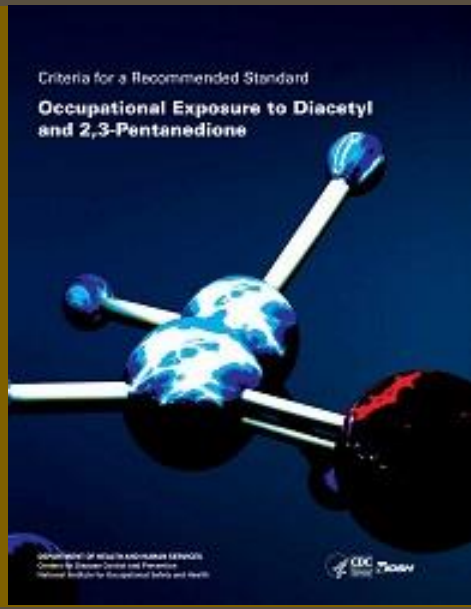
The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

John Piacentino, MD, MPH

Associate Director for Science, NIOSH

National Toxicology Program
Board of Scientific Counselors
February 15, 2019

NIOSH and the National Toxicology Program



National Toxicology Program was established in 1978 to:

- Coordinate toxicology testing programs within the federal government.
- Strengthen the science base in toxicology.
- Develop and validate improved testing methods.
- Provide information about potentially toxic substances to health, regulatory, and research agencies, scientific and medical communities, and the public.

https://ntp.niehs.nih.gov/about/index.html

NIOSH NTP Partnership

- Characterize occupational exposure to agents of mutual interest to NTP and NIOSH and assess potential health effects
- Workers exposure is greater than non-workers
- Capitalize on NIOSH access to worker populations and work sites to provide real-world context for toxicology studies
- Guide decision-making for NIOSH epidemiologic studies
- Provide toxicologic and epidemiologic evidence for guidance documents

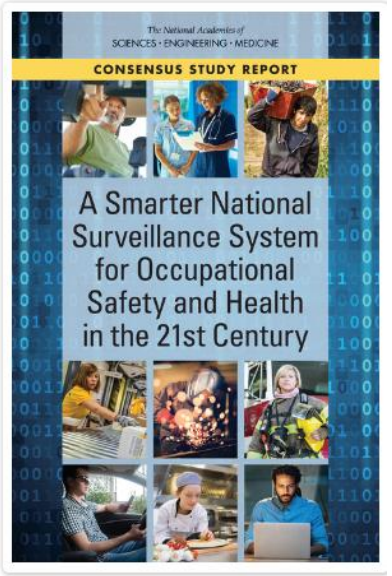
Human Exposure Assessment Studies

Selected Human Exposure Assessment Studies

- Indium
- 1-Bromopropane
- Diacetyl
- Manganese fractions in welding fume
- Carbon nanotubules and carbon nanofibers
- Bisphenol A
- PAHs and coal tar sealant applications
- Flame retardants
- PFAS

Smarter Surveillance for the Future

- National Academies of Sciences report on a smarter national surveillance system
- Prioritize and coordinate OSH surveillance
- Improve data collection
- Expand biomedical informatics use and capabilities
- Strengthen data analysis and information dissemination for prevention



http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24835

Direct Reading and Sensor Technologies

Related Topics

Aerosols

Nanotechnology

Follow NIOSH

Facebook

Flickr

Pinterest

Twitter

YouTube

NIOSH Homepage

NIOSH A-Z

Workplace Safety & Health Topics

Publications and Products

Overview

Direct-reading methods and sensors are being used more frequently in many different settings ranging from personal monitoring of individual health to applications in research and in clinical practice. NIOSH began organized research in this area in 2008 with the creation of the DREAM initiative (Direct Reading Exposure Assessment Methods). NIOSH will build upon and expand the DREAM program to address lessons learned, advances in technology, and stakeholder contributions. NIOSH researchers have developed a number of direct-reading methods and monitors and are exploring new ways to use these technologies to improve occupational safety and health.

The use of sensors has increased exponentially as countless remote wireless sensors are now employed for monitoring the environment, work sites, disaster response, "smart" buildings and facilities, and in agriculture and health. Wireless data transfer based on cell phone networks and smart phone technology is enhancing the adoption of these sensors, and allowing integration of geographically disperse sensors to produce comprehensive exposure pictures. Wearable and even implantable sensors are being developed that could aid in exposure assessment and clinical practice.

NIOSH Center for Direct Reading and Sensor Technologies

The NIOSH Center for Direct Reading and Sensor Technologies (NCDRST) was established in May 2014 to coordinate research and to develop recommendations on the use of 21st century technologies in occupational safety and health. The NCDRST is a virtual center hosted by the NIOSH Division of Applied Research and Technology and the NIOSH Exposure Assessment Cross Sector Program.

NCDRST Objectives

1. Coordinate a national research agenda for direct-reading methods and sensor technologies. Research on these technologies has been incorporated into the goals of the NIOSH Strategic Plan for fiscal years 2019-2023.
2. Develop guidance documents pertinent to direct-reading methods and sensors, including validation and performance characteristics;
3. Develop training protocols; and
4. Establish partnerships to collaborate in the Center's activities.

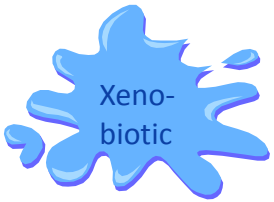
Can we ever get away from human studies?

- Missing information
  - There is an inherent variability with observing occupational exposures to humans. This leads to an advanced understanding of human behaviors, observances of differences in susceptibility, differences in work processes and exposures.
  - This variability is hard to simulate in predictive studies
- Bridging uncertainty
  - The ultimate goal is to gauge toxicity in humans. This seems to be an important anchor for corroborating information from other study designs or bridging areas of uncertainty.
- Benefits to workers, employers and NIOSH
  - Workers, employers and NIOSH benefit from establishing research collaborations to better understand the workplace, how toxins may affect human health, and know more about workplace hazards.

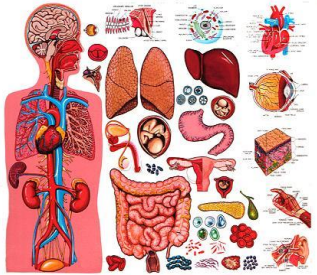
Immunotoxicity of Workplace Xenobiotics

Targeted Risk Assessment of Xenobiotics Overview

- NIOSH uses a multidisciplinary approach to rapidly evaluate biological responses to occupational toxins.
- The goal is to provide assessment of potential toxicity within 6 months to a year instead of 10 years—95% faster.



Testing	Develop an exposure method for animal testing
	Identify potential health effects
	Identify the mechanism of toxicity
	Characterize dose response



Cancer
Cardiovascular
Immune
Nervous
Pulmonary

Example of subchronic immunology and toxicology studies

- NTP B6C3F1/N mice
- Test articles
  - *Aspergillus fumigatus* B-5233/ATCC 13073 conidia
  - *Stachybotrys chartarum* (2 mycotoxin producing strains)
  - *Aspergillus versicolor* (Vuillemin) Tiraboschi ATCC 9577/NRRL 238
- Heat inactivated conidia used as a biological/particulate control
- Mice exposed twice/week for 13 weeks and then euthanized at 24 or 48 hours after the final exposure
- Endpoints – 1) pulmonary inflammation, clinical pathology, (2) immune and molecular endpoints and histopathology 3) cardio (4) neuro

Outcomes

- Developed an exposure system that simulates occupational fungal exposures and/or mimics the conditions found in damp or water-damaged buildings.
- Mice exposed repeatedly to viable *A. fumigatus* demonstrate pulmonary inflammation, airway remodeling, and germination of fungal spores in vivo.
- Mice exposed repeatedly to viable *S. chartarum* demonstrate pulmonary inflammation, a mixed Th1 and Th2 response, and pulmonary arterial hyperplasia.
- These studies are providing critical information on the potential toxicity of fungi in the environment using a relevant exposure paradigm.

Evolution of NIOSH approach to examining the immunotoxicity of xenobiotics

Question	Current	Future
What are the long term health effects associated with a xenobiotic?	Conduct a long term animal studies for 1-2 years	Use long term cell culture models (e.g. up to 6 months) with a comparison to animal models
Are cellular interactions required for a toxic effect?	Conduct an animal study for 28 days	Use 2 and 3D cell culture models for 14-21 days to assess chemical and cellular interactions
What biomarkers predict toxicity in animals?	Conduct an animal study for 28 days	Conduct proteomic or metabolomics studies in animals over 7 days and use *machine learning* approaches to predict earlier biomarkers of toxicity
Does this xenobiotic cause sensitization?	Conduct an animal study for 6 weeks	Develop and publish allergenicity screening tests using *in vitro* systems in 30 -60 minutes

Subject Matter Expertise and Impact

Examples of subject matter expertise

Report on Carcinogens	Office of Health Assessment and Translation Reviews
• Trichloroethylene • Cadium • Cobalt • 1-Bromopropane • O-toluidine • Formaldehyde • Styrene • Shift work	• Bisphenol A • Chemotherapy Use During Pregnancy • Low-level Lead • Risk of bias workshop

Impact of the NIOSH-NTP Collaboration Internally

- Findings inform testing priorities
- Guides selection of relevant laboratory test exposures and doses (e.g. carbon nanotubes)
- Has led to the development of methods for generation of laboratory test exposures (e.g. welding and asphalt fumes)
- CNT/CNF findings used in NIOSH guidance to reduce the recommended exposure limit from 7 $\mu g/m^3$ to 1 $\mu g/m^3$

Examples of International Impact Beyond NTP

- 1-Bromopropane study findings were used as part of IARC determination of 1-BP as a Group 2B carcinogen
- Nordic Expert Group used CNT/CNF findings for a criteria document to be used by regulatory authorities as the scientific basis for setting occupational exposure limits

NIEHS Spurs NIOSH to Develop Occupational Systematic Review

Accepted: 14 August 2017
DOI: 10.1002/ajim.22771

COMMENTARY

WILEY AMERICAN JOURNAL OF INDUSTRIAL MEDICINE

Using systematic review in occupational safety and health

John Howard | John Piacentino | Kathleen MacMahon | Paul Schulte

National Institute for Occupational Safety and Health, Washington, District of Columbia

Correspondence
John Howard, National Institute for Occupational Safety and Health, 395 E Street, S.W., Suite 9200, Washington, DC 20201.
Email: zkz1@cdc.gov

Evaluation of scientific evidence is critical in developing recommendations to reduce risk. Healthcare was the first scientific field to employ a systematic review approach for synthesizing research findings to support evidence-based decision-making and it is still the largest producer and consumer of systematic reviews. Systematic reviews in the field of occupational safety and health are being conducted, but more widespread use and adoption would strengthen assessments. In 2016, NIOSH asked RAND to develop a framework for applying the traditional systematic review elements to the field of occupational safety and health. This paper describes how essential systematic review elements can be adapted for use in occupational systematic reviews to enhance their scientific quality, objectivity, transparency, reliability, utility, and acceptability.

KEYWORDS
evidence integration, occupational safety and health assessment, systematic review, weight of evidence

National Toxicology Program
U.S. Department of Health and Human Services

Search

Testing Information | Study Results & Research Projects | Public Health | About NTP

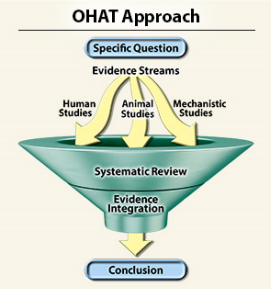
Home » Public Health » About OHAT » **OHAT Systematic Review**

Health Assessment and Translation

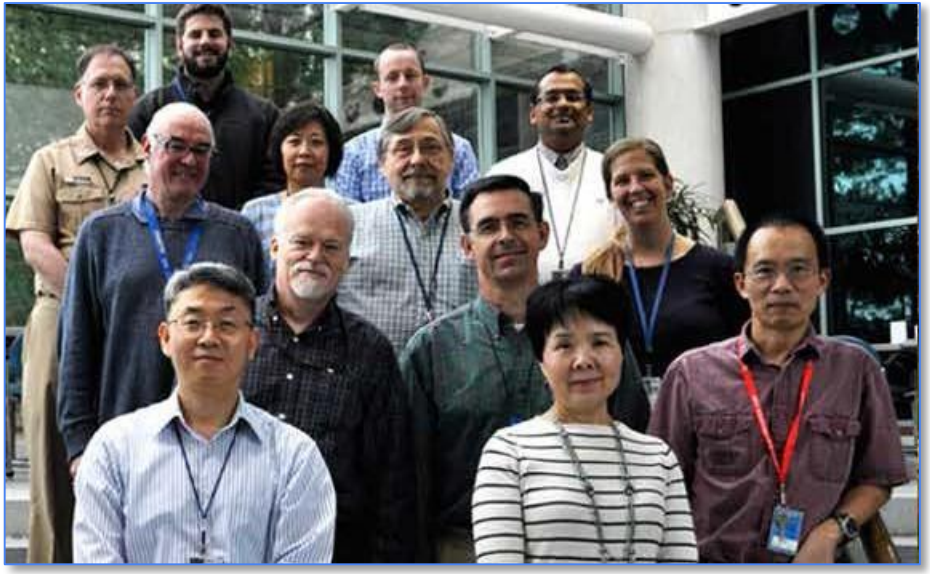
- OHAT Systematic Review
- Completed Reports
- Ongoing Evaluations
- Topics Under Consideration
- Nominate a Topic
- Contact OHAT

OHAT Systematic Review

The NTP Office of Health Assessment and Translation (OHAT) develops literature-based evaluations to reach conclusions about potential human health hazards and to examine the state of the science. In 2012, OHAT began exploring and developing an approach for implementation of systematic review methodology to carry out these evaluations (Birnbaum et al. 2013). The output from an evaluation can vary including, but not limited to: NTP Monograph, state-of-



Thank you to NIOSH staff



Thank you to all of our partners

John Piacentino, MD, MPH
Associate Director for Science
National Institute for Occupational Safety and Health
jpiacentino@cdc.gov

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov