

Interagency Agreement Between the National Institute of Environmental Health Sciences and the National Institute for Occupational Safety and Health

Comprehensive Toxicological Assessment of Occupationally Relevant Exposure

The Centers Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH) provides services to the National Institute for Environmental Health Sciences (NIEHS) under an Interagency Agreement.

Purpose:

The purpose of the Interagency Agreement is to enable the NIEHS and NIOSH, as member agencies of the NTP, to take full advantage of research capabilities of NIOSH to address the problems of mutual interest related to characterizing the adverse effects of complex occupational exposures. A significant number of complex industrial mixtures or occupational exposures have been nominated to the NTP for assessment. Unlike more traditional nominations to the NTP, the health hazards associated with these complex exposures present unique challenges with regard to (1) selection of relevant test exposures and doses and (2) design and performance of special studies that might maximize the predictive value of standard bioassays. This agreement enlists NIOSH research capabilities to enhance the relevance of NTP data generated in the toxicological assessment of complex occupational exposures by:

- Capitalizing on NIOSH's unique access to human populations and work sites to provide real-world context for toxicological studies.
- Employing NIOSH's unique mix of disciplines (toxicologists, engineers, industrial hygienists, chemists, epidemiologists, occupational practitioners, etc.) in characterizing complex exposures, and designing and performing special studies.
- Utilizing NIOSH's toxicological expertise, animal facilities, and inhalation exposure capabilities and facilities to complement NIEHS intra- and extramural capabilities.

Projects Completed (1998-2007)

NIOSH has completed five studies under the IAG in which workers were either exposed to substances that potentially could cause harm in the workplace or methods were developed to generate specific fumes.

1. Exposure Assessment of Cellulose Insulation Applicators

Cellulose insulation (CI) was nominated to the NTP for comprehensive toxicological evaluation. The evaluation included a bulk analytical characterization CI and an exposure assessment of contractors applying CI in residential and commercial buildings. NIOSH conducted the exposure assessment of 10 U.S. contractors applying CI in residential and commercial buildings. Respirable dust air sampling and real time monitoring with particle size discrimination indicated low levels of respirable dust were generated. There was little evidence of adverse effects to the lower respiratory tract associated with CI exposure to low levels of respirable dust.

2. Physical and Chemical Characterization of Asphalt Fumes and Generation System at Simulated Road Paving Conditions

An impediment to laboratory-based toxicity studies of road paving asphalt fumes was the lack of an acceptable method for generation of controlled test fume atmospheres. To remedy these

deficiencies, NIOSH purchased a continuous flow fume generator, which it modified and improved. NIOSH characterized the system by assessing the effect of generation conditions on asphalt and airflow rates, asphalt temperature, and humidity. Chemical and physical characterization included fume-simulated boiling point profiles of both particulate and vapor fractions, infrared spectral analysis, specific PAH content, particle size distribution, and nature of the aerosol. A comparative study of the chemical profile of the NIOSH fume to that being used by the Fraunhofer Institute, Germany was also conducted. Multiple in-house, NIOSH-funded toxicity/biological studies were performed with the system.

3. Brominated Propanes: Characterization of Industrial Uses and Occupational Exposure Assessment of General Industry Workers in the U.S

In this study, the Occupational Safety and Health Administration (OSHA) requested that the NTP evaluate the toxicity of 1-bromopropane because of its increased use in both industrial and consumer products, which could potentially expose thousands of workers and the general public. NIOSH characterized occupational exposures by measuring inhaled and exhaled breath of adhesive manufacturers, adhesive users (i.e., foam fabricators, furniture, transportation seating, etc.), and workers in the metal degreasing (i.e., allied metal finishers, automotive, etc.) and electronics industries.

4. Design, Construction, and Characterization of a Welding Fume Generation and Inhalation Exposure System

Epidemiology suggests that pulmonary exposure to welding fumes causes adverse health effects, such as lung inflammation, cancer, and neurotoxicity. However, more information is required to determine causality, evaluate temporal and dose-response relationships, and elucidate mechanisms. This project constructed a welding fume inhalation system for exposure of laboratory animals to tightly controlled, well-characterized welding fumes generated from different welding processes and materials. The physical and chemical compositions of the generated fumes were characterized. Studies were completed that evaluated exposure conditions, generator parameters, and welding processes as well as materials that induced acute lung injury, inflammation, and immuno-modulation in a rat model.

5. Exposure Assessment of Tungsten-Containing Fibers in Tungsten Refining and Manufacturing Processes

In tungsten refining and manufacturing processes, a series of tungsten oxides are typically formed as intermediates in the production of tungsten powder. A study was conducted to characterize airborne tungsten-containing fiber dimensions, elemental composition, and concentrations in the U.S. tungsten refining and manufacturing industry during the course of normal employee work activities. Overall, the airborne fibers detected had a geometric mean length of $\approx 3 \mu\text{m}$ and a diameter of $\approx 0.3 \mu\text{m}$. Ninety-seven percent of the airborne fibers identified were in the thoracic fraction (i.e., aerodynamic diameter $\leq 10 \mu\text{m}$). Energy dispersive x-ray spectrometry results indicated that the airborne fibers consisted primarily of tungsten and oxygen, with other elements being detected in trace quantities. The finding of airborne tungsten-containing fibers in this occupational setting needs to be confirmed in similar settings and demonstrates the need to obtain information on the durability and associated health effects of these fibers.

On-going Projects (2007-2009)

Highlights of the projects are described below.

1. Tungsten Oxide Fiber Dissolution and Persistence in Artificial Human Lung Fluids

The aims of this study are to (1) characterize five tungsten oxide powders and (2) determine their relative solubility in artificial human extracellular lung fluid and lung macrophage phagolysosomal fluid. The dissolution of dispersed and aggregated tungsten oxide fibers in artificial human extracellular lung fluid and lung macrophage phagolysosomal fluid will then be measured.

To date, the relative mass fraction of fibers in the study powders has been determined. Pilot dissolution experiments were performed using tungsten oxide powders with artificial extracellular lung fluid and macrophage phagolysosomal simulant fluid. Evaluation of the dissolution data indicated that the concentration of tungsten dissolved from the powders could be measured by an inductively coupled plasma mass spectrometer (ICP) as the levels exceeded the analytical detection limits. Evaluation of the pilot dissolution data also revealed that alkylbenzyltrimethylammonium chloride (ABDC), added to artificial lung fluids to inhibit mold growth, strongly influenced dissolution; thus full-term dissolution experiments will be performed without ABDC.

Activities planned for fiscal year 2009 are to conduct full-term dissolution studies of tungsten oxide powder materials in artificial human extracellular lung fluid and phagolysosomal simulant fluid using optimized conditions determined from the pilot studies and to measure the dissolution of dispersed and aggregated tungsten oxide fibers in artificial human extracellular lung fluid and artificial human lung macrophage phagolysosomal fluid.

2. Exposure Assessment in Domestic Tungsten Refining and Manufacturing Occupations

This exposure assessment research augments the knowledge of the range and scope of tungsten oxide fiber exposures in tungsten refining and manufacturing operations, and downstream tungsten users in the U.S. Currently, the project is investigating the presence of airborne tungsten containing fibers in down-stream consumers, manufacturers, and industrial users that consume or incorporate tungsten in their products. The study design is an observational inhalation exposure assessment of approximately 40 workers. The research will identify tasks and jobs with elevated risk of exposure, document exposure patterns among tasks and jobs, and characterize airborne particle morphology in domestic tungsten production in two facilities that manufacture tungsten-containing products. Samples will include full-shift personal breathing zone (PBZ) and area air sampling for airborne tungsten-containing fibers. Samples will also be analyzed to determine fiber morphology and physicochemical properties. New analytical methods will be investigated to provide surface chemistry information on the identified fibers, in addition to the suite of analyses currently being conducted. Limited demographics for the population identified as at risk will also be documented to assist future researchers in selecting populations for long-term health effect studies.

3. Assessing the Feasibility of Industry-wide Exposure and Epidemiology Studies of Workers Exposed to Engineered Nanomaterials

The health effects from workplace exposure to engineered carbonaceous nanomaterials (e.g., single-walled and multi-walled carbon nanotubes) are uncertain, but may include malignant and non-malignant lung disease and cardiovascular disease. The specific aims of this project are (1) to collect and compile information on the size, characteristics, and future trends of the U.S. workforce involved in the manufacture of engineered carbonaceous nanomaterials and (2) to develop a report on the feasibility of conducting industry-wide exposure surveys and epidemiologic studies among this workforce. This work will include reviewing and compiling information on companies identified as manufacturers of engineered carbonaceous nanomaterials in the Lux Report (4th and 5th Editions), supplemented with information collected from Dun & Bradstreet. The NIOSH contractor will then conduct interviews with Health and Safety managers at each identified company to confirm the information collected on workforce size, location, characteristics of the nanomaterials produced, and use of engineering controls and personal protective equipment. The contractor has compiled information on 150 companies to be profiled.

4. Exposure Assessment of Engineered Nanoparticles

The purpose of this project is to identify workplaces engaged in the synthesis, manufacture and use of engineered nanomaterials and to characterize workplace exposure to selected engineered nanoparticles. The nanoparticles under study are commercially and scientifically exploitable and may pose a risk for adverse health effects, particularly respiratory disease. This study is focused on addressing the lack of human exposure data. NIOSH has developed a standardized protocol for data collection that is flexible and allows for additional measurements to be taken as needed to adapt to different exposure scenarios.

During fiscal year 2008, specialized air sampling equipment was procured in preparation for an expanded schedule of field site visits beginning in fiscal year 2009. Equipment, supplies, and services procured by NIOSH include air sampling pumps, direct-reading instruments for particle number concentration and particle size distribution, laboratory and sampling supplies including membrane filters, surface sampling materials, calibration materials, and other supplies needed for aerosol sampling. Laboratories that can provide elemental analysis and classification of size distribution and surface area of bulk materials using transmission electron microscopy (TEM) and/or scanning electron microscopy (SEM) particle analysis have been identified.

NIOSH has identified the geographical location and conducted a search of a data repository specifically of nanotechnology companies to identify the materials they either create, process or handle. Additional efforts have been made to contact a subset of these companies and seek their collaboration regarding field studies.

New Projects (2009)

1. Cardiovascular Toxicity Assessment of Subchronic Inhalation Exposure to Fullerene C60

Rationale:

The most attractive properties of engineered nanomaterials for technological applications are their small size, large surface area, and high reactivity, which are also the main factors for their potential toxicity. Based on ambient ultrafine particle research, it is predicted that nanosized particles may deposit in the lower lobe of the lung where they would have higher biological activity and a tendency for extrapulmonary translocation compared to larger particles. Nanoparticle exposure may lead to unexpected distant responses involving the immune system, heart, liver, kidney, and brain. The systemic effects may induce or modify the progression of existing diseases such as cardiovascular disease. The initial data demonstrated that pulmonary instillation of multiple doses of single wall-carbon nanotubes (CNTs), which induces lung toxicity, also causes oxidative modification of blood vessels and production of proteins that facilitate blood coagulation, resulting in pathophysiological outcomes involved in atherosclerosis-related cardiovascular diseases.

Humans may be exposed to fullerenes during the processing, application, and use of products. The NTP is currently conducting studies on the exposure of rats and mice to nano sized and micro sized fullerene C60 by inhalation for 90 days. NIOSH will investigate the cardiovascular outcomes of this regimen by examination of the heart, aorta, and blood.

Objectives:

The objectives of this study will be to evaluate the atherogenic and cardiovascular toxicity of fullerene exposure by inhalation. Quantitative DNA, RNA expression RT-PCR, and focused gene expression array analysis will evaluate the aorta and heart for stress and mitochondrial oxidative damage. Heart proteins will be analyzed by Western blot for early mediators of atherogenesis including Mac-1, VCAM-1, MCP-1, tissue factor (TF), and PAI-1.

The response of blood cells to fullerene exposure will also be measured. RNA will be isolated and assessed by focused array and real-time PCR for expression of gene coding markers related to inflammation and coagulation activities contributing to atherogenesis.

Defining the modulation of vascular homeostatis resulting from fullerene exposure will provide the foundation for designing experiments \ to characterize the effects of fullerene on atheroma formation and progression in ApoE^{-/-} and LDLR^{-/-} knock out mice that are genetically predisposed to develop atherosclerosis.

2. Exposure Assessment for 2-methoxy-4-nitroaniline in a Manufacturing Setting

Rationale:

2-Methoxy-4-nitroaniline (2-MeO-4-NA) was nominated in 2006 to the NTP by the National Cancer Institute for toxicology and carcinogenesis studies based on its high and increasing annual production volume, potential for worker exposures, lack of adequate toxicology and carcinogenicity data, positive mutagenicity data, and the determination that a closely related chemical, 2-methoxy-5-nitroaniline, was a multisite carcinogen when tested by the NTP.

There are limited environmental and occupational exposure data to assess the acute exposure/response relationship, and potential chronic long-term adverse effects of 2-MeO-4-NA. Also, there are no formally documented sampling and analytical methods to quantitatively measure airborne and surface concentrations. There are no OSHA regulations specific to 2-MeO-4-NA. NIOSH has not established a time-weighted average Recommended Exposure Level (REL), and the American Conference of Governmental Industrial Hygienists (ACGIH) has not established a time-weighted average Threshold Limit Value (TLV[®]) for 2-MeO-4-NA. Hence, there is a critical research need to assess workplace inhalation and surface exposures to 2-MeO-4-NA in a commercial manufacturing setting.

Objectives:

The proposed research study will identify worker populations at elevated risk of exposure at facilities that produce raw 2-MeO-4-NA, and facilities that use 2-MeO-4-NA for the manufacture of end use products. The first task will be to determine the total number of workers industry-wide and characterize the occupational exposure levels of a representative sample of workers exposed to 2-MeO-4-NA. Twenty workers from 2 facilities will be recruited for inclusion in the study. Newly developed industrial hygiene sampling and analytical methods will be used to measure occupational exposure. Real time airborne exposure monitoring concurrent with video work task recording will also be conducted. NIOSH will develop an analytical method for quantitatively assessing 2-MeO-4-NA in airborne gases and particulates, and on surfaces. Depending on the work environment and process, both full shift and task based airborne and surface wipe sampling schemes may be employed.

Findings from this research will provide the human exposure data needed by NIEHS, CDC, EPA, and NCI to assess chemical hazards and will also guide animal bioassay research conducted or supported by the NTP.

3. A Pilot Exposure Assessment for 2',2'''-Dithiobisbenzanilide (DTBBA) in a Manufacturing Setting

Rationale:

2',2'''-Dithiobisbenzanilide (DTBBA) was nominated in 2007 by the National Cancer Institute to the NTP for toxicology and carcinogenesis studies based on high and increasing production volume, the potential for occupational and consumer exposures, the lack of adequate toxicology and carcinogenicity data, and suspicion of toxicity based on the structure of the chemical. There are limited environmental and occupational exposure data available in the scientific literature to assess the scope of industrial exposure to DTBBA, and there is currently no analytical method to quantitatively assess DTBBA in airborne particulates and on surfaces. Hence, NIOSH has identified a research need for developing an analytical method for DTBBA and assessing worker exposure and deposition in a manufacturing setting.

The study will involve exposure surveys among facilities representing manufacturers and/ or industrial users of DTBBA compounds. The targeted study population size includes approximately 20 process workers who will be recruited from two selected facilities. Analytical methods for DTBBA will be developed for quantitatively assessing DTBBA airborne particulates and surface exposures. Depending on the work environment and process, both full shift and task based air and surface wipe sampling schemes may be implemented.

Objectives:

1. Develop an analytical method to characterize industry-wide occupational exposures including total number of workers and evaluate patterns of exposure to DTBBA (using

available industrial hygiene sampling methods, including video exposure monitoring, and the newly developed laboratory analysis methods).

2. Provide appropriate recommendations based on the analytical results for reducing exposure including engineering controls and work practice interventions.

4. An Exposure Assessment for Diacetyl and Other Flavorings in Food Production Industries

Rationale:

In 2007, the United Food and Commercial Workers Union nominated diacetyl for long-term inhalation testing by the NTP because of potential worker exposure via inhalation. NIOSH has identified critical research needs for workers exposed to diacetyl including the measurement of workplace inhalation to diacetyl in food production industries. Adverse respiratory effects have been anecdotally reported by workers in cheese production facilities in Wisconsin, and in yogurt and potato chip manufacturing plants. However, the potential for both exposure and disease in the flavored food production industry has not been studied. This research will fill an important gap in the understanding and quantification of exposures downstream from the flavoring manufacturer.

The study will involve exposure surveys over a two-year period among facilities representing food producers that use flavorings that contain diacetyl and other compounds of concern to document high exposure activities and processes in the industries.

Objectives:

The objectives will be to identify work practices and procedures which affect exposure potential, and document engineering controls and field test novel sampling techniques for both gravimetric, bulk and volatile sampling for diacetyl. Depending on the work environment and process, both full shift and task-based air sampling schemes may be implemented. The targeted study population size includes a minimum of 40 workers recruited from 10 facilities.

5. Use of Indium and Indium Compounds in the Workplace

Rationale:

Use of indium in manufactured materials may be increasing in certain electronic devices such as flat panel displays. Studies in experimental animals and human case reports indicate that indium tin oxide may cause pulmonary disease in humans. The International Agency for Research on Cancer (IARC) has classified indium phosphide as a probable carcinogen to humans (Group 2A) based on a determination of sufficient evidence of carcinogenicity in experimental animals.

Limited information is available on the actual users of indium compounds in the United States and the potential for occupational exposure among these users. Information on likely downstream users of indium is especially needed in order to conduct more systematic informational surveys of potential indium users, to identify candidate companies for exposure assessment measurements, and to estimate the number of indium-exposed workers.

Objectives:

The objectives of the study are to obtain updated information on the users and uses of indium and indium compounds, including indium tin oxide (ITO) and indium phosphide (InP), among: (a) producers and processors of indium and indium compounds, (b) down stream users of indium and indium compounds, and (c) recyclers, if any, of products containing indium or indium

compounds. Use information would include nature of the exposure (chemical and physical state), work processes, jobs with potentially exposed workers, exposure controls in place, company/industry collected monitoring data, and indium use trends.

Secondly, NIOSH will identify and summarize any existing published data on worker or human exposure for indium and indium compounds including air, dermal, and biological matrices. Attempts will be made to obtain unpublished data as well.

6. Occupational Exposure Assessment of Workers Exposed to Welding Fume with Emphasis on Manganese Compounds in Mild Steel

Rationale:

NIOSH nominated welding fume (WF) for testing for its neuropsychiatric effects in 2002. Specific concern was the potential of manganese in welding fume to cause neurotoxicity in exposed workers. The Bureau of Labor Statistics estimated that approximately 386,000 U.S. workers were employed as welders, cutters, solders, and brazers. Welding generates a complex, nanometer-sized aerosol consisting of base and electrode metals, which often includes manganese (Mn). Manganism is a form of Parkinsonism resulting from high Mn exposures observed in ore mining and refining, ferroalloy production, and the dry cell battery industries. Diagnosis is challenging because early signs and symptoms are typically subtle, sub-clinical neurobehavioral in nature, and occur gradually over time. More pronounced symptoms might not become apparent until after the disease has progressed to an irreversible state. However, the relationship between chronic low level Mn exposure and manganism is uncertain. Research is needed to determine critical information pertaining to WF exposure and the risk of developing neurological symptoms resembling Parkinson's disease.

Occupational exposure limits for Mn are inconsistent between OSHA and the American Conference of Governmental Industrial Hygienists (ACGIH) and are based on different biological effects and short-term exposure. Currently, occupational evaluation of Mn is based on chemical measurement of elemental Mn without further differentiation of specific Mn compounds. However, Mn in WF complexes with many other cations and anions including iron, oxides, and fluoride and may exist in several valence states. Moreover, the exposure dose of Mn amongst different groups of welders is also not fully understood.

The studies will be designed to address the following questions:

1. What forms of Mn are important in welding emissions in field settings?
2. Can analytical methods for air sampling be developed to measure the different valence states and solubility of Mn compounds utilizing industrial hygiene sampling methodologies?
3. What particle size distributions are associated with welding? Can the mass, number, and surface area concentrations of the nanometer particles be effectively measured for determining "personal" exposure concentrations?
4. Does particle size and agglomerate formations change significantly between different welding processes and construction materials?

Objectives:

The objectives will be to identify industries, companies, and/or unions involved in welding operations where substantial manganese exposure exists appropriate for a thorough research endeavor. Analytical methods to identify specific manganese compounds, valence states, and solubility within various welding fume matrices will be developed. Field studies for the characterization of welding exposures including chemical analysis and particle size

concentrations of WF and Mn aerosols based on welding-associated jobs, tasks, and processes will be initiated.

Publications

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