

Occupational and Inhalation Exposures Program

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Problem Statement

Inhalation exposure to substances that are potentially harmful—in both the workplace and our everyday environments—can cause adverse health effects to the respiratory tract and other organ systems. Experimental studies that evaluate the toxicity and carcinogenicity of inhaled substances are challenging to design and conduct due to the complex methods and systems required to characterize, deliver, and monitor exposures in the laboratory testing environment. Nonetheless, robust hazard characterization is critical to creating safe living and working environments and reducing the disease burden associated with inhalation exposures. In addition to inhalation, exposure via skin contact that results in allergic and irritant dermatitis constitutes a portion of occupational health issues.

Objectives

The Occupational and Inhalation Exposures (OIE) program is one of three programs in the Division of the National Toxicology Program's (DNTP) Exposure-based Research strategic area of focus. The purpose of the programs in this strategic area is to solve contemporary public health problems related to environmental and occupational exposures and improve our ability to carry out substance-based hazard evaluations that are more translational, innovative, and responsive.

Over many years, DNTP has worked with partners to develop scientific and engineering capabilities to design and construct complex inhalation exposure generation and monitoring systems for vapors, gases, liquid aerosols, particles, and fibers. In preparation for collaborative studies on fungal particles, National Institute for Occupational Safety and Health (NIOSH) investigators developed an acoustical generator system for the aerosolization of fungal test articles. Exposure to physical agents (e.g., radiofrequency radiation [RFR]) presents many of the same challenges for a rigorous evaluation in experimental settings. As an example, DNTP leveraged expertise to design, construct, and qualify a novel exposure system to evaluate the potential health effects of RFR, using engineering features similar to those of the inhalation systems. The investment in these fundamental capabilities and relationships enables DNTP to design and conduct studies to model human exposures to a broad variety of chemical, biological, and physical substances. The OIE program will extend and expand these capabilities to provide impactful human-relevant data for specific public health concerns identified by stakeholders.

The OIE program has the following objectives:

1. Assess the human health hazard potential of current and emerging airborne substances of concern to the general population and in the workplace using a tailored combination of traditional and alternative experimental approaches to address substance-specific key data needs.
2. Predict adverse human health effects to the airways and lungs and generate mechanistic data to support human health risk assessments through the evaluation and utilization of human-

relevant microphysiological systems (e.g., air-liquid interface (ALI) cell cultures and lung-on-chip systems).

3. Enhance the human translational relevance of in vivo and in vitro experimental models for evaluating airborne exposures via the application of novel tools and refinement of traditional approaches (e.g., human exposure studies, literature-based assessments, physiological monitoring of animals for in vivo studies, specialized histopathology techniques, and use of humanized rodent models).

Rationale

Public Health Context

According to NIOSH, fatalities from respiratory diseases and cancers caused by inhalation exposures account for approximately 70% of all occupational disease deaths. Respiratory diseases caused by occupational inhalation exposures include those affecting the large and small airways, such as allergy/asthma and fibrosis; interstitial (fibrotic) lung diseases, such as silicosis/asbestosis; pleural disease; and lung cancers. These adverse health effects can be linked to acute or chronic (high- or low-dose) inhalation exposures in a wide variety of workplace settings and range from mild, reversible conditions to progressive, irreversible and/or fatal disorders. Inhalation exposures to toxic compounds tend to occur more frequently in occupational settings, although the general population can also be exposed to similar hazards via inhalation in the environment or through consumer use. However, the magnitude of exposures in the workplace tends to be relatively higher compared with lower-level exposures for the general population. Although noninhalation routes of exposure are important in the context of workplace health hazards (e.g., dermal sensitization), the OIE program focuses primarily on the cause of adverse health effects to the respiratory tract and other organ systems after inhalation exposure.

Alignment with Mission, Goals, Strategic Pipeline

The OIE program aligns strongly with the DNTP goal to generate and communicate trusted scientific information to support decision-making on environmental hazards of public interest. Results from hazard characterization studies enable mitigation of health risks related to exposures by providing information for establishing safe industrial or environmental exposure levels. In addition, this program will actively engage stakeholders and subject matter experts, in coordination with other programs in DNTP and the National Institute of Environmental Health Sciences (NIEHS), to enhance the goal of developing and applying innovative tools and strategies for addressing occupational/inhalation toxicology. This program will also examine current in-house approaches and processes to evaluate translatable toxicological responses more effectively and efficiently. Research within the OIE program will use and integrate numerous aspects of the DNTP Translational Toxicology Pipeline that include systematic review, human exposure assessment, in vitro approaches using human and rodent models, and short- and long-term in vivo approaches. The OIE program will focus on improving the management of multiple parallel processes to increase the operational efficiency of the pipeline and ultimately decrease the time required to deliver information to stakeholders.

Stakeholder Interest and Engagement

Stakeholder engagement to date has been primarily with other federal agency partners. DNTP leverages and values the resources from these federal agencies to ascertain public, industry, and regulatory viewpoints on inhalation and occupational hazards and actively collaborates with some of these partners through interagency agreements (IAAs). These IAAs create a foundation for idea generation, data sharing, and resource sharing. In addition to the IAAs, several DNTP research programs and projects have originated from unique collaborations with NIOSH and the Environmental Protection Agency (EPA), and these agencies continue to monitor our ongoing progress, as well as provide relevant human exposure data, method development information, and advice on project prioritization and risk assessment needs. Agencies such as the Agency for Toxic Substances and Disease Registry (ATSDR), Occupational Safety and Health Administration (OSHA), Food and Drug Administration (FDA), Federal Communications Commission (FCC), National Cancer Institute (NCI), and United States Geological Survey (USGS) are also stakeholders for specific DNTP projects related to inhalation and/or occupational exposures.

Ongoing and Continuing Interactions

Stakeholder	Issue	Role of Stakeholder
ATSDR	Community exposures to naturally occurring asbestos	Partner, user
NIOSH	Asbestos, alpha-pinene, abrasive blasting agents, fungal particles, per-and polyfluoroalkyl substances (PFAS), nanomaterials	Partner, collaborator
EPA	Asbestos, alkylbenzenes, rodent physiological monitoring	Partner, user
FCC	Responsible for regulations and compliance pertaining to radiation emissions of communication equipment and devices (e.g., mobile phones)	Partner, user
FDA	ALI models, asbestos, RFR	Partner, collaborator
IT'IS Foundation*	RFR system design, engineering, and construction	Collaborator, technical advisor
NCI	Human health effects of RFR exposure	Partner
NIST**	RFR exposure system design and validation	Collaborator, technical advisor
OSHA	Trimethylsilyldiazomethane (TMSD), asbestos	Partner, user
USGS	Generation and characterization of Libby amphibole asbestos fiber test material	Partner
Battelle	Primary contract partner for the development of inhalation exposure generation and monitoring methods and conduct of in vivo and in vitro inhalation studies	Service provider

*Foundation for Research on Information Technologies in Society.

**National Institute of Standards and Technology.

Depending on the project, interested agencies provide input on DNTP testing strategies and research directions, aid in method development, and advise on priority risk assessment needs. For example,

DNTP engaged with the Interagency Asbestos Working Group (members include EPA, NIOSH, FDA, OSHA, NIST, U.S. Consumer Product Safety Commission [CPSC]) and Libby Action Plan Workgroup (members include EPA, ATSDR, USGS) when developing a project to address outstanding data gaps regarding the health effects of asbestos. In a second example, EPA has provided technical advice to enhance our capabilities for monitoring human-relevant physiological outcomes in rodents during inhalation exposures. EPA's experience with physiological monitoring technologies aided in the design of pilot studies and provided valuable insight into data management strategies, which is a long-term goal of the OIE program.

In accordance with its mission to protect worker health and safety, NIOSH conducts collaborative research projects with DNTP to assess exposure and health effects for occupational substances of mutual interest. These IAA-funded projects allow NIEHS and NIOSH to leverage resources and expertise and reduce undue duplication of effort. These assessments provide critical information for DNTP to contextualize the results of in vivo rodent studies, as well as to inform testing priorities and choices related to exposure paradigms and concentrations. Current collaborative projects include occupational exposure assessments and in vivo rodent studies of the following inhaled substances: fungal particles, graphene and other two-dimensional nanomaterials, emerging PFAS, and alpha-pinene and related monoterpenes.

Much of the work managed within the OIE program leverages the extensive inhalation engineering and exposure capabilities of Battelle Memorial Institute (Battelle) via a research and development contract. Capabilities include the design, construction, and utilization of generation systems capable of exposing rodents to various substances via whole-body or nose-only inhalation. DNTP, in consultation with Battelle, the National Center for Toxicological Research (NCTR), and NIOSH, is building robust capabilities for in vitro exposures using microphysiological systems (e.g., ALI and lung-on-chip platforms). Furthermore, organizations such as NIST and IT'IS Foundation have provided technical expertise regarding the development of novel exposure systems for RFR.

The OIE program will continue to present numerous opportunities for engagement on ongoing projects and to facilitate the development of new capabilities. Going forward, efforts will increase to forge relationships with a broader array of stakeholders with shared interests and to communicate scientific findings to interested groups and to the public.

Milestones and Metrics

The OIE program consists of a large portfolio of related projects, many of which align to more than one of the program objectives. Likewise, individual projects often use and integrate multiple approaches and capabilities. Accordingly, the metrics of program success and project milestones are presented separately for each objective. Milestones are grouped by expected timeframe as short term (1 year), medium term (2–3 years), and long term (4–5+ years). All research conducted as part of the OIE program yields publicly available information that is housed in the Chemical Effects in Biological Systems (CEBS) database and in publications of key findings in the NTP technical report series and/or peer-reviewed scientific journal articles.

Objective 1: Assess the human health hazard potential of current and emerging airborne substances of concern to the general population and in the workplace using a tailored combination of traditional and alternative experimental approaches to address substance-specific key data needs.

- Close out certain existing projects by discontinuing any further work (tungsten fibers, nanocrystalline cellulose) that is hampered by logistical challenges associated with inhalation exposure generation (short term).
- Publish technical reports on shorter-term toxicity studies of specific molds, artificial butter flavorings, and C8- and C9-alkylbenzenes and chronic toxicity studies of alpha-pinene and multiwalled carbon nanotubes (short–medium term), which provide data to characterize the toxicity/carcinogenicity of these materials and evaluate potential human health concerns; conduct and report chronic toxicity studies of mixed xylenes (long term).
- Establish exposure system (short term) to conduct follow-on studies of RFR, including evaluations of behavior/stress, thermal effects, and DNA damage and repair (medium term). Evaluate additional exposure paradigms and wireless technologies relative to the initial studies and report findings in a timely manner to inform public health decisions (long term).
- Report studies associated with development of methods for generation of asbestos fiber atmospheres and assessment of lung burden in asbestos-exposed rats (short term), report short-term toxicity studies of Libby amphibole fibers (medium term), and conduct/report chronic toxicity studies of Libby amphibole fibers to provide comprehensive, high-quality data to address fundamental questions that will add context to human exposure and provide data for use in risk assessment (long term).
- Monitor and respond to public health concerns that may arise by designing and conducting studies tailored to addressing the specific question or concern in a timely manner.

Objective 2: Predict adverse human health effects to the airways and lungs and generate mechanistic data to support human health risk assessments through the evaluation and utilization of human-relevant microphysiological systems.

- Establish in vitro airway/lung exposure and toxicity evaluation capabilities (short term) and conduct pilot studies to optimize experimental and assay conditions (medium term); qualify these in vitro models within the framework of a defined context of use (medium term).
- Evaluate multiple previously tested chemical compounds using in vitro airway/lung capabilities systems and compare/correlate the results of a subset of previous in vivo studies (medium term).
- Incorporate these new platforms, depending on utility in the context of our research, into projects aimed at evaluating the potential respiratory toxicity of agents, either alone or in combination with other approaches (long term).

Objective 3: Enhance the human translational relevance of in vivo and in vitro experimental models for evaluating airborne exposures via the application of novel tools and refinement of traditional approaches.

- Implement the use of monitoring human-relevant endpoints (respiration, heart rate, and blood pressure) to enhance husbandry and housing of rodents (short term) and establish baseline data for their use in the context of inhalation exposures (medium term). Incorporate these endpoints into inhalation and other toxicology studies (long term).
- Leverage the NIEHS/DNTP-NIOSH IAA to evaluate occupational exposures to joint chemicals of mutual interest including 2D nanomaterials (short term), PFAS (medium term), and monoterpenes (long term). NIOSH reports and publications will inform future decision-making on potential occupational exposure standards and will evaluate potential hazards to human health.
- Use methods for thoroughly evaluating lung, visceral, and pleural tissues in rats chronically exposed to Libby amphibole fibers (medium term). Discuss findings from these enhanced

methods in study reports in the context of the literature on human pathology and disease associated with asbestos exposure (long term).

- Conduct and report literature-based cancer health hazard assessment for p-Chloro- α,α,α -trifluorotoluene (PCTFT)

Value Proposition and Summary

The value of the OIE program is exemplified by the past and current successes of DNTP research related to inhalation and occupational exposures. For many years, stakeholders have relied on DNTP to provide trusted science to facilitate decision-making specifically for occupational exposures and/or inhalation toxicity. For example, institutions or federal agencies, such as the EPA, NIOSH, OSHA, American Conference of Governmental Industrial Hygienists (ACGIH), and the International Agency for Research on Cancer (IARC), have used our study results for hazard classification of various environmental or industrial chemicals. Hazard classification with solid scientific evidence allows for a change in industry standards, as well as protections for the general population. Furthermore, results from DNTP inhalation toxicity studies have been used to adjust or establish new permissible exposure limits for workers. These processes mitigate risk and disease burden in the workplace.

DNTP has established robust and unique capabilities to conduct state-of-the-art hazard assessments for inhalation/workplace exposures, enabled by internal resources and external partnerships with federal agencies and contract research laboratories. Through these partnerships, DNTP has the experienced personnel and specialized facilities required for performing these complex exposure studies that represents a rare, if not unique, research infrastructure. Beyond the capabilities for in vivo animal research, DNTP partnerships with other agencies allow for human exposure assessments. The cumulative data collected from animal studies and human assessments provide a more comprehensive evaluation of human health. This long-term investment allows DNTP to address the health hazards of recognized and emerging substances of concern via inhalation and other complex exposure routes that are applicable to the general public and workplace settings.

Not only is the OIE program poised to conduct state-of-the-art hazard assessments, it is also well-positioned to advance the field of inhalation toxicology. Recognized technical challenges for assessing inhalation toxicity with in vitro models (e.g., exposure systems for volatile chemicals, capturing accurate physiological parameters) are currently being addressed by the implementation of microphysiological systems including ALI and lung-on-chip platforms. These new tools and approaches aim to increase the efficiency and translatability of in vitro or animal work for human risk assessment. To our knowledge, no other organization has the resources and established infrastructure to systematically and robustly evaluate their context of use, include them routinely in research/testing paradigms, and make their data publicly available, in a robust or timely manner. By thoroughly investigating these novel technologies, DNTP will effectively expand its available tools for responding to specific stakeholder needs, as well as provide guidance about the value of these tools and data to the broader scientific community and to the public.