NIOSH Portfolio in Support of the National Toxicology Program

John Piacentino, MD, MPH

Associate Director for Science, NIOSH

National Toxicology Program
Board of Scientific Counselors
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Presentation Outline

About NIOSH Partnerships

Principles of Successful Partnerships

- Mission alignment
- Planning and development of activities
- Work inside and outside of the partnership
- Coordinating internally
- Reconciling timelines
- Meeting federal requirements
- Managing intellectual property
- Demonstrating success

About NIOSH Partnerships

NIOSH Mandate

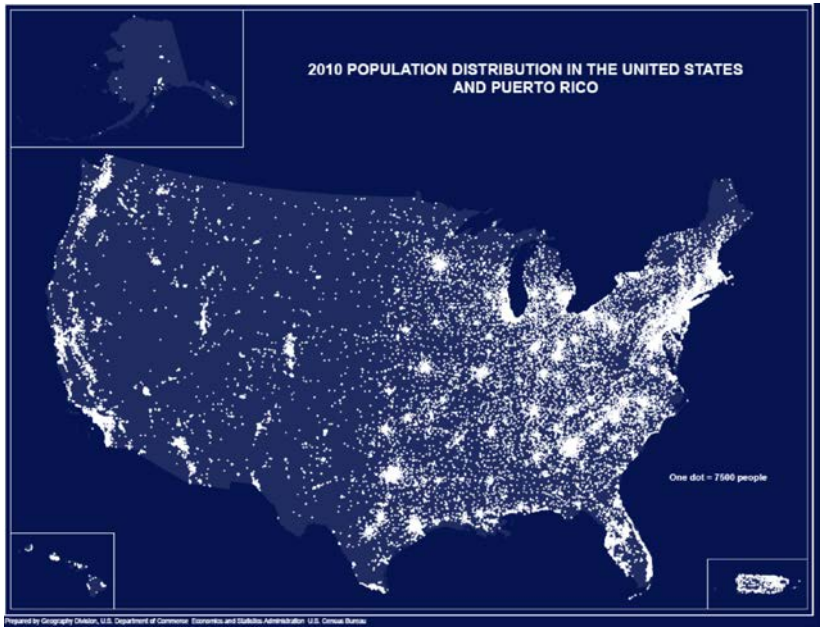
NIOSH has the mandate to assure “every man and woman in the Nation safe and healthful working conditions and to preserve our human resources.”

Occupational Safety and Health Act of 1970

US Workforce Statistics

Around 160 million workers in the United States[1]

$250 billion in medical costs and productivity losses[2]



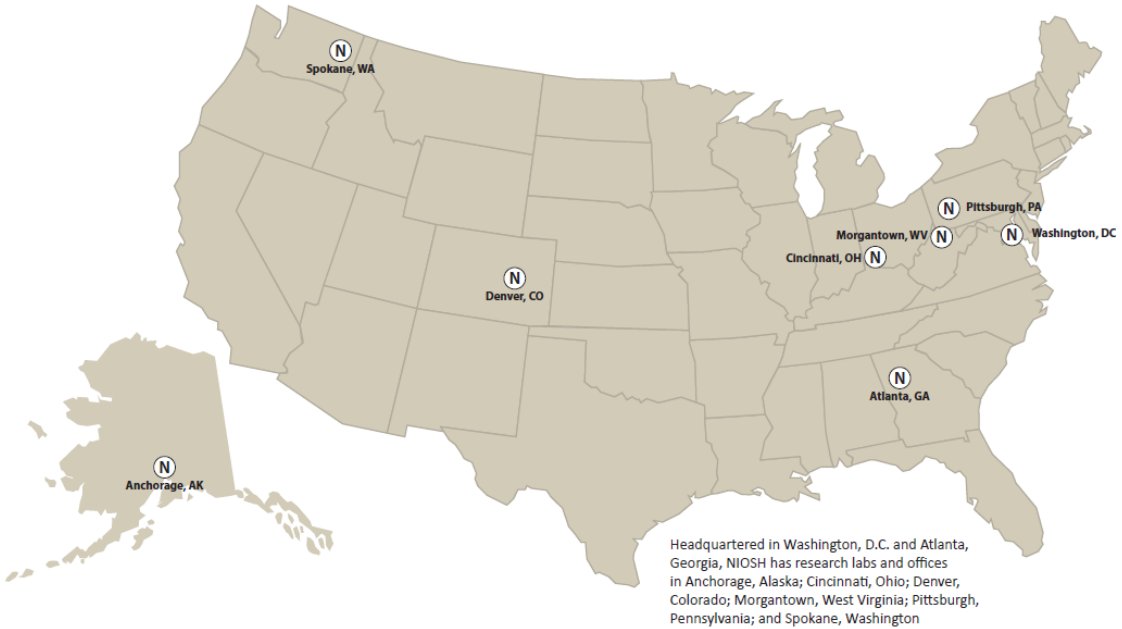
1. U.S. Department of Labor, Bureau of Labor Statistics. Current Population Survey. 2017. http://www.bls.gov/cps/cpsaat01.pdf.
2. Leigh JP. Economic burden of occupational injury and illness in the United States. Millbank Q 2011;89:728-72.

Chemicals are one of the most significant occupational hazards

- 52.1 Million workers estimated exposed to chemicals in their work[1]
- From 2011-2015
  - 71,140 illnesses or injuries associated with chemical exposures[2]
  - 4,836 chemical-related fatalities[3]
- Difficult to estimate number of chronic diseases: cancer, pulmonary, cardiovascular, neurologic related to chemicals
  - 2–8% of cancers attributed to occupational exposures[4]
  - Severe underestimation has been identified

1.Calvert et al 2013
2.BLS 2011-2015
3.BLS 2011-2015
4.Purdue et al 2015

The NIOSH mission is to develop new knowledge in the field of occupational safety and health, and to transfer that knowledge into practice.



NIOSH Work is Inherently Collaborative

Government, Industry, Labor, Professional Societies, Academia, Others

Why?

- Broad mission
- Large, diverse and geographically dispersed workforce
- Changing economic conditions
- Evolving technology and science
- Inherent challenge of moving science into practice

Why engage in partnership?

- Solve complex problems
- Accelerate discovery or innovation
- Facilitate knowledge translation or diffusion
- Optimize resource management
- Create value

Lessons Learned from NIOSH Partnerships

- Ensuring mission alignment of participants
- Engaging partners in the planning and development of activities
- Conducting work inside and outside of the partnership
- Coordinating internal NIOSH engagement with the partnership
- Reconciling differences in organizational timelines
- Meeting federal requirements for scientific activities
- Managing intellectual property
- Demonstrating the success of the partnership

National Academies of Science [1999]. Overcoming Barriers to Collaborative Research: Report of a Workshop.
National Council of University Research Administrators and Industrial Institute [2006]. Guiding Principles for University-Industry Endeavors

Ensuring Mission Alignment

NIOSH Mission Goals (2016 – 2020)

Conduct research to reduce worker illness and injury, and to advance worker well-being

a. Track work-related hazards, exposures, illnesses, and injuries for prevention.
b. Generate new knowledge through intramural and extramural research programs.
c. Develop innovative solutions for difficult-to-solve problems in high-risk industrial sectors.

Promote safe and healthy workers through interventions, recommendations and capacity building

a. Enhance the relevance and utility of recommendations and guidance.
b. Transfer research findings, technologies, and information into practice.
c. Build capacity to address traditional and emerging hazards.

Enhance worker safety and health through global collaborations

a. Take a leadership role to share knowledge and best practices.
b. Provide workplace illness and injury reduction strategies.
c. Build professional capacity to address workplace hazards through information sharing and research experience.

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.

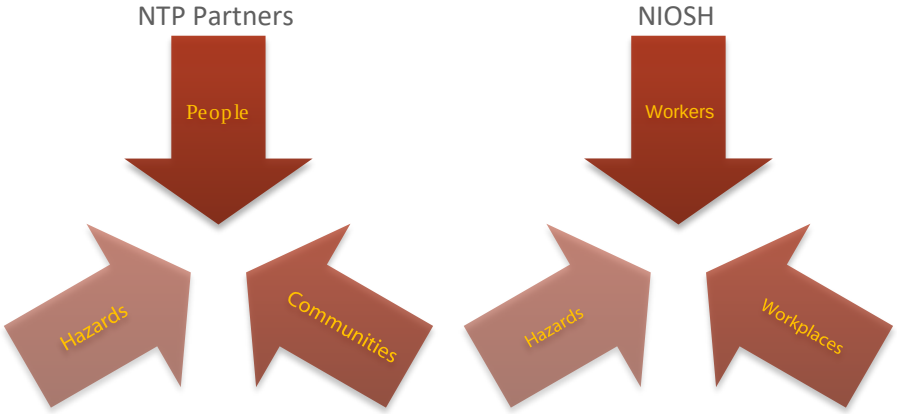
https://ntp.niehs.nih.gov/about/index.html

Features of the 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

NIOSH Mission and NTP Goals Overlap

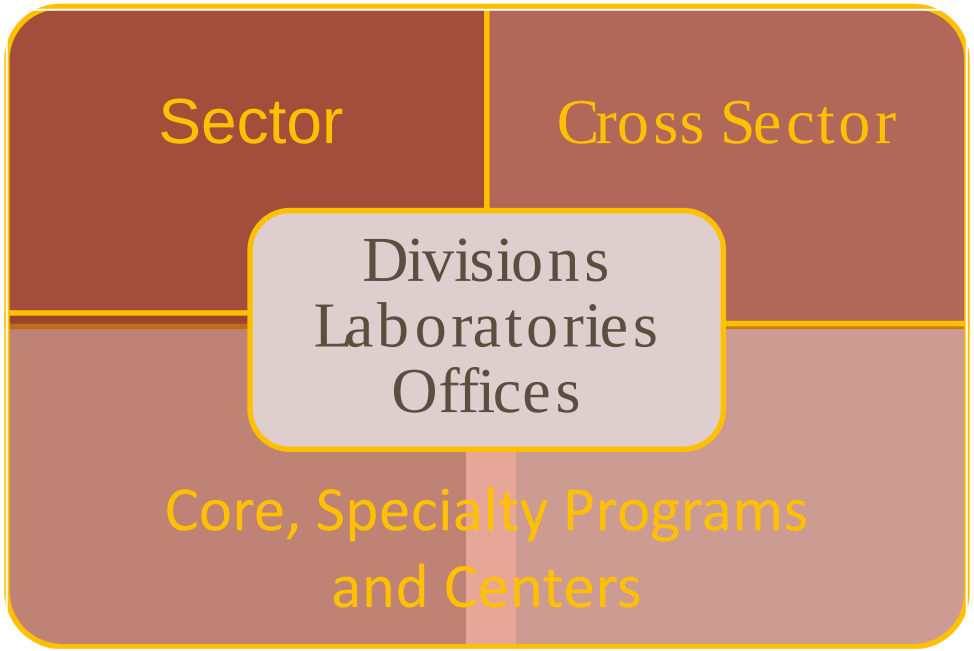
- Assessing new hazards
- Developing and validating methods
- Strengthening science
- Providing information to interested and affected communities



Engaging partners in the planning and development of activities

The National Occupational Research Agenda (NORA) is a partnership program to stimulate innovative research and improved workplace practices.

NIOSH Programs Overlap the NIOSH Organizational Structure



Ten Industry Sectors

- Agriculture, Forestry and Fishing
- Construction
- Healthcare and Social Assistance
- Manufacturing
- Mining
- Oil and Gas Extraction
- Public Safety
- Services
- Transportation, Warehousing and Utilities
- Wholesale and Retail Trade

Seven Health and Safety Cross Sectors

- Cancer, Reproductive and Cardiovascular
- Hearing Loss Prevention
- Immune, Infectious & Dermal
- Musculoskeletal Health
- Respiratory Health
- Traumatic Injury Prevention
- Healthy Work Design and Well-being

Core and Specialty Programs

- Authoritative Recommendations
- Emergency Preparedness and Response
- Engineering Controls
- Exposure Assessment
- Health Hazard Evaluations
- Nanotechnology
- Occupational Health Equity
- Personal Protective technology
- Prevention through Design
- Safe Skilled Ready Workforce
- Small Business Assistance
- Surveillance
- Translation Research

NIOSH Centers

- Center for Direct Reading and Sensor Technologies (DRS)
- Center for Maritime Safety and Health Studies (MAR)
- Center for Motor Vehicle Safety (MVS)
- Center for Occupational Robotics Research (ROB)
- Center for Workers' Compensation Studies (WCS)
- National Center for Productive Aging and Work (PAW)

	Cancer, Reproductive, Cardiovascular, and Other Chronic Disease Prevention	Hearing Loss Prevention	Immune, Infectious, and Dermal Disease Prevention	Musculoskeletal Health	Respiratory Health	Traumatic Injury Prevention	Healthy Work Design and Well-Being
Agriculture, Forestry, and Fishing	• 1.1 Pesticide exposure and neurologic disorders • 1.2 Renal diseases		• 3.1 Skin exposure to pesticides and total body burden • 3.2 Infectious disease transmission	• 4.1 Exposure to vibration and repetitive motion	• 5.1 Fixed airways diseases	• 6.1 Traumatic injury among high risk populations	
Construction		• 2.1 Engineering controls to reduce noise exposure • 2.2 Hearing loss prevention education for employers and workers		• 4.2 MSDs and emerging technologies (e.g. robots, exoskeletons)	• 5.2 Exposure to mineral dusts • 5.3 Mixed exposures	• 6.2 Falls • 6.3 Injuries related to emerging technologies (e.g. robots and exoskeletons)	• 7.1 Non-standard work arrangements
Healthcare and Social Assistance	• 1.3 Adverse reproductive outcomes • 1.4 Work organization and cancer, CVD		• 3.3 Infectious disease transmission • 3.4 Exposures related to asthma and other immune diseases	• 4.8 MSD interventions	• 5.4 Work-related asthma • 5.12 Interstitial/fibrotic lung disease	• 6.4 Injuries caused by patients (human and animal)	• 7.2 Work organization
Manufacturing	• 1.5 Exposure to carcinogens • 1.6 Adverse reproductive outcomes • 1.7 Exposure to welding fumes and neurologic disorders	• 2.3 Exposure to hazardous noise and ototoxic chemicals • 2.4 Hearing loss prevention education for employers and workers	• 3.8 Hazardous exposures and immune diseases	• 4.3 MSDs and emerging technologies (e.g. robots, exoskeletons)	• 5.5 Dust-induced respiratory diseases • 5.6 Fixed airways diseases • 5.7 Work-related asthma	• 6.5 Machine-related injuries	

Conducting work inside and outside of the partnership

Inside the Partnership

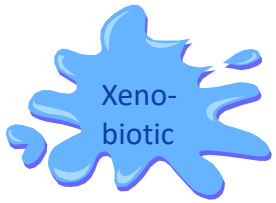
Selected Human Exposure Assessment Studies

- 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 (proposed)

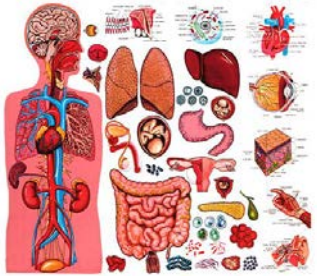
Should we add early biomarkers of effect?

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

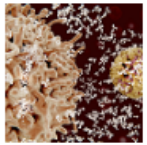
Outcomes from Etiologic Research

- 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.

NTP at NIOSH

About NTP at NIOSH

NIOSH research projects for NTP assess the effects of exposures to substances following its mandate to protect worker health and safety.



NTP at NIOSH: Immunotoxicology Research

A list of studies to evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases.

NTP at NIOSH: Occupationally Relevant Exposures

A summary and list of projects to identify and assess worker exposures in FY 2018.

Examples of exchange of subject matter expertise

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

Outside the Partnership

Intramural Research Outside the Partnership

Etiologic Research – Pulmonary

- An Exposomic Approach for Early Detection & Prevention of Silicosis
- T Helper 2 Immune Mechanisms in Particulates-Inducted Pulmonary Fibrosis
- Nanoparticle Induced Lung Inflammatory, Fibrotic and Resolution Pathways (NTRC)
- Examining Cellular and Molecular Mechanisms Following Pulmonary Fungal Challenge
- Identifying Causes of Occupational Fixed Airways Disease

Etiologic Research – Pulmonary and Cardiovascular

- Pulmonary and Cardiovascular Responses to Aerosolized Emissions from 3-D Printers
- Association of Pulmonary, Cardiovascular, and Hematologic Metrics with Carbon Nanotube and Nanofiber Exposures in U.S. Workers
- Prevalence of Cardiovascular Health by Occupation
- Telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA)

Etiologic Research – Cancer

- Evaluation of Welding Fume as a Lung Carcinogen in Mice Exposed by Inhalation
- Mechanistic Studies of Inflammation and Carcinogenesis in Pathogenicity of Different Types of Asbestos/Cleavage Fragments
- Chromosome Translocations and Cosmic Radiation Dose in Airline Pilots
- Mortality among Styrene-exposed Workers in the Boat Building Industry
- Mortality and Cancer Incidence in a Pooled Cohort of U.S. Firefighters

Etiologic Research – Reproductive Health

- Maternal Occupational Pesticide Exposure and Risk of Congenital Heart Defects
- Risk of Miscarriage among Flight Attendants
- Occupational Use of High-level Disinfectants and Fecundity
- Work Schedule and Risk of Miscarriage in Nurses
- Reproductive Health Risks associated with Occupational Exposures to Antineoplastic Drugs

Etiologic Research – Immune and Other

- Immunotoxicological Evaluation of Occupational Chemicals
- Identification of Occupational Allergens
- (Pilot) Non-invasive and/or Minimally Invasive Biomarkers for Nanotoxicity
- Toxicity Assessment of CNT and CNF from U.S. Facilities
- Effects of Antimicrobial Chemical Exposures on Influenza Vaccination and Antiviral Immunity
- Antimicrobials and allergic Disease: Biomarkers and Mechanisms of Action
- Characterization and Health effects of Aerosols from Thermal Spray coating

Extramural Research Outside the Partnership

Extramural Research - Cancer

- LUNG DISEASE IN CHINESE TEXTILE WORKERS
- CASE-COHORT STUDY OF CANCERS IN EXCESS IN POULTRY WORKERS
- A NANOPARTICLE RESPIRATORY DOSE SAMPLER FOR METAL-BASED NANOPARTICLES
- RESPIRATORY DISEASES AND EXPOSURE TO ELONGATED MINERAL PARTICLES IN TACONITE ORE
- RANDOMIZED CONTROLLED TRIAL TO IMPROVE ONCOLOGY NURSES' PROTECTIVE EQUIPMENT USE
- MORTALITY AND RENAL-DISEASE AMONG LEAD-EXPOSED WORKERS
- ORGANIZATIONAL APPROACHES TO TOTAL WORKER HEALTH FOR LOW-INCOME WORKERS

Extramural Research - Cancer

- DEVELOPING A GENERAL POPULATION JOB EXPOSURE MATRIX FOR STUDIES OF WORK-RELATED MSD
- OCCUPATIONAL SAFETY AND HEALTH RESEARCH (R01)
- COMBINED ANALYSIS OF LUNG CANCER AMONG URANIUM MINERS
- INTEGRATED APPROACH FOR ENVIRONMENTAL HEALTH MONITORING: EXPOSURE SIGNATURES OF PESTICIDES
- SUGARCANE WORKERS, MEDICAL VISITS, AND KIDNEY FUNCTION
- A DIRECT-READING INHALABLE PARTICLE SIZER WITH ELEMENTAL COMPOSITION ANALYZER

Extramural Research - Cardiovascular and Cancer

- OCCUPATIONAL EXPOSURE TO PM2.5 AND CARDIOVASCULAR DISEASE(CVD)
- MODIFYING THE WORKPLACE TO DECREASE SEDENTARY BEHAVIOUR AND IMPROVE HEALTH.
- QUANTIFYING ECONOMIC & HEALTH EFFECTS OF PSYCHOSOCIAL WORKPLACE EXPOSURES
- ADVERSE HEALTH EFFECTS OF SHIFT WORK
- RENAL DISEASE KIDNEY CANCER AND METALWORKING FLUID EXPOSURE IN AUTOWORKERS
- STRESSORS AND CARDIO-METABOLIC DISEASE IN POLICE: A 12-YEAR LONGITUDINAL STUDY

Extramural Research - Cardiovascular and Cancer

- ALTERNATIVE FUEL USE TO REDUCE DIESEL EMISSIONS EXPOSURE AND TOXICITY IN MINING
- EVALUATING IMPACTS OF OCCUPATIONAL EXPOSURE LIMITS FOR SILICA USING G-ESTIMATION
- TRANSGENERATIONAL WORK EXPOSURES, EDCS AND MALE FERTILITY
- LONGITUDINALLY-ASSESSED HEALTH IMPACTS OF WILDLAND FIREFIGHTING
- US AND CANADIAN URANIUM PROCESSING COHORTS: EXPOSURE, RISK AND RELEVANCE

Extramural Research – Risk Assessment and Toxicology

- WHICH SAFETY STANDARDS MATTER?
- FORECASTING PULMONARY INFLAMMATION FROM IN VITRO ASSAY RESULTS FOR NANOPARTICLES
- NOVEL CIRCADIAN EXPOSURE METRICS FOR SHIFT WORKERS
- THE LOW BACK CUMULATIVE TRAUMA INDEX:A FATIGUE-FAILURE BASED RISK ASSESSMENT TOOL
- POPULATION-BASED GENETIC MODEL FOR DIISOCYANATE-INDUCED ASTHMA
- GENETIC SUCEPTIBILITY FOR OCCUPATIONAL ASTHMA
- THE ROLE OF IL-6 RECEPTOR IN IRRITANT DERMATITIS

Extramural Research – Risk Assessment and Toxicology

- SYSTEMIC HEALTH IMPLICATIONS OF OCCUPATIONAL NANOMATERIAL EXPOSURE
- DECIPHERING OCCUPATIONAL ASTHMA PATHOGENESIS CAUSED BY ISOCYANATE
- MULTIPLEX SENSOR PLATFORM FOR BIOLOGICAL MONITORING
- LIGHTING INTERVENTIONS TO REDUCE CIRCADIAN DISRUPTION IN ROTATING SHIFT WORKERS

Coordinating internal NIOSH engagement with the partnership

Reconciling differences in organizational timelines

Meeting federal requirements for scientific activities and managing intellectual property

The push for transparency in science and public health policy

Data Management	OSTP February 2013, “Increasing Access to the Results of Federally Funded Scientific Research” and OMB May 2013, “Open Data Policy-Managing Information as an Asset”
Plain Writing	Public Law 111-274, October 2010 “Plain Writing Act of 2010”
Good Guidance	OMB January 2007, “Final Bulletin for Agency Good Guidance Practices”
Peer Review	OMB December 2004, “Final Information Quality Bulletin for Peer Review”
Information Quality	Public Law 106-554; H.R. 5658), section 515(a), Information Quality Act

Demonstrating the success of the partnership

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 1-21 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

NIEHS Spurs NIOSH to Develop Occupational Systematic Review

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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
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Health Assessment and Translation

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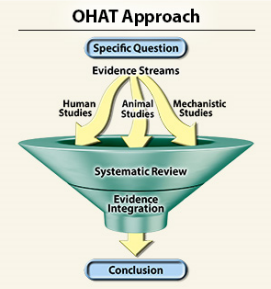
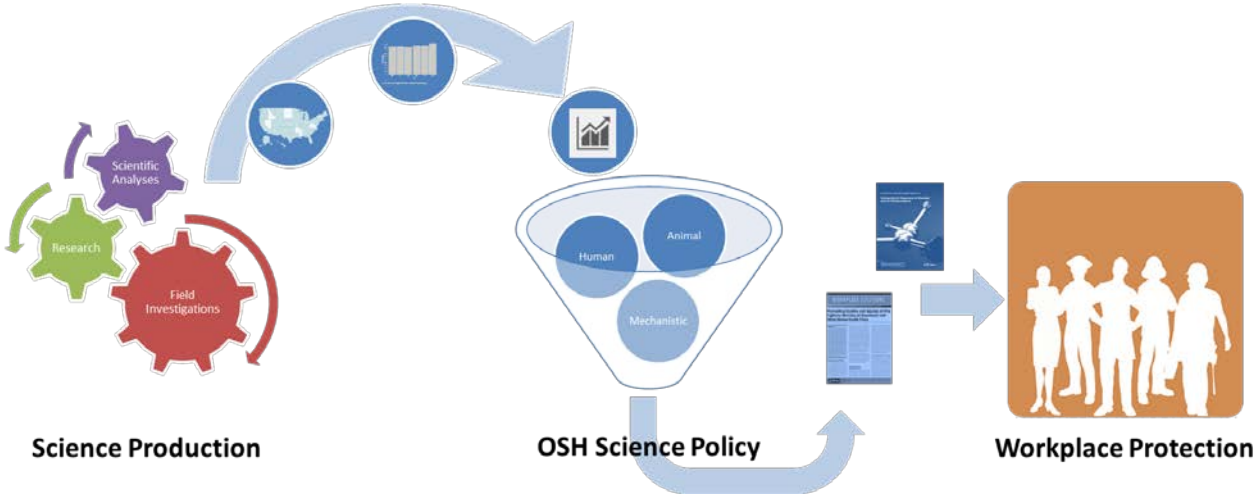
- Ongoing Evaluations
- Topics Under Consideration
- Nominate a Topic
- Contact OHAT

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-



Developing and disseminating information is a common tool for influencing workplace protection.

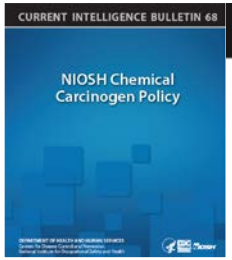


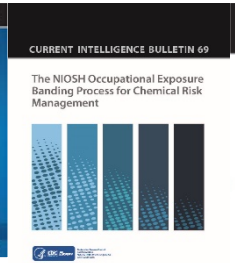
Current Recommended Exposure Limits (REL) under Development

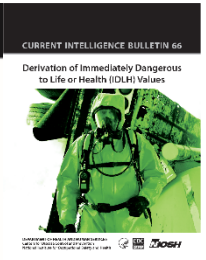
- Glutaraldehyde—widely used
- 1-Bromopropane—replacement for ‘ozone depleters’
- Manganese—neurobehavioral effects
- Diethanolamine—widely used
- Lead—neurobehavorial effects
- Toluene diisocyanate—sensitizer
- Silver nanoparticles—high volume nanomaterials

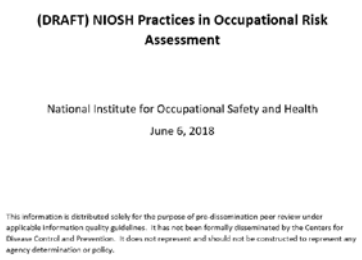
Authoritative Recommendations and Guidelines

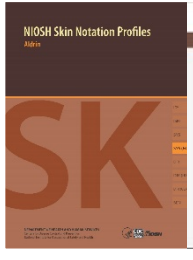
- Chemical Carcinogen Policy
- Development of IDLH values and Skin Notation Profiles
- NIOSH Pocket Guide
- NIOSH Manual of Analytic Methods
- Draft NIOSH Practices in Occupational Risk Assessment
- Draft Occupational Exposure Banding

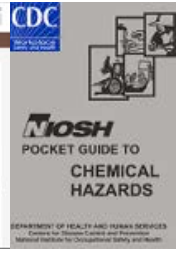












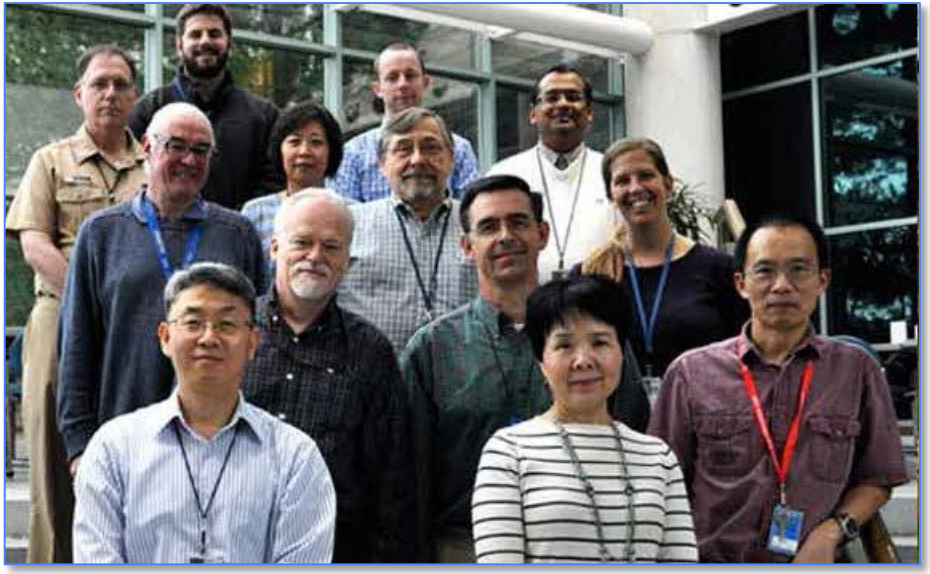
Impact of the NIOSH-NTP Collaboration Internally

- 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

Thank you to NIOSH staff



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

For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov