Jesse Saffron for their critical review of this manuscript and their partnership in NTP activities. This work was supported by the NIH, National Institute of Environmental Health Sciences via contracts 75N96025C00003 and GS00Q14OADU417 (Order No. HHSN273201600015U). The contributions of the authors are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the U.S. Department of Health and Human Services.

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