Synergistic Science

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NTP
National Toxicology Program

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

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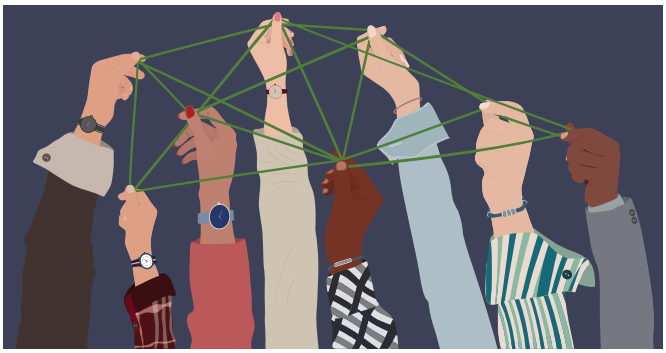
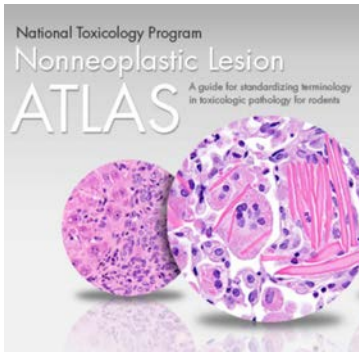
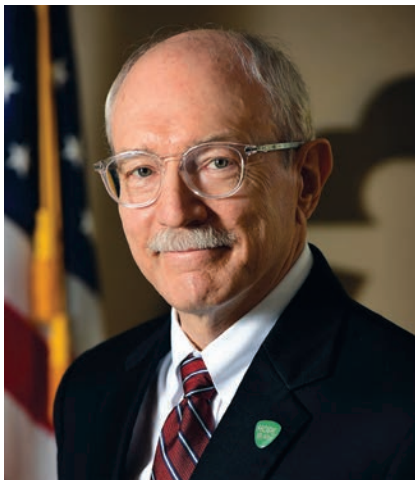







Letter from the National Toxicology Program's Director

Letter from the Director



I am pleased to share with you information about recent initiatives for the National Toxicology Program (NTP) that highlight toxicological research and interagency collaboration and coordination. NTP has made notable advancements in the past two years, including:

- Publication of 10 peer-reviewed reports on substances of concern, including acetoin and 2,3-pentanedione (used in artificial butter flavorings), botanicals, and flame retardants.
- Development of an interactive online tool that demonstrates the Report on Carcinogen's influence and impact on public health.
- Interagency coordination on 6PPD-quinone, an emerging contaminant of concern.

In 2020, we established a vision for an improved interagency NTP model, aiming for greater engagement, coordination, and communication across the core NTP partners: the National Institute of Environmental Health Sciences, the Food and Drug Administration's National Center for Toxicological Research, and the National Institute for Occupational Safety and Health. Throughout the past 2 years, this vision has guided our efforts to ensure NTP's research and other activities align with and address contemporary toxicological issues to safeguard public health. Our interagency model, which is built on four foundational modalities—communication, coordination, collaboration, and conduct—has fostered an environment that prioritizes transparency and cooperation.

NTP's research has resulted in valuable insights into public health concerns such as mold, the antimicrobial agent triclosan, and botanical supplements. Additionally, the interagency coordination on 6PPD-quinone has been critical, bringing together scientists from various federal agencies to address contemporary and emerging concerns related to human health and the environment. We have also emphasized public engagement and transparent communication to ensure our findings are accessible and beneficial to all stakeholders. Our sessions at the 2023 and 2024 Society of Toxicology conferences provided a platform for NTP leadership to discuss key topics related to toxicological studies and public health decision-making.

NTP plays a key role in generating, interpreting, and communicating toxicological information to protect and promote human health.

I invite you to read this report to learn about our work and what we've accomplished. Thank you for your continued support and interest in NTP.

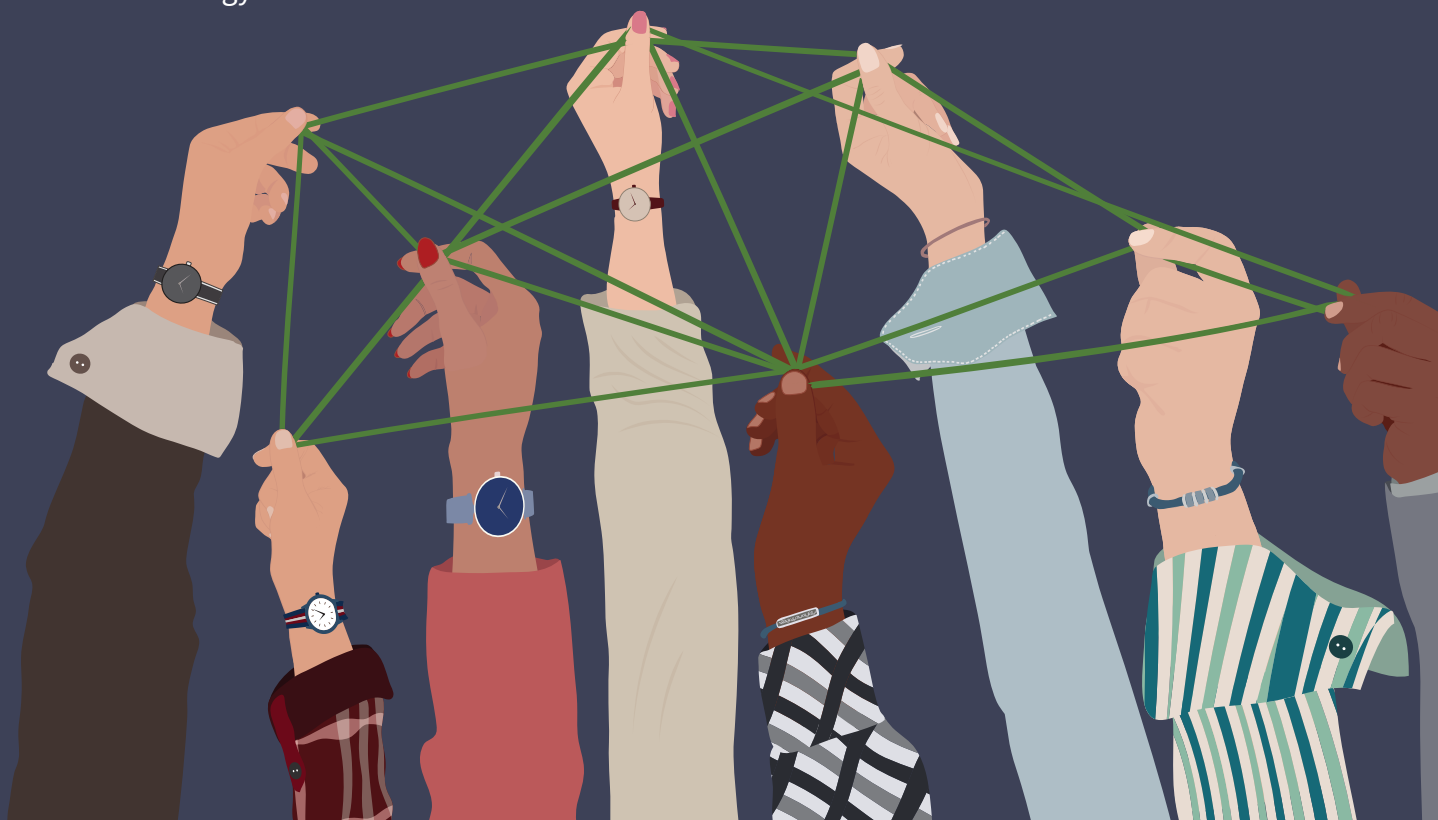
Rick Woychik, Ph.D.
Director, National Toxicology Program and
National Institute of Environmental Health Sciences

1.0.

About the National Toxicology Program

The National Toxicology Program (NTP) is integral to public health protection, providing critical scientific data and tools and promoting interagency collaboration.

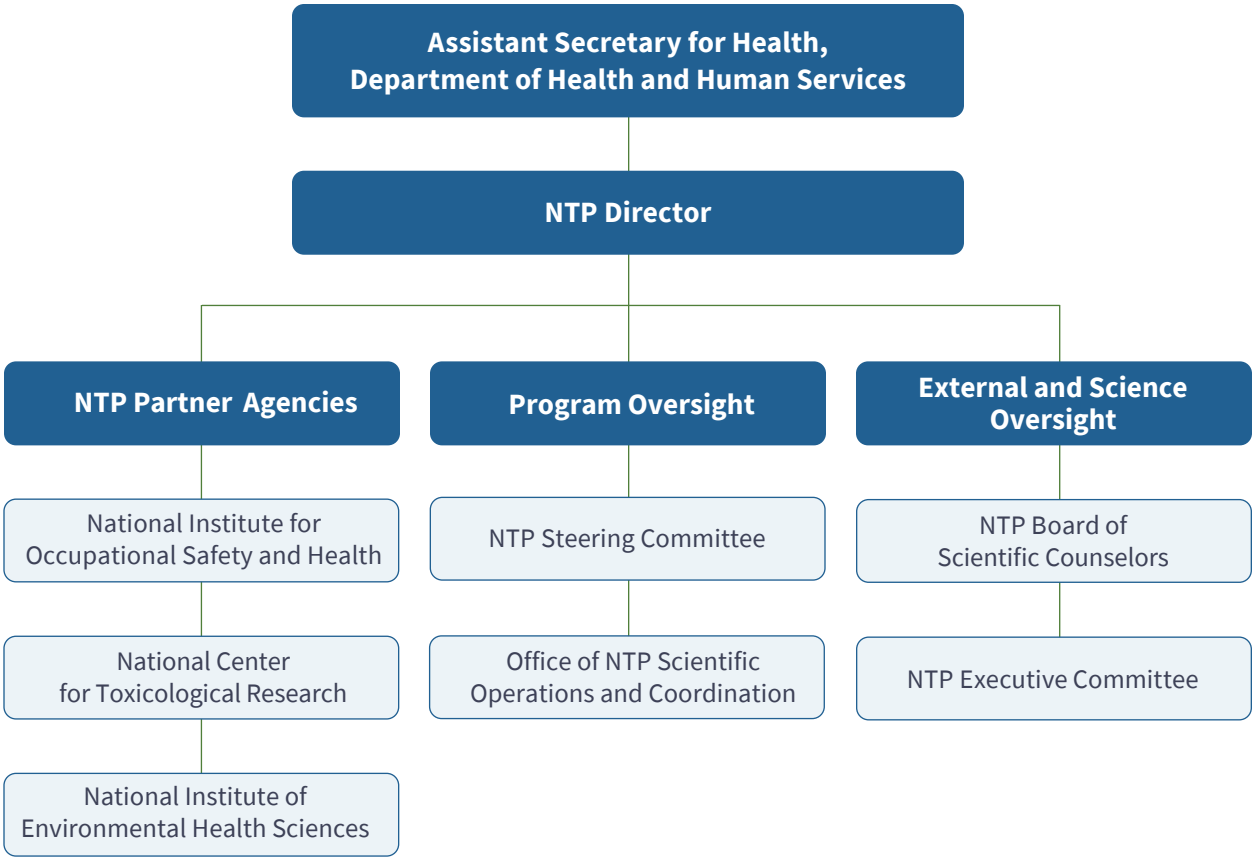
Established in 1978, NTP has played a role in generating, interpreting, and sharing toxicological information about hazardous substances. By leveraging its extensive network of affiliated federal agencies, NTP ensures that toxicological data are accessible and actionable, thereby facilitating public health initiatives and regulatory and policy decisions. Through its rigorous research and collaborative efforts, NTP continues to play a role in safeguarding human health and advancing the field of toxicology.



1.1. NTP Organization

The organizational structure of NTP is designed to facilitate interagency coordination and promote the advancement of toxicological sciences through a collaborative partnership.

NTP includes four main groups: the NTP Steering Committee, the Office of NTP Scientific Operations and Coordination (ONSOC), the NTP Executive Committee, and the NTP Board of Scientific Counselors (BSC). Each group plays a critical role in guiding the Program's strategic direction and ensuring effective oversight.



The **NTP Steering Committee**, led by NTP Director Rick Woychik, Ph.D., is composed of senior leaders from the three NTP partner agencies. This Committee provides high-level guidance and strategic direction for NTP activities. Current members include:

- Heather Patisaul, Ph.D., NTP Deputy Director and Scientific Director of the Division of Translational Toxicology (DTT, formerly the Division of National Toxicology Program), National Institute of Environmental Health Sciences (NIEHS).
- John Howard, M.D., Director of the National Institute for Occupational Safety and Health (NIOSH).
- Tucker Patterson, Ph.D., Director of the National Center for Toxicological Research (NCTR).

Established in 2022, **ONSOC** plays a central role in the implementation of NTP activities and is responsible for the management and coordination of NTP's scientific operations. This office ensures that NTP's research initiatives are aligned with its strategic goals and that there is effective communication, coordination, and collaboration among the NTP partners. The NTP Steering Committee and ONSOC work collaboratively to advance the mission and vision of NTP, ensuring the Program's activities are aligned with the needs of its partners and stakeholders. ONSOC's key areas of focus include:

Fostering *the identification of new NTP initiatives.*

Implementing *a transparent and effective communication model.*

Establishing *interagency work groups to address toxicological public health concerns.*

Developing *research strategies and implementation plans.*

Ensuring *responsive public-facing communications about NTP.*

ONSOC, led by Nigel Walker, Ph.D., NIEHS, includes key representatives from NIEHS, NCTR, and NIOSH:

NIEHS

- Mary Wolfe, Ph.D.
- Gayle Bernabe, Dr.P.H.

NCTR

- Gonçalo Gamboa da Costa, Ph.D.
- Dana van Bemmel, Ph.D.

NIOSH

- CDR Matthew Dahm, Ph.D.
- Christina Lawson, Ph.D.
- John Piacentino, M.D.
- Dale Porter, Ph.D.

The **NTP Executive Committee**, chaired by John Howard, M.D., Director of NIOSH, provides programmatic advice to the NTP Director. The Committee includes representatives from the core NTP partners and key federal agencies such as the Consumer Product Safety Commission, the Department of Defense, the U.S. Environmental Protection Agency, the National Cancer Institute, the National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, and the Occupational Safety and Health Administration. The NTP Executive Committee works together with the NTP Steering Committee and ONSOC to identify and address contemporary public health challenges and emerging issues in toxicology.

The **NTP BSC**, governed by provisions of the Federal Advisory Committee Act, provides external scientific advice to NTP. The NTP BSC advises on the scientific program content and scientific merit of NTP's interagency and collaborative programs and provides external scientific guidance on NTP activities.

1.2. NTP Operations

NTP's organizational structure is designed to foster collaboration, enhance communication, and ensure toxicological research is conducted in a scientifically rigorous and transparent manner.

The NTP partners have instituted a new interagency model built on four foundational modalities, the 4 Cs: communication, coordination, collaboration, and conduct. These modalities are designed to enhance and increase interagency engagement across NTP projects. While recognizing that not all NTP activities will encompass all four modalities, NTP leverages these pillars to engage in various types of activities, ensuring a comprehensive and integrated approach to its mission. This model not only enhances interagency coordination but also increases engagement across NTP projects, ultimately contributing to the advancement of public health.

Through open communication, the NTP partners are well informed and actively involved in decision-making. Coordination efforts streamline activities and optimize resources, allowing for more efficient and effective research and information-sharing. Collaboration brings together the expertise and resources of NTP partners with other federal agencies, creating a synergistic environment that drives innovation to advance toxicological sciences. Finally, the conduct modality ensures all research activities are carried out with the highest standards of scientific integrity and transparency.

This comprehensive approach has strengthened NTP's ability to address contemporary toxicological issues and emerging public health concerns.

COMMUNICATION

Open dialogue keeps partners informed and engaged in decision-making.

COORDINATION

Streamlined efforts optimize resources for efficient research.

COLLABORATION

Partnerships with federal agencies drive innovation in toxicological sciences.

CONDUCT

Research follows the highest standards of integrity and transparency.

1.3. Recent Events and Highlights

DECEMBER 15, 2022

NTP Board of Scientific Counselors Meeting

The Board reviewed three "contract concepts" related to the provision of chemistry, toxicology, and pathology support services to NIEHS for NTP research. The Board unanimously approved the use of contract mechanisms to obtain these research support services.

MARCH 20, 2023

NTP Exhibitor-hosted Session at the Annual Society of Toxicology (SOT) Conference

NTP leadership shared information about NTP, its research, and current activities to enhance the federal partnership between NCTR, NIEHS, and NIOSH.

MAY 4 AND 16, 2023

NTP Board of Scientific Counselors Meeting

Members deliberated on the report of the Board Working Group that evaluated the adequacy of NTP's responses to external peer review and/or federal agency comments regarding NTP's state-of-the-science monograph on fluoride and the corresponding meta-analysis manuscript. At the May 4 meeting, the Board voted to accept the Working Group Report in full, except for one item. The Working Group reexamined and revised this item. The Board accepted this revision at the May 16 meeting, and the Board Chair then transmitted the final version of the Working Group Report to the NTP Director.

JULY 11, 2023

NTP Board of Scientific Counselors Meeting

The Board reviewed a contract concept to provide predictive toxicology and evidence integration support capabilities to NIEHS for NTP research. The Board unanimously approved using a contract mechanism to obtain these research support services.

MARCH 12, 2024

NTP Exhibitor-hosted Session at the Annual SOT Conference

NTP leadership highlighted the Program's interagency activities and its research, products and tools, and the NTP work group model, highlighting activities of the Interagency 6PPD-Quinone Work Group.

2.0.

Recent Publications, Impact, and Other Activities

Collaboration between core NTP partners, other federal agencies, and the scientific community is essential for advancing the field of toxicology and addressing public health concerns.

This collaborative approach enables NTP to leverage a wide range of expertise and resources. By engaging and coordinating with scientists from various disciplines and federal agencies, NTP can tackle complex environmental health challenges more effectively and strategically. Transparent communication of research findings helps inform regulatory decisions, guide health policies, and raise awareness about potential health risks. NIEHS, primarily through DTT, along with NCTR and NIOSH, carry out toxicological research in support of the NTP.

2.1. Completed NTP Reports and Publications

The findings of NTP studies and research projects are published in the following types of NTP reports:

- NTP Technical Reports, which document long-term studies to evaluate the potential toxicity and carcinogenic activity of substances.
- NTP Developmental and Reproductive Toxicity Reports, which document the potential of substances to affect development and reproduction.
- NTP Toxicity Reports, which document short-term studies to evaluate the potential toxicity of substances.
- NTP Immunotoxicity Reports, which evaluate the potential of substances to damage the immune system.
- NTP Research Reports, which provide the results of research studies, rapid communications, and literature surveys that do not fall under the scope of the other report series.
- NTP Monographs, which document the assessments for whether exposure to substances causes adverse health effects.
- Report on Carcinogens (RoC) Monographs, which document cancer hazard assessments prepared on candidate substances selected for possible listing in the Report on Carcinogens.

All published NTP reports are peer reviewed by experts who are screened for conflict of interest before confirming their service.

From October 2022 through October 2024, NTP published three technical reports, five toxicity reports, one research report, and one monograph.

REPORT SERIES	REPORT NUMBER	SUBSTANCE OR TOPIC ADDRESSED	PUBLISHED DATE
NTP Technical Report	602	Isomeric Mixture of Tris(chloropropyl) Phosphate	June 2023
	603	Black Cohosh Root Extract	December 2023
	604	Triclosan	May 2024
NTP Toxicity Report	104	(+)-Usnic Acid	October 2022
	105	*Usnea* Lichens	October 2022
	106	Sodium Metavanadate and Vanadyl Sulfate	February 2023
	98	Acetoin and 2,3-Pentanedione	March 2023
	107	*Stachybotrys chartarum*	October 2024
NTP Research Report	19	Trend Test for Binary Data	November 2023
NTP Monograph	08	State of the Science Concerning Fluoride Exposure and Neurodevelopment and Cognition	August 2024

In addition to these recently completed and published reports, there is ongoing NTP research on other substances and topics. The NTP Website has a full list and provides free access to NTP publications and related data and other research topics. There are also additional materials and updated information for completed and ongoing research available on the NTP Website, including links to fact sheets on an array of topics and supporting files for endocrine disruptor screening studies for various UV filters.

2.2. Research Highlights

NTP has a broad mandate to provide toxicological characterizations for chemicals and agents of public health concern and strives to balance the selection of substances for study.

This mandate has resulted in a multi-faceted research program with emphasis on synthetic industrial chemicals, pesticides, drugs, metals, and food additives. NTP continues to explore new areas of research. In general, these initiatives are wide-ranging and include various health-related endpoints. This section highlights research topics that one or more NTP partner agencies (NCTR, NIEHS, or NIOSH) carried out in support of NTP.

Artificial Butter Flavorings

Artificial butter flavorings (ABF) components are widely used in the food industry to impart a buttery taste and aroma to various products.

These flavorings chemicals, such as diacetyl (2,3-butanedione) and acetoin, have been linked to respiratory issues in workers exposed to their vapors. In 2000, eight employees at a microwave popcorn packaging plant were diagnosed with bronchiolitis obliterans—a rare lung disease. Subsequently, a NIOSH health hazard evaluation identified 2,3-butanedione and acetoin as the major volatile ABF constituents. NIEHS/DTT conducted inhalation studies of ABF constituents in rodents to understand their potential toxicity. The NTP report on 2,3-butanedione (NTP 2018) investigated potential health effects, including respiratory toxicity and carcinogenicity. NTP short-term toxicity studies of acetoin and 2,3-pentanedione, detailed below, were published in March 2023. The findings from these studies have been crucial in setting inhalation exposure limits to protect workers' health. By providing valuable data and insights, NTP's research on ABF components plays a significant role in ensuring workplace safety and advancing scientific understanding of chemical exposures. Additional information is available on the NTP Website.

Acetoin and 2,3-Pentanedione

Acetoin and 2,3-pentanedione are both naturally occurring and synthetically produced substances that provide a characteristic "butter" flavor and aroma. Both chemicals are used primarily as ingredients in ABF formulations, and acetoin is also widely used in perfumes and essences. NIEHS/DTT conducted 2-week and 3-month inhalation studies to better understand the effects of the ABF components acetoin and 2,3 pentanedione on the respiratory tract. Because of concerns about respiratory toxicity from 2,3 butanedione, 2,3 pentanedione has been used as a replacement in some ABFs. However, 2,3 pentanedione is structurally similar and has been reported to present similar toxicological potency; thus, NTP selected it for further study. Under the conditions of these studies, rats and mice exposed to 2,3 pentanedione for 3 months showed significant respiratory tract toxicity, as well as significant eye toxicity, whereas acetoin did not cause toxicity at significantly higher concentrations.

Botanical Dietary Supplements

Dietary supplements, including botanical supplements, are widely used across the United States. FDA regulates dietary supplements under the Federal Food, Drug, and Cosmetic Act (FD&C Act) as a category of foods.

FDA does not approve supplements for safety and effectiveness; rather, dietary supplement firms are responsible for evaluating the safety and labeling of their products before marketing to ensure they meet all of the requirements of the FD&C Act and FDA's regulations. FDA is responsible for any action against any unsafe or otherwise unlawful dietary supplements, which typically occurs after the products enter the marketplace. This can present particular concerns when considering the potential effects botanical supplements can have on the body, depending on the doses consumed and the presence of other substances. Because of the consequences that improper safety evaluations and labeling can have on consumers, NTP aims to conduct studies and provide data that assist the public, health care professionals, industry, and regulators to make informed decisions. NTP studies continue to assist FDA in its monitoring of the dietary supplement market. Additional information on botanical supplements is available on the NTP Website.

Black Cohosh Root Extract

Black cohosh root extract (BCE) is used for various purposes in women's reproductive health, such as stimulating labor or relieving menopausal symptoms. To understand the long-term and potential cancer-related effects of this supplement, NIEHS/DTT conducted 2-year rat and mouse studies to mirror women's exposure throughout pregnancy and lactation. In the rat study, which looked at rats exposed to BCE throughout gestation and lactation, pup (infant) weights declined with increased levels of BCE, total and live litter sizes decreased in groups exposed to BCE, and the body weights of mothers exposed to BCE were lower than the weights of those not exposed. Neoplasms (tumors) were observed in the uterus of rats exposed to the highest dose of BCE, but evidence that BCE causes uterine cancer was uncertain. For rats exposed, BCE was also observed to lead to other health effects, such as dilation, hemorrhage, thrombus, and ulcers in the uterus. Mice exposed to BCE had decreased body weights and disruption of normal hematological processes.

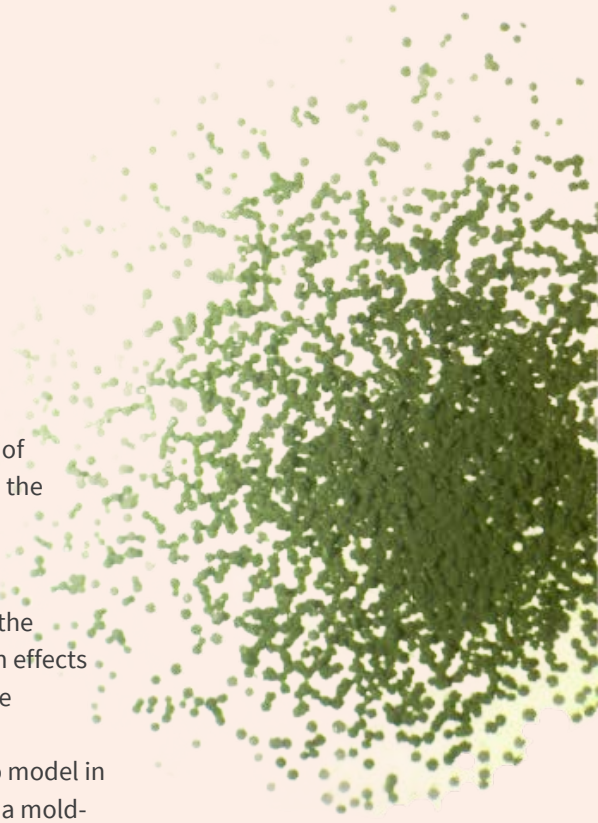
Usnea Lichens and Usnic Acid

Usnea lichens are a genus of lichens and a source of usnic acid. They have been used historically in traditional herbal medicines as bactericidal and antimicrobial agents. The use of usnic acid as an ingredient in dietary and weight-loss supplements has come under scrutiny due to concerns regarding adverse events affecting the liver, including severe liver damage (hepatoxicity) (Guo et al. 2008). Two companion NTP studies were published in October 2022. NCTR and NIEHS/DTT investigated the effects of 3-month dietary exposures to (+)-usnic acid and *Usnea* lichens in rodents to identify potential toxicity in humans.

In the TOX-104 study, 3-month dietary exposure to (+)-usnic acid was hepatotoxic in male rats at doses above 120 ppm but was less toxic in female rats such that only the highest dose of 720 ppm elevated serum enzymes and disrupted the estrous cycle. (+)-Usnic acid was relatively nontoxic to male and female mice at the exposure concentrations used in this study.

In the TOX-105 study, short-term dietary exposure to ground *Usnea* lichens appeared to be more toxic than equivalent concentrations of pure usnic acid that were used in the companion study.

Mold



Molds are a type of fungus found everywhere in the environment and are encountered every day.

Exposure can occur by direct contact, ingestion, or inhalation of spores and fragments. Most molds are not harmful; however, exposure to some species of mold can cause negative health effects, including respiratory effects such as the development or worsening of asthma, and nonrespiratory effects such as dermal irritation or neurological symptoms.

Wet environments provide the perfect growth conditions for mold and with the occurrence of water damage or flooding events, the potential adverse health effects associated with mold exposure in indoor water-damaged environments have increased public concern. To investigate potential health effects associated with exposure to mold, NIOSH developed an acoustical generator system to model in rodents the natural exposure that a worker or occupant would encounter in a mold-contaminated environment.

The first set of studies on mold focused on *Aspergillus fumigatus*, which is found abundantly in indoor, outdoor, and occupational environments. NIOSH studies found that exposure of mice to live *A. fumigatus* caused adverse effects in the lung versus air only or heat-inactivated particles (Buskirk et al. 2014; Croston et al. 2016; Nayak et al. 2018; Nayak et al. 2016). NIOSH and NIEHS/DTT then conducted 3-month inhalation studies in mice as an NTP collaboration to investigate the toxicological response of exposure to *A. fumigatus.* The studies found that live *A. fumigatus* caused effects in the larynx, lung, and bronchial lymph nodes. These results built on the NIOSH findings and demonstrated that the effects of *A. fumigatus* exposure could be enhanced by the viability of the spores.

The second set of studies focused on *Stachybotrys chartarum* ("black mold"), which is commonly found in soil and as a contaminant in water-damaged building materials. NIOSH studied two different isolates of *S. chartarum* and found that exposure to fungal fragments was the leading driver for the immune system's response in the lung (Croston et al. 2020; Lemons et al. 2019). Additionally, as an NTP collaboration, NIOSH and NIEHS/DTT conducted 3-month inhalation studies in mice to investigate the toxicological response to *S. chartarum.* Live *S. chartarum* caused effects in the larynx, lung, and bronchial lymph nodes versus air only or heat-inactivated particles. These reults built on the NIOSH studies and demonstrated that immunological and toxicological effects could be mediated by live *S. chartarum.*

Vanadium Compounds

Vanadium is a metal that occurs naturally in the earth's crust and in minerals. Human exposure occurs mostly by ingesting vanadium present in food, drinking water, and dietary supplements.

To better understand how ingesting vanadium compounds can affect human health, NIEHS/DTT studied their effects in mice exposed to sodium metavanadate or vanadyl sulfate through drinking water, beginning in adolescence and over the course of 3 months, and in rats exposed throughout gestation and lactation and over the course of 3 months after weaning.

While tests of these compounds' ability to cause DNA damage were mostly negative, other effects were observed. Under the conditions of these studies, the 3-month exposure of rats and mice to sodium metavanadate and vanadyl sulfate resulted in hematological effects, such as decreased red blood cell size and increased incidences of noncancerous abnormalities in the intestines, primarily increased cell growth in the lining of the small intestine.

Flame Retardants

Flame retardants are chemicals applied to materials to prevent the start—or slow the growth—of fires.

These chemicals are widely used in various products, including furnishings, electronics, and building materials, to enhance fire safety. However, flame retardants are associated with potential health risks, including endocrine disruption, reproductive toxicity, and adverse effects on fetal and child development. Due to their persistence in the environment and potential for bioaccumulation, flame retardants are a significant concern for both human health and the environment, emphasizing the need for safer alternatives.

Isomeric Mixture of Tris(chloropropyl) Phosphate

Tris(chloropropyl) phosphate (TCPP) is an organophosphorus flame retardant (OFR) produced as an isomeric mixture. TCPP is found in textiles, furniture foam and similar products, paints, coatings, and adhesives and has been proposed as a replacement for other structurally similar OFRs that were removed from commercial products due to concerns about toxicity. Consequently, the expected rise in TCPP usage has raised concerns about increased human exposure through ingestion, skin contact, and inhalation.

In light of limited publicly available data on the toxicity of TCPP and at the request of the Consumer Product Safety Commission, NIEHS/DTT initiated a research program to assess the health effects in rats and mice of different exposures and durations of exposure to TCPP. These studies found TCPP has the ability to cause cancer in rats and mice as well as an increase in the occurrence of noncancerous lesions in the liver and kidney. Additional research is needed to better understand this relationship and what it could mean for humans.

Fluoride Exposure and Neurodevelopment and Cognition

Fluoride is a common environmental exposure that comes from various sources and is widely recognized for its dental and overall oral health benefits.

Contributions to an individual's total exposure come primarily from fluoride in drinking water, food, beverages, and dental products. A 2006 National Research Council (NRC) evaluation found support for an association between high levels of fluoride in drinking water and adverse neurological and cognitive effects in humans. Since the NRC evaluation, there has been an increase in the number and location of studies examining these health effects.

In 2016, NTP initiated a systematic review of the published human, animal, and mechanistic literature to evaluate the extent and quality of the evidence linking fluoride exposure to neurodevelopmental and cognitive effects in humans. In 2024, NTP released its findings in a State of the Science Monograph after undergoing rigorous scientific evaluation. The findings showed, with moderate confidence, that higher levels of fluoride exposure, such as drinking water containing more than 1.5 milligram of fluoride per liter (mg/L), were associated with lower IQ in children. The NTP monograph was designed to evaluate total fluoride exposure from all sources and was not designed to evaluate the health effects of fluoridated drinking water alone. The evaluation found no evidence that fluoride exposure had adverse effects on adult cognition.

The moderate confidence in the inverse association between fluoride exposure and children's IQ was based primarily on epidemiology studies in non-U.S. countries, where some pregnant women, infants, and children had total fluoride exposures higher than 1.5 mg/L of drinking water. There were insufficient data to determine whether the low fluoride level of 0.7 mg/L currently recommended for U.S. community water supplies has a negative effect on children's IQ. More research is needed to better understand whether there are health risks associated with low fluoride exposures.

2.3. NTP Regulatory Science Impact

NTP research contributes study data and is used by federal and state health regulatory and research agencies to inform science-based decision-making and help protect human health.

Examples of recent final rules and regulations informed by NTP research are highlighted below:

Federal Regulatory Updates

Environmental Protection Agency (EPA) | **Perfluorooctanoic Acid**

- EPA designated perfluorooctanoic acid (PFOA), including its salts and structural isomers, as hazardous substances under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (EPA 2024). EPA considered substantial evidence from epidemiological and toxicological studies indicating that human exposure to PFOA is linked to adverse human health effects. NTP's Technical Report 598 (NTP 2023) was cited as support that exposure to PFOA may pose a hazard based on evidence of carcinogenic effects in long-term animal studies.

Food and Drug Administration (FDA) | **Brominated Vegetable Oil**

- FDA revoked the authorization for the use of brominated vegetable oil in food (effective August 2, 2024) based on NTP dietary studies in rodents that found thyroid toxicity and bioaccumulation of lipid-bound bromine at doses relevant to human exposure (FDA 2024; Woodling et al. 2022).

California Regulatory Updates

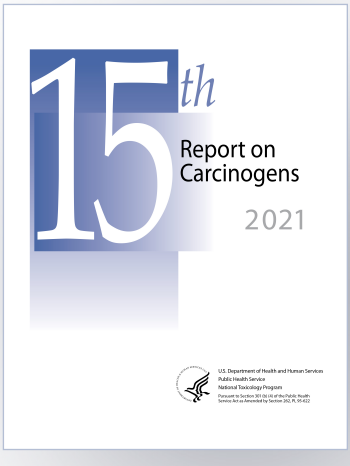
Office of Environmental Health Hazard Assessment (OEHHA) | **1-Bromopropane**

- OEHHA adopted a new cancer inhalation unit risk (IUR) and slope factors for 1-bromopropane (1-BP) for use in the Air Toxics Hot Spots Program (OEHHA 2022). IURs are used to estimate lifetime cancer risks associated with inhalation exposure to a carcinogen. OEHHA used the animal data from NTP Technical Report 564 (NTP 2011) to derive the IUR factor. Additionally, OEHHA cited several other NTP publications as supporting data regarding the carcinogenicity of 1-BP, including the Report on Carcinogens Monograph (RoC Monograph-01), NTP Technical Reports 206, 210, 321, and 350, and the Chemical Effects in Biological Systems (CEBS) database.

The NTP Website has a more extensive list of NTP studies and citations used in regulatory settings, including draft guidelines, final guidelines, rules, and regulations.

2.4. Report on Carcinogens

The RoC is a science-based, cumulative public health report required by law 42 U.S.C § 241(b)(4). The RoC identifies cancer hazards—such as mixtures, exposure circumstances, and chemical, physical, and biological agents— as *known* or *reasonably anticipated to cause cancer* in humans.



It is one of the top public interest resources viewed on the NTP Website, and the current 15th edition of the RoC was the most downloaded NTP resource in 2024. The RoC is used by a wide array of audiences, including the public, scientific community, and health research and regulatory agencies, to inform decision-making.

For over 40 years, the RoC has had a major influence on cancer prevention efforts. Listings in the RoC have been used by regulatory agencies to help prioritize chemical evaluations, support regulatory-based assessments, and influence regulatory actions (Mackar 2024). A new interactive online tool (Mehta et al. 2023), allows users to explore how these cancer hazard assessments influence public health regulations and policies.

In addition, several states and federal agencies use the RoC as an authoritative source of information in communicating the listed hazards to workers and the public (Mackar 2024; Mehta et al. 2023). In 2023 and 2024, the RoC was cited in over 10 final rules and one regulation. In addition to the 256 substances currently listed in the 15th edition of the RoC, there are ongoing evaluations of substances including halogenated flame retardants, parachlorotrifluorotoluene, selected nitropolycyclic aromatic hydrocarbon compounds, polycyclic aromatic hydrocarbons, and wood smoke.

Key Points

- *Scientific, public health document identifying substances that pose a cancer hazard.*
- *Lists a substance as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen.*
- *Includes information on 256 listings.*
- *Prepared by NTP for the Secretary of the Department of Health and Human Services.*

2.5. Interagency Coordination

6PPD-Quinone: A Contaminant of Emerging Concern

6PPD [*N*-(1,3-dimethylbutyl)-*N'*-phenyl-p-phenylenediamine] is a chemical used to protect tire rubber from degrading (forming cracks) and to make tires last longer. Concerns have been raised about the breakdown of 6PPD when it reacts with ozone and forms 6PPD-quinone (6PPD-Q).

As vehicles travel, their tires undergo constant wear and tear, resulting in the release of tiny particles known as tire wear particles that can enter stormwater-affected creeks, streams, and other water bodies and have potential environmental effects. This could lead to aquatic species being exposed to 6PPD-Q.

Coho salmon seem to be particularly sensitive to the toxic effects of 6PPD-Q from urban runoff and leaching from tire wear particles. 6PPD-Q has been found in runoff at levels high enough to cause death among juvenile coho salmon in the Pacific Northwest of the United States (Tian et al. 2021).

Interagency 6PPD-Quinone Work Group

In 2023, the White House Office of Science and Technology Policy's National Science and Technology Council Joint Subcommittee on Environment, Innovation, and Public Health (JEEP) identified 6PPD-Q as an emerging contaminant. In response to this outreach, NTP, in coordination with JEEP, formed an interagency work group to share information about research and other activities occurring across the federal government on 6PPD-Q and to facilitate coordinated efforts. This work group focuses on understanding the potential effects of 6PPD-Q exposure on human health, although its coordination effort is broader and includes ecotoxicology and environmental toxicology, reflecting the variety of activities, expertise, and research interests of the participating agencies. The goals of this information-sharing are to raise agencies' awareness about the extent of federal research, identify activities that are complementary, reduce duplicative effort, and focus research on key data needs that advance scientific understanding of 6PPD-Q exposure.

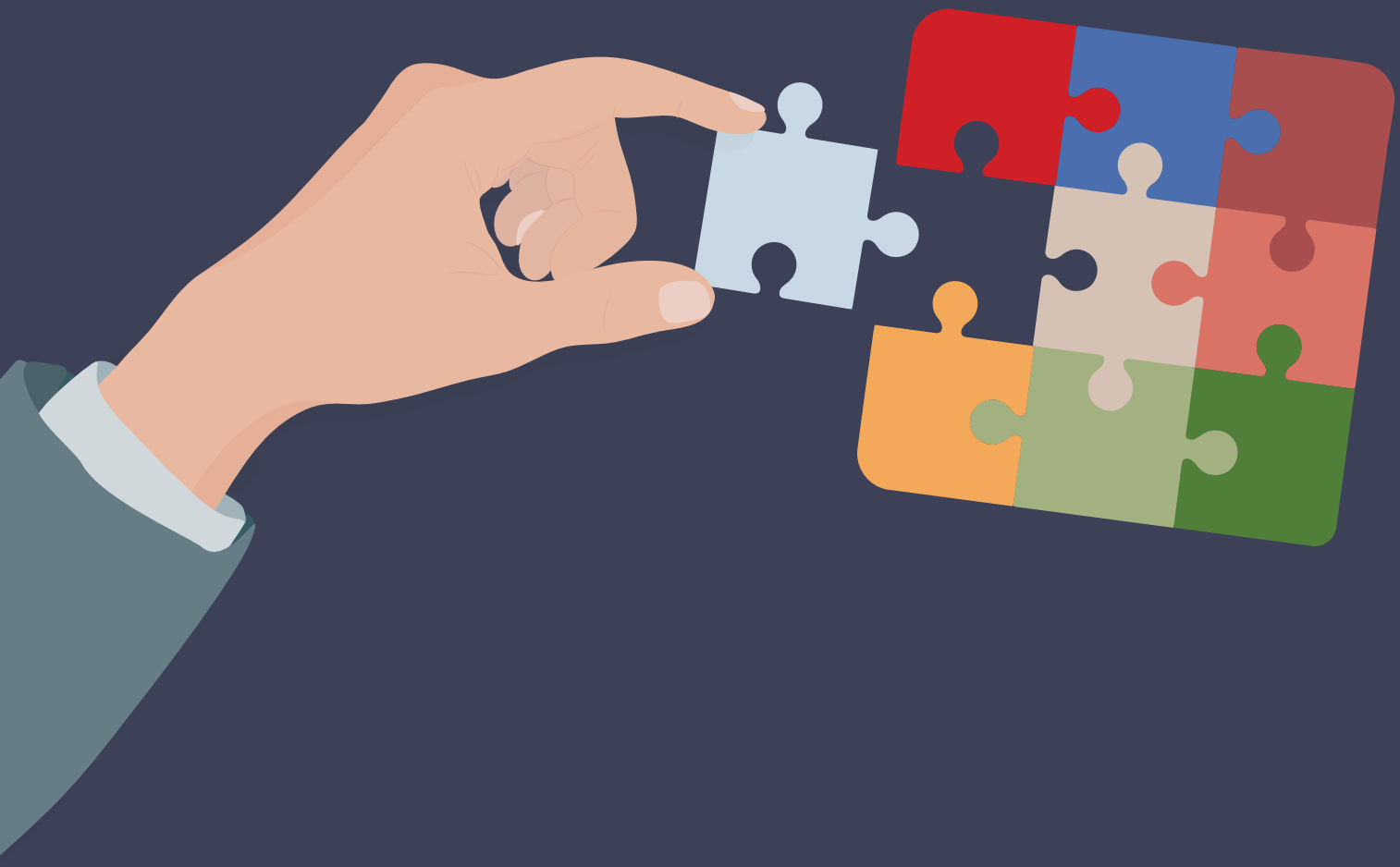
For NTP, the implementation of its new operational work group model, which embraces the 4 Cs, provides a mechanism to foster cross-governmental communication and coordination on an emerging environmental issue in a timely, collaborative, and effective manner.

The work group includes members from:

- National Center for Environmental Health/Agency for Toxic Substances and Disease Registry
- National Institute for Occupational Safety and Health
- National Institute of Environmental Health Sciences
- National Institute of Standards and Technology
- National Oceanic and Atmospheric Administration
- Office of Science and Technology Policy
- U.S. Department of Defense
- U.S. Department of Energy
- U.S. Department of Transportation
- U.S. Environmental Protection Agency
- U.S. Fish and Wildlife Service
- U.S. Food and Drug Administration
- U.S. Geological Survey

The NTP 6PPD-Q web page includes publicly available resources, such as literature search portals, data resources, publications, and other information on 6PPD-Q.

3.0.
Resources



3.1. Data and Tools

NTP offers a comprehensive suite of powerful tools designed to advance and inform scientific research.

Among those tools are the Chemical Effects in Biological Systems (CEBS) database, which integrates decades of research on chemical safety, the NTP Nonneoplastic Lesion Atlas, which documents tissue changes in laboratory animals in response to chemical exposures, and the NTP Archives, which provide historical data from over 2,000 NTP studies. Additionally, an interactive dashboard associated with the Report on Carcinogens provides users easy access to comprehensive data on substances *known* or *reasonably anticipated to cause cancer* in humans. These resources, along with other tools developed by the National Institute of Environmental Health Sciences, such as the Integrated Chemical Environment platform, are accessible through user-friendly interfaces and are regularly updated with new scientific discoveries. These tools and others, found on the NTP Website, play a role in advancing scientific knowledge for the protection of public health.

NTP Website

Over 1 million views *by users from 209 countries/territories.*

The NTP Website offers numerous resources and sections with comprehensive information on toxicology, environmental health, and the scientific research conducted by the NTP partners in support of NTP to assess the potential health effects associated with exposure to substances such as chemicals, botanicals, physical agents, mixtures, and drugs. In 2023 and 2024, the NTP Website had over 1 million views by users from the United States and around the world. In addition to the United States, visitors to the NTP Website represent a broad international audience, from as many as 208 countries/territories in the last two years. The website features NTP research findings, ongoing research efforts and collaborations in toxicology, and links to tools and databases that support NTP's research. The website's design focuses on user-friendly access to toxicological research through an enhanced navigation system that includes search capabilities, clear pathways to information, and improved organization of NTP research findings and publications. The streamlined interface, complete with accessibility features and direct access to key resources, reflects NTP's commitment to making toxicological data and hazard assessments easily accessible to all users.

CEBS Database

*Integrates data from **over 4 decades** of NTP research.*

As the primary database used by NTP to store and share information, CEBS integrates data from over four decades of NTP research on chemical safety into accessible formats for public use. The database helps scientists understand how chemicals can affect health in rodents, including the effects on organs, genes, reproduction and development, immune system function, brain function, and the development of cancer. CEBS combines both historical and current research, making it easy for researchers to access this information through a user-friendly website. Users can download datasets or analyze the data for their research. CEBS additionally offers helpful tools that allow users to search for information, create charts and graphs, and connect with other scientific databases. These features can help researchers find patterns in the data, leading to better understanding and decision-making about chemical safety.

NTP Archives

*Includes a vast collection from **over 2,100** NTP studies.*

Since 1984, the NTP Archives has served as the definitive repository for toxicological research in the United States, maintaining a vast collection that includes millions of specimens, images, and research documents from over 2,100 NTP studies. The Archives is more than a storage facility; it represents a living library of toxicological knowledge. The facility maintains world-class educational materials and training resources on rodent pathology, including specialized pathology training sets and high-quality digital images of histopathological lesions, all available through a simple request process (subject to approval), with expert staff ready to guide users to relevant materials. The Archives maintains these materials according to rigorous standards, ensuring their preservation for future generations of researchers.

Nonneoplastic Lesion Atlas

*Refined **over 10 years** to make research more efficient, reliable, and collaborative.*

The NTP Nonneoplastic Lesion Atlas serves as a guide for understanding how exposure to substances affects human health by documenting tissue changes in laboratory animals. Each entry in the Atlas combines carefully selected pictures with clear explanations, helping researchers identify important tissue changes that are not cancerous. The Atlas adheres to international standards for naming and describing these changes, while retaining some unique features that match NTP's historical research. This balance ensures that new findings can be compared with decades of previous studies. In FY 2024, the Atlas was the most viewed section of the NTP Website.

Refined over 10 years, the Atlas is designed to make research more efficient, reliable, and collaborative. Its intuitive interface allows researchers to quickly access the tools they need, compare results across studies, and build on previous findings. Regular updates keep the Atlas current with new scientific discoveries, while maintaining a consistent approach to evaluating tissue changes. In this way, the Atlas serves as a useful tool for training pathologists and scientists and facilitating researchers working together worldwide.

Report on Carcinogens Data Exploration Dashboard

*Designed for exploring and visualizing **256 substances**.*

The Report on Carcinogens (RoC) Data Exploration Dashboard is designed for exploring and visualizing the 256 substances currently listed in the 15th RoC. This tool provides a comprehensive overview of the substances, including their listing status of *known* or *reasonably anticipated to be a human carcinogen*, and primary uses. Users can navigate through the data to understand the associations between these substances and various types of cancer, making it a valuable resource for researchers, policymakers, and public health professionals.

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