NORA

NATIONAL OCCUPATIONAL RESEARCH AGENDA (NORA)

NATIONAL OCCUPATIONAL RESEARCH AGENDA FOR RESPIRATORY HEALTH

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Developed by the NORA Respiratory Health Cross-Sector Council

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INTRODUCTION

What is the National Occupational Research Agenda?

The National Occupational Research Agenda (NORA) is a partnership program to stimulate innovative research and workplace interventions. In combination with other initiatives, the products of this program are expected to reduce the occurrence of injuries and illnesses at work. Unveiled in 1996, NORA has become a research framework for the Nation and the National Institute for Occupational Safety and Health (NIOSH). Diverse parties collaborate to identify the most critical issues in workplace safety and health and develop research objectives for addressing those needs.

NORA enters its third decade in 2016 with an enhanced structure. The ten sectors formed for the second decade will continue to prioritize occupational safety and health research by major areas of the U.S. economy. In addition, there are seven cross-sectors organized according to the major health and safety issues affecting the U.S. working population. While NIOSH is serving as the steward to move this effort forward, it is truly a national effort. NORA is carried out through multi-stakeholder councils, which are developing and implementing research agendas for the occupational safety and health community over the decade (2016-2026). Councils address objectives through information exchange, partnership building, and enhanced dissemination and implementation of evidence-based solutions.

NORA groups health and safety issues into seven cross-sectors. The Respiratory Health Cross-Sector focuses on the acquisition and dissemination of information that is necessary to plan and implement efforts to prevent occupational respiratory diseases and improve workers' respiratory health. This includes identifying and understanding occupational exposures that have the potential to adversely impact the respiratory health of workers; recognizing and characterizing the respiratory diseases resulting from these exposures; understanding exposure-response relationships for development of work-related respiratory diseases; and documenting and disseminating effective preventive interventions. All types of research are needed to achieve the objectives, including basic/etiologic, translational, intervention, and surveillance.

What are NORA Councils?

Participation in NORA Councils is broad, including stakeholders from universities, large and small businesses, professional societies, government agencies, and worker organizations. Councils are co-chaired by one NIOSH representative and another member from outside NIOSH.

Statement of Purpose

NORA councils are a national venue for individuals and organizations with common interests in occupational safety and health topics to come together. Councils will start the third decade by identifying broad occupational safety and health research objectives for the nation. These research objectives will build from advances in knowledge in the last decade, address emerging issues, and be based on council members and public input. Councils will spend the remainder of the decade working together to address the agenda through information exchange, collaboration, and enhanced dissemination and implementation of solutions that work.

Although NIOSH is the steward of NORA, it is just one of many partners that make NORA possible. Councils are not an opportunity to give consensus advice to NIOSH, but instead a way to maximize resources towards improved occupational safety and health nationwide. Councils are platforms that help build close partnerships among members and broader collaborations between councils and other organizations. The resulting information sharing and leveraging of efforts promotes widespread adoption of improved workplace practices based on research results.

Councils are diverse and dynamic, and are open to anyone with an interest in occupational safety and health. Members benefit by hearing about cutting-edge research findings, learning about evidence-based ways to improve safety and health efforts in their organization, and forming new partnerships. In turn, members share their knowledge and experiences with others and reciprocate partnerships.

The Respiratory Health Cross-Sector Council

The Respiratory Health Cross-Sector Council (RHCC) began to take shape in August 2016 when Dr. Akshay Sood from the University of New Mexico agreed to be a Co-Chair together with Dr. Paul Henneberger from NIOSH. During September through November 2016, the co-chairs invited a variety of stakeholders to join the council, and others volunteered to join once they learned about the third decade of NORA and the RHCC in particular. Affiliations and number of RHCC members as of December 2017 are: NIOSH (n=5), other federal agencies (n=2), state government (n=2), non-US national institute of occupational health (n=1), academia (n=9), patient representatives (n=2), and a management health and safety director (n=1). The RHCC was very active during December 2016 through July 2017, with five online meetings, one in-person meeting, and numerous email messages among members. Council members considered numerous inputs, including published scientific literature, personal experience, and suggestions from members of the public in response to a blog posted in the NIOSH website in June 2016, and then proposed, discussed, and ranked research objectives for work-related respiratory health. This resulted in ten primary strategic objectives and several sub-objectives to address work-related respiratory health. The Council then composed statements describing the health and economic burdens addressed by each objective. The RHCC looks forward to refining and implementing the third decade of NORA Respiratory Health Strategic Objectives, in part by facilitating engagement of other interested individuals and organizations in a range of activities. These activities could include organizing seminars and symposiums, developing publishable papers or statements that further refine the objectives or propose actions based on them, generating communication products, and conducting demonstration projects for interventions.

What does the National Occupational Research Agenda for Respiratory Health represent?

The National Occupational Research Agenda for Respiratory Health is intended to identify the research, information, and actions most urgently needed to prevent work-related respiratory disease and improve workers' respiratory health. This National Occupational Research Agenda for Respiratory Health provides a vehicle for stakeholders to describe the most relevant issues, gaps, and safety and health needs for the cross-sector. Each NORA research agenda is meant to guide or promote high priority research efforts on a national level, conducted by various entities, including: government, higher education, and the private sector. Because the Agenda is intended to identify priorities for national efforts to prevent work-related respiratory disease and improve workers' respiratory health, it cannot at the same time be an *inventory* of all issues worthy of attention. The omission of a topic does not mean that topic was viewed as unimportant. However, those who developed this Agenda believed that the number of topics should be small enough so that resources could be focused on a manageable set of objectives, thereby increasing the likelihood of real impact in the workplace.

NIOSH will use the Agendas created by the sector and cross-sector NORA Councils to develop a NIOSH Strategic Plan. Programs will use criteria based on the *burden* associated with issues addressed in plans, the *need* for specific types of efforts to reduce burden, and the potential *impact* of these efforts ("BNI criteria") to write research goals that articulate and operationalize the components of the NORA Sector and Cross-Sector Agendas that NIOSH will take up. NORA Agendas and the NIOSH Strategic Plan will be separate but linked.

Who are the target audiences?

The RHCC target audience is diverse, as are the strategic goals. This audience includes:

- Front-line occupational safety and health professionals, including occupational physicians, occupational nurses, industrial hygienists, and safety officers.
- Researchers from a variety of specialties, including epidemiologists, survey researchers, exposure scientists, basic and applied laboratory researchers, clinical scientists, and intervention scientists.
- Workers in all occupational groups.
- Patients with work-related respiratory diseases.
- Management of both small and large companies.
- Unions concerned with the workplace safety and health of their members.
- Academic and professional organizations with an interest in preventing work-related respiratory disease and improving workers' respiratory health.
- Health-related agencies at the federal, state, and local levels of government in the U.S.
- Health-related agencies in non-U.S. governments concerned with work-related respiratory health.

How was the research agenda developed?

The National Occupational Research Agenda for Respiratory Health was developed over several months starting in December 2016. Council members contributed by taking part in online meetings and an in-person meeting, and by completing assignments. The focus of each of five online meetings was:

- December 2, 2016: RHCC members introduced themselves, heard background on the third decade of NORA, and were asked to submit their lists of priority issues for occupational respiratory health.

- January 6, 2017: Council members discussed possible research priorities, and were asked to prepare strategic objectives based these priorities.
- February 16, 2017: Council members discussed the research strategic objectives and sub-objectives, and were asked to rank them.
- March 31, 2017: Council members discussed and further revised the top 10 research objectives that were identified by the ranking.
- July 25, 2017: Council members reviewed statements describing the burden related to issues addressed by objectives and sub-objectives ("burden statements") that they had helped to compose and provided further suggestions for changes and additions. They also began to discuss activities for the implementation phase, planned to start after completion of the objectives.

An optional in-person meeting took place on May 20, 2017, in conjunction with the annual American Thoracic Society International Conference in Washington, DC. This meeting provided the opportunity to complete assignments to write burden statements for each of the 10 RHCC strategic objectives.

THE OBJECTIVES

Work-related exposures make a substantial contribution to the overall burden of respiratory diseases in the U.S. NIOSH researchers recently estimated the frequency of occupational illnesses in the U.S. using data from the Bureau of Labor Statistics (Groenewold, Brown, Smith, Pana-Cryan, & Schnorr, 2017). They concluded that new non-malignant occupational respiratory diseases represented the most numerous type of occupational illness in the U.S. This category of illnesses included occupational asthma, chronic obstructive pulmonary disease (COPD), and pneumoconiosis, and numbered 400,000 to 600,000 new cases in 2012.

The 10 strategic objectives are organized into three sections. Strategic objectives 1-4 address occupational respiratory diseases. Strategic objectives 4-7 address occupational respiratory exposures. Finally, strategic objectives 8-10 focus on the fundamental activities of surveillance, exposure assessment, and communications that are needed for a comprehensive research and prevention program.

STRATEGIC OBJECTIVES 1-4: WORK-RELATED RESPIRATORY DISEASES

Objective 1: Prevent and reduce work-related lower and upper airways diseases

1.1 Prevent and reduce work-related asthma

Approximately 7.7% of adults in the U.S. have current asthma (Moorman et al., 2012). Work-related asthma (WRA) includes both occupational asthma that is caused by work, and work-exacerbated asthma that is worsening of existing asthma due to workplace conditions. An estimated 16.3% of adult-onset asthma cases are attributable to occupation (Torén & Blanc, 2009), and the prevalence of work-exacerbated asthma is approximately 21.5% among adults with asthma (Henneberger et al., 2011). Follow-up studies of occupational asthma cases reported rates of prolonged unemployment ranging from 14% to 69% and of income loss ranging from 44% to 72% (Vandenplas, 2008). The 1996 estimated annual cost associated with WRA was $1.6 billion, or $1082 per worker (Leigh, Romano, Schenker, & Kreiss, 2002). Adjusting for a 111% increase in medical care costs between 1996 and 2016 (BLS, 2017a), the 2016 cost for a WRA case was $2281 per worker. As many as 2.7 million U.S. workers may have WRA (Dodd & Mazurek, 2016); therefore, the annual cost of WRA in 2016 was an estimated $6 billion.

Basic/etiologic research is needed to address a variety of issues. Additional work is needed to clarify mechanisms and improve the ability to diagnose immune sensitization and asthma caused by low molecular weight agents. Validated biomarkers of relevant exposures and biological response that could potentially be used for secondary prevention are also needed. Intervention research is an important need. Effectiveness and return on investment of interventions to prevent WRA needs additional documentation. Many asthma researchers are skeptical that asthma can be prevented, and additional studies are needed to confirm effectiveness of primary prevention efforts. Secondary prevention activities, notably removal from exposure, frequently result in job loss and/or a decline in income. These consequences require additional elaboration. Translational research is needed to identify and address barriers to dissemination of known effective primary and secondary preventive interventions for WRA. Surveillance research is needed because WRA is poorly quantified by routinely-available data sources, despite available evidence documenting its great burden. Tracking the burden of disease through existing and innovative data sources is therefore a very great need.

1.1.1 Develop and validate diagnostic algorithms for work-related asthma that can be used by primary care providers (PCPs) prior to referral to a specialist.

A 2017 critical review of diagnostic procedures for work-related asthma resulted in a recommended diagnostic algorithm (Vandenplas, Suojalehto, & Cullinan, 2017). However, many of the techniques in the algorithm are only found in specialized centers, and the authors called for the development of additional centers that can implement these techniques. This means that primary care providers (PCPs) still have the responsibility of deciding when to send their asthma patients to occupational or pulmonary physicians who can provide the necessary evaluations to confirm a suspected case of work-related asthma. PCPs need their own algorithms to make informed referrals. Further work is needed to develop, validate, and disseminate diagnostic algorithms for work-related asthma that PCPs will use to decide when to refer a patient to a specialist.

1.1.2 Prevent and reduce work-related asthma related to indoor environmental quality

Non-industrial indoor work environments can pose a serious threat to the respiratory health of workers in many industry sectors in the U.S. (NAS, 2017). For example, respiratory health has been threatened by poor indoor environmental quality (IEQ) in schools associated with moisture damage, mold, dust, and other exposures (Kielb et al., 2015), and in healthcare associated with damp and mold, cleaning and disinfecting products, and construction materials (Kurth et al., 2017). New indoor moisture and mold problems can occur in workplaces where flooding during extreme weather events is followed by ineffective remediation of water damage.

Prominent scientific organizations and work groups have concluded that additional research is needed to improve our understanding of the association of respiratory health with IEQ. The National Academies of Sciences (NAS) published a 2017 consensus document entitled "Microbiomes of the Built Environment: A Research Agenda for Indoor Microbiology, Human Health, and Buildings" that is applicable to indoor workplaces (NAS, 2017). The committee of experts enumerated several knowledge gaps, including the need to better understand mixed exposures in damp buildings and the associations of these exposures with respiratory and allergic health outcomes. The NAS committee called for significant additional research to address these and other gaps. The Cochrane Collaboration produced a 2015 systematic evaluation of literature to evaluate whether remediating damp and moldy buildings prevents or reduces respiratory diseases including asthma (Sauni et al., 2015). The report concluded that existing evidence was of low or moderate quality, and there is a need for better research with validated outcome measures. Finally, the Alfred P. Sloan Foundation sponsored a workshop on the state of the science related to the human health effects of microbial exposures in indoor environments. The experts who attended the workshop concluded that there is still not a broad consensus that indoor microbial exposures cause asthma (Mensah-Attipoe, Täubel, Hernandez, Pitkäranta, & Reponen, 2017). They recommended additional research that includes robust cross-sectional epidemiologic studies, intervention studies, studies to validate exposure assessment methods, and toxicological exposure studies.

One industry of concern regarding IEQ and respiratory health is educational services. It is the second largest U.S. industry with about 13.3 million workers, including approximately 7.7 million teachers. The education industrial sector has a high prevalence of current asthma with 9.1%, or about 1.2 million workers (Dodd & Mazurek, 2016). Given reliable estimates of the incidence of asthma (Winer, Qin, Harrington, Moorman, & Zahran, 2012), as well as the burden of occupational asthma (Torén & Blanc, 2009) and work-exacerbated asthma (Henneberger et al., 2011), 8,200 workers had onset of occupational asthma and 260,000 asthma cases experienced work-exacerbated asthma in educational services in 2016. The National Education Association has brought attention to the poor state of schools in the U.S., specifically that two-thirds of the nation's 80,000 public schools have unhealthy environmental conditions (NEA, 2011). These conditions can potentially impact respiratory health. For example, research conducted in New York State indicated that current asthma among teachers was associated with moldy odors, visible mold, moisture damage, dust, and odors from perfumes/air fresheners (Kielb et al., 2015). Thus, IEQ continues to be an important issue in educational settings.

Basic/etiologic, intervention, translational, and surveillance research are all needed to better understand and prevent work-related asthma related to IEQ. More specifically, a better understanding of how mixed exposures (including cleaning chemicals, microbial agents, and stress) in indoor work environments contribute to the onset and exacerbation of asthma would help to inform prevention. Also, longitudinal studies are needed to demonstrate the effectiveness of different intervention strategies.

1.1.3 Prevent and reduce irritant-induced work-related asthma

A 2014 position paper prepared by the European Academy of Allergy and Clinical Immunology (EAACI) provides guidance for research and intervention activities needed to prevent and reduce irritant-induced work-related asthma (Vandenplas et al., 2014). The paper includes a thorough discussion of the causes, pathogenesis, clinical characteristics, diagnosis, and management of this type of work-related asthma. The EAACI recommends additional research regarding the assessment of exposures, identification of host factors including biomarkers, and development of objective diagnostic tests for irritant-induced asthma. The position paper also recommends primary prevention by reducing exposures and education, and tertiary prevention by optimizing case management.

1.2 Prevent and reduce work-related chronic obstructive pulmonary disease (COPD)

1.2.1 Identify risk factors for work-related COPD that can inform strategies for prevention

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease that impedes airflow and is a major cause of morbidity and mortality worldwide (Murray et al., 2012; WHO, 2016). In the U.S., COPD was responsible for 137,693 deaths and 739,000 hospitalizations in 2008 (NHLBI, 2012), and in 2006 hospitalizations for acute exacerbations of COPD among persons 40 years and older were estimated to cost $11.9 billion dollars (Perera, Armstrong, Sherrill, & Skrepnek, 2012). While cigarette smoking is the primary risk factor for COPD (Eisner et al., 2010), an official statement of the American Thoracic Society estimated that 15% of the population burden of COPD can be attributed to occupational exposures (Balmes et al., 2003). The population attributable fraction for occupational exposure is higher among never smokers, with a recent estimate of 48% (Würtz, Schlünssen, Malling, Hansen, & Omland, 2015). Because occupation makes such an important contribution to the burden of COPD, additional efforts are needed to both identify risk factors and develop strategies to prevent work-related COPD.

1.2.2 Investigate how occupational exposures contribute to the exacerbation and progression of COPD

Exacerbation of symptoms is common among COPD patients and is associated with adverse outcomes. A longitudinal study of 1,105 COPD patients determined that 49% had at least one acute exacerbation during the three years of follow-up, 7% at least one such exacerbation event each of the three years, and 2% had two or more exacerbations in each of the three years (Han et al., 2017). The most common phenotypes were COPD patients with no exacerbations during the three years (51%) and those who changed exacerbation status from year to year. Both lower quality of life (Seemungal et al., 1998) and accelerated decline in lung function (Donaldson, Seemungal, Bhowmik, & Wedzicha, 2002) are associated with the frequency of COPD exacerbation events. While many studies have investigated demographic, management, biomarker, and symptom characteristics related to exacerbation of COPD, there has been no serious effort to investigate the contribution of occupational exposures to these unfortunate events. The recognition of work-site conditions that cause COPD exacerbations would help to inform prevention.

1.2.3 Delineate the phenotype of work-related chronic bronchitis

Chronic bronchitis (CB), defined by the presence of chronic cough and phlegm, is common among COPD patients. From a multicenter study in the U.S., 27% of COPD patients had CB (V. Kim et al., 2011). COPD patients with CB have more exacerbation events and worse mortality than non-CB COPD patients (V. Kim & Criner, 2013). Several studies conducted over ten years ago identified an association of CB with occupational exposures, especially dust, that were defined by self-reports or job-exposure matrices (Ehrlich et al., 2004; Matheson et al., 2005; Trupin et al., 2003). Additional research is needed to contrast work-related COPD cases with and without CB to determine differences in the types of precipitating workplace exposures, progression of disease (e.g., exacerbations, changes in pulmonary function), quality of life, and effectiveness of management strategies such as decreasing or eliminating harmful workplace exposures. As part of this effort, the characterization of occupational exposures should be improved relative to prior studies in order to generate more effective guidance for interventions.

1.3 Prevent and reduce asthma-COPD overlap (ACO) by identifying occupational risk factors and defining the inflammatory mechanisms (i.e., endotypes) for ACO

The combination of asthma and COPD has been recognized for decades, and it is relatively recently that this condition was given the label of asthma-COPD overlap (ACO) (GINA, 2015). There is still disagreement about the clinical definition of ACO; how it differs from both asthma and COPD; and the prevalence of disease that varies considerably due to differing diagnostic criteria (Mannino, Gan, Wurst, & Davis, 2017). Early reports suggest that ACO is associated with exposure to biomass burning (Morgan et al., 2017), but little else is known about environmental risk factors. A PubMed search (conducted on June 16, 2017) using the search terms "asthma-COPD overlap" and "occupation" resulted in no matches. A variety of basic/etiologic research is needed to answer fundamental questions about the work-relatedness of this condition. Which occupations and industries have an elevated risk for ACO? Which workplace exposures, including combinations of exposures, are associated with ACO? What are the inflammatory mechanisms of occupational ACO?

1.4 Define, prevent, and reduce work-related upper airways disease

1.4.1 Define work-related upper airways disease such as rhinitis, sinusitis, and pharyngeal and laryngeal diseases, and identify occupational risk factors.

1.4.2 Develop and validate diagnostic algorithms for work-related upper airways disease that primary care providers (PCPs) can use prior to referring patients to a specialist.

1.4.3 Identify and validate effective strategies to prevent and reduce work-related upper airways disease

The definition, classification, diagnostic evaluation, risk factors, and treatment of work-related upper airways disease (disorders of the nose, sinuses, pharynx, and larynx) remain rudimentary in comparison to its lower airway counterpart. Despite relative under-recognition, it has become clear that such disorders are prevalent and adversely impact quality of life and work capacity (Airaksinen, Luukkonen, Lindström, Lauerma, & Toskala, 2009; Groenewoud, De Groot, & Van Wijk, 2006). In fact, occupational rhinitis is at least twice as common, and perhaps even four times as common, as occupational asthma (Moscato et al., 2009). Of the few studies delineating prevalence, one in Norway suggested between 23 and 50% among bakers alone (Hytönen et al., 1997). Indeed, the risk of developing occupational rhinitis (OR) was highest among bakers, along with furriers, livestock breeders, food-processing workers, veterinarians, farmers, electronic product assemblers, and boat builders (Storaas, Steinsvåg, Florvaag, Irgens, & Aasen, 2005). Another study reported rates of OR as high as 40% among animal handlers (Folletti, Forcina, Marabini, Bussetti, & Siracusa, 2008), demonstrating that high prevalence of OR is indeed likely, at least in certain occupations. In fact, incidence of “sinusitis” (probably strongly overlapping with rhinitis) was estimated at 42.3% in the largest cohort of World Trade Center dust-exposed workers (Wisnivesky et al., 2011). Although the upper airway is a continuum, and the distal segments (i.e., the pharynx and larynx) are most likely affected by similar toxicants as the sinonasal passages, much less is known about resulting occupational disease in those locations. Additional work is needed to define work-related upper airways disease, identify occupational risk factors, develop and validate diagnostic algorithms that can be used by primary care providers, and identify and validate prevention strategies.

Objective 2: Prevent and reduce work-related interstitial/dust-induced lung diseases

2.1 Increase the role of exposure assessment in the evaluation of patients diagnosed with idiopathic pulmonary fibrosis (IPF) to improve identification of possible workplace contribution

Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of Usual Interstitial Pneumonia (UIP) (Raghu et al., 2011). This diagnosis requires the exclusion of other known causes of interstitial lung disease, such as occupational and environmental exposures. IPF has no known cure, has an estimated prevalence in the U.S. of 18.2

cases per 100,000 persons (Raghu, Chen, Hou, Yeh, & Collard, 2016), and accounted for 27% of all adult lung transplantations in the U.S. from 2004 to 2015, which cost an average of $450,400-$657,800 per transplant (Hauboldt, Hanson, & Bernstein, 2008; Yusen et al., 2016). Known occupational exposures associated with development of UIP-pattern pulmonary fibrosis include those associated with development of hypersensitivity pneumonitis (of which there are many) (Selman, 2003; Spagnolo et al., 2015), asbestos (Raghu et al., 2016), inorganic dusts (coal mine dust, silica, and uranium dust), and certain metals. These occupational lung diseases can be prevented through interventions such as controlling exposures and, in some cases, cessation of exposure (for example, after development of immune sensitization to an agent).

Epidemiologic literature suggests that patients with IPF have higher rates of exposure to occupational dusts, including wood, metal, and animal dusts (Hubbard, 2001; Hubbard et al., 2000; Hubbard, Lewis, Richards, Johnston, & Britton, 1996; Miyake et al., 2005), and are more commonly working in jobs that involve farming, raising birds, hair dressing, stone cutting/polishing, and exposure to livestock (Raghu et al., 2011). If recognition of occupational exposures to hazardous agents were increased, there might be greater opportunities for primary and secondary prevention of IPF, which is currently an untreatable, irreversible lung disease. For this reason, it is important to increase the role of exposure assessment in evaluation of patients diagnosed with IPF and with other forms of pulmonary fibrosis, in order to improve identification of possible workplace contribution. This knowledge ultimately could lead to better exposure controls and improved prevention of disease.

2.2 Prevent and reduce coal workers' pneumoconiosis and other dust-induced lung diseases, including those associated with nanomaterials

Millions of working and retired miners as well as workers in other dusty trades are at risk for a spectrum of lung diseases including pneumoconioses. Beginning in 2000, surveillance of working U.S. coal miners showed an unexpected increase in the proportion of miners with chest radiographic findings of pneumoconiosis. Among coal miners with pneumoconiosis, 35% showed rapidly progressive disease and 5% had severe progressive massive fibrosis that occurred mainly in underground Appalachian coal miners (V. C. D. S. Antao et al., 2005). Analysis of lung tissue samples in affected coal miners showed a preponderance of silica and silicate particulates, implicating exposure to respirable silica in disease pathogenesis (Cohen et al., 2016). In the U.S., the Occupational Safety and Health Administration (OSHA) estimates 2.3 million workers are exposed to respirable crystalline silica in a variety of occupations such as mining, stone and synthetic countertop cutting, sandblasting, and foundry work (OSHA, 2016). An estimated 1,437 deaths in the U.S. had silicosis as the underlying or contributing cause of death during 2001-2010 (Bang et al., 2015). Based on asbestos consumption per capita, it has been estimated that nearly 30,000 asbestosis deaths will occur during the period 2005 – 2027, an average of 1290 deaths per year (V. C. D.S. Antao, Pinheiro, & Wassell, 2009). Less well recognized exposures also contribute to the burden of dust-induced lung diseases. Nanomaterials, defined as having a length scale between one and 100 nanometers, exhibit unique properties that affect physical, chemical, and biological behavior. Animal and other toxicological studies have shown adverse lung effects include inflammation and fibrosis (Maynard & Kuempel, 2005). Since there is no known effective treatment for any of the pneumoconioses, primary prevention to control workplace fibrogenic dust exposures, medical surveillance for early disease detection, and other interventions from across the hierarchy of controls are essential.

Objective 3: Prevent and reduce work-related respiratory infectious diseases

3.1 Improve the technology of respiratory protection to prevent infectious diseases and improve the way the protection is used at the workplace

Respiratory protection can protect users from inhalation of infectious agents associated with small particle aerosols and thus can potentially reduce the burden of occupationally acquired infectious diseases, but a variety of factors may limit effective use and compliance with recommended practices. These range from user factors, such as comfort, ability to communicate, interference with work tasks, increased work of breathing, skin irritation, and psychological factors, to issues with self-contamination from doffing, to issues with cleaning and decontamination of reusable respirators (Gosch et al., 2013; J. H. Kim, Benson, & Roberge, 2013; Palmiero, Symons, Morgan, & Shaffer, 2016). In order to maintain a healthy, viable workforce, particularly in the event of emergency events like infectious disease epidemics and pandemics associated with risk for transmission via the aerosol route, focus must remain on improving the technology of respiratory protection to prevent infectious diseases and improve the way that protection is used.

3.2 Evaluate optimal methods to prevent influenza transmission in healthcare workers, including the role of protection against transmission by small particle aerosols

The annual direct costs, such as hospital and doctor's office visits, and medications for influenza in the U.S. are an estimated $4.6 billion (Molinari et al., 2007). Influenza causes U.S. workers to lose up to 111 million workdays at an estimated cost of $7 billion a year in sick days and lost productivity (Molinari et al., 2007). An evolving body of research demonstrates that influenza virus can remain suspended in the air in association with small particles that can remain airborne for prolonged periods and potentially travel over long distances (Blachere et al., 2009; Blachere et al., 2007; Cummings et al., 2014; Lindsley et al., 2010). Also, influenza associated with small particle aerosols can retain in vitro infectivity (Lindsley et al., 2016; Lindsley et al., 2015). Respiratory protection can effectively limit inhalation of such small airborne particles. Most current hospital practices, however, are based on limited epidemiology about occupationally acquired infections and the theory that influenza viruses are primarily transmitted by large droplets directly projected from infected individuals onto recipients' mucous membranes or onto surfaces where they can subsequently be transmitted via indirect contact transmission (Gralton & McLaws, 2010). Given current uncertainties about the relative importance of various routes of transmission, it is not surprising that controversy remains as to the most appropriate strategies to protect healthcare workers from influenza infection in order to maintain a healthy, viable and ready healthcare workforce. Thus, focus must remain on documenting the relative importance of potential modes of transmission, the effectiveness of preventive interventions addressing potential modes of transmission including small particle aerosol transmission, and disseminating known effective interventions such as hand washing and influenza vaccination.

Objective 4: Prevent and reduce work-related respiratory malignancies

4.1 Prevent and reduce lung cancer induced by diesel exposure

4.2 Delineate the genetic and epigenetic signatures of occupational respiratory cancers

4.3 Evaluate optimal approaches to computed tomography (CT) screening for lung cancer in workers with histories of exposures to lung carcinogens

The International Agency for Research on Cancer currently lists a number of substances/work situations/occupations with sufficient evidence of causing lung cancer in humans (IARC Group 1)(Algranti, Buschinelli, & De Capitani, 2010; Field & Withers, 2012). Classes of agents include ionizing radiation and various chemicals and mixtures, metals, and dusts and fibers. In a frequently cited paper, Peto and colleagues conservatively estimated that occupational exposures are responsible for 15% and 5% of lung cancer in men and women, respectively, in the U.S. (Peto et al., 1985). Other literature suggests that more than half of the occupational lung cancers are due to asbestos (Steenland, Loomis, Shy, & Simonsen, 1996). The 2008 to 2009 President's Cancer Panel Report indicated that the cancer risk estimates proposed by Peto and colleagues, as well as risk estimates from similar studies, "are woefully out of date, given our current understanding of cancer initiation as a complex multifactorial, multistage process" (NCI, 2010). In one Slovenian study, the proportion of patients with lung cancer working in professions with exposures to known carcinogens was as high as 34% (Rajer, Zwitter, & Rajer, 2014). A recent review noted that there is extensive literature on lung cancer caused by some carcinogens such as asbestos, silica, and diesel exhaust exposures, but there is less extensive literature for many carcinogens, including on their interactions with tobacco (Delva, Andujar, Lacourt, Brochard, & Pairon, 2016). In addition, there is a need for better understanding of the interactions between genetic and epigenetic factors and occupational exposures in occupational respiratory cancer causation. In view of recent changes in diesel technology that reduce and change the character of emissions, it will be important to assess the implications to cancer risk of transition to modern Tier IV diesel engines (Diesel Technology Forum, 2018; McClellan, Hesterberg, & Wall, 2012). Documenting whether occupationally-related respiratory cancers are associated with identifying genetic and epigenetic signatures could have implications for prevention and potentially allow for improved attribution of causation at the individual level. Because early diagnosis can markedly improve the clinical outcome of lung cancer, and because screening a subset of smokers for early stages of lung cancer with low-dose chest CT scans has been shown to be effective, it is important to document whether screening some subset of workers with histories of exposure to lung carcinogens is also effective.

STRATEGIC OBJECTIVES 5-7: OCCUPATIONAL RESPIRATORY EXPOSURES

Objective 5: Advance the understanding of how acute and lifetime mixed occupational exposures and mixed occupational and non-occupational exposures impact respiratory health

Basic/etiologic research is needed to assess the risk for respiratory health outcomes by co-exposures to individual components of complex mixtures. Are effects additive, supra-additive, or multiplicative? Intervention studies are also needed to demonstrate effectiveness of addressing these complex exposures, whether they are exclusively occupational or a combination of occupation and non-occupational risk factors.

5.1 Prevent and reduce work-related respiratory diseases associated with mixed occupational exposures

Mixed occupational exposures are common, and the following examples highlight how these exposure circumstances can lead to a variety of adverse respiratory outcomes.

From the first descriptions of miners' phthisis, the effect of mixed exposures on causation of occupational lung disease has remained a concern. While single exposure-single disease research has more often been the focus of attention, significant occupational epidemiological findings of the 20th century pointed to the residual or unexplained causation left by this research approach. One relatively recent example was provided by the World Trade Center-related investigations, which revealed a complex but poorly characterized mixture of toxicants (particulates, fibers, smoke, gases, fumes) that seems to have led to mixed respiratory health outcomes, such as a nonspecific chronic bronchitis, asthma, chronic bronchiolitis, and aggravated obstructive lung disease (De La Hoz, 2010; de la Hoz et al., 2008; Wisnivesky et al., 2011). That research has also unveiled adverse respiratory health effects from physical (De La Hoz, 2010) and psychological comorbidities (De La Hoz, Jeon, Miller, Wisnivesky, & Celedón, 2016). Novel approaches that integrate the totality of human exposures, including environmental and occupational, psychosocial, behavioral, and genetically determined factors invite the development of appropriate epidemiological methods (DeBord et al., 2016) and promise to increase our understanding of the complexity of chronic occupational respiratory diseases.

There are also emerging issues in respiratory disease and mixed occupational exposures encountered by military personnel, defense department contractors, and U.S. government employees deployed in military operations. These workers are potentially exposed to multiple poorly-characterized sources of lung injury during deployment, ranging from direct physical injury to the lung from explosive devices (blast-related acute lung injury) (Mackenzie & Tunnicliffe, 2011) to airborne particulate exposures including smoke from burn pits, desert dust, and dusts containing metals such as cadmium, titanium, aluminum, and lead (Abraham, DeBakey, Reid, Zhou, & Baird, 2012; Engelbrecht et al., 2009a, 2009b; Rose, 2012; Sanders et al., 2005; Taylor et al., 2013; Weese & Abraham, 2009). Exposure to cigarette smoke is a common additional lung health risk factor in these individuals. The long-term effects of these exposures remain incompletely characterized, but mounting evidence indicates that deployed military personnel have nearly twice the rate of respiratory symptoms (cough or shortness of breath) compared to non-deployed personnel, and that the incidence of respiratory symptoms increases with length of deployment (Morris et al., 2014; Roop, Niven, Calvin, Bader, & Zacher, 2007; Smith et al., 2009). In some cases, these symptoms are attributable to chronic lung diseases such as asthma, bronchiolitis, and eosinophilic pneumonia (King et al., 2011; Morris et al., 2014; Shorr et al., 2004; Szema, Peters, Weissinger, Gagliano, & Chen, 2010). These complex, variable, and mixed deployment inhalational exposures along with the wide spectrum of lung disease outcomes among deployers are an example of a newer occupational exposure circumstance for which multidisciplinary research approaches will be critical in developing targeted prevention.

Another example of a potential source of mixed exposures is coal slag, which is a recycled byproduct of coal combustion that is often used for abrasive blasting. A NIOSH investigation revealed that this product can include low levels of dust and silica (Mugford, Boylstein, Armstrong Gibbs, & McCague, 2016). However, the same samples included varying amounts of the metals beryllium, chromium, cobalt, copper, iron, manganese, nickel, titanium, and vanadium, with somewhat higher levels of iron and titanium. The exact content of coal slag is likely to vary based on regional differences in geology and coal formation. The preparation of this product in manufacturing facilities and its use in construction and manufacturing as a blasting material may pose a risk to the respiratory health and for beryllium sensitization of workers. It is also possible that the combined effects of the different constituents may exceed the impact of each individually.

5.1.1 Investigate the impact of mixed exposures in the hydraulic fracturing and petroleum industries to benzene, toluene, ethyl benzene, and xylene (BTEX), polycyclic aromatic hydrocarbons (PAHs), respirable crystalline silica, and other agents on the respiratory health of workers, in particular airways disease and cancer

The natural gas obtained by hydraulic fracturing (also called hydrofracturing or fracking) burns much cleaner than coal, which means fewer air emissions. However, a recent review of emerging occupational and environmental respiratory diseases highlighted concerns about the airborne exposures from hydraulic fracturing (Moitra, Puri, Paul, & Huang, 2015). Investigations of exposures at fracking sites have identified a variety of potential threats to the respiratory tracts of both workers and the general population, including benzene, toluene, ethyl benzene, and xylene (BTEX), polycyclic aromatic hydrocarbons (PAHs), respirable crystalline silica, hydrogen sulfide, diesel exhaust, and other airborne agents (Carpenter, 2016; McCawley, 2015; McKenzie, Witter, Newman, & Adgate, 2012). These exposures could pose a risk to the respiratory health of workers and others living close enough to the fracking sites, and of particular concern is their contribution to airways disease and respiratory cancers. Studies of human health effects have focused on community environmental exposures. For example, a recent study reported that the exacerbation of asthma among people living near fracking well sites was associated with phases of well development such as pad preparation, well drilling, actual hydraulic fracturing, and production (Rasmussen et al., 2016). Additional studies are needed to investigate the impact of these exposures on the respiratory health of workers at well sites.

5.2 Prevent and reduce work-related respiratory diseases associated with mixed occupational and non-occupational exposures, with research focused on the non-occupational factors of cigarette smoking, older age, and overweight/obesity

5.2.1 Investigate how cigarette smoking interacts with occupational exposures to adversely impact respiratory health

Cigarette smoke is a complex exposure that alone has its own harmful effects on the respiratory system and beyond, and can also modify and worsen the effect of occupational exposures. For example, a recent investigation in the U.S. reported that airflow limitation was associated with occupational vapor-gas, dust, and fume exposure among those with a history of smoking, but not among never smokers (Doney et al., 2014).

Based on the National Health Interview Survey (NHIS), the percentage of working adults who were currently smoking declined from 22.4% in 2004 to 18.1% in 2012 (Syamlal, Mazurek, Hendricks, & Jamal, 2015). By the 2012-2014 NHIS, 17% of working adults were current smokers and this figure varied by industry (Syamlal, Jamal, & Mazurek, 2016). The six industries with the highest percentages for current smoking were: construction 26.2%, accommodation and food services 25.5%, mining 25.2%, administration and support and water management and remediation services 22.6%, transportation and warehousing 21.4%, and manufacturing 21.3%. While some segments of the services industry had high percentages, notably 25.5% for accommodation and food services, other segments were below the average, such as 8.0% for educational services. Additional basic/etiologic research is needed to better understand how cigarette smoking and occupational exposures interact to impact the respiratory tracts of workers.

5.2.2 Investigate how older age interacts with occupational exposures to adversely impact respiratory health

The median age of the workforce in the United States has been increasing, rising by nearly 5 years from a median of 37.7 years in 1994 to 42.2 years in 2016 (BLS, 2017b; Toossi, 2015). Older workers present their own set of health and performance issues, as discussed in a book from the National Academy of Sciences (Wegman, 2004). With respect to respiratory health, pulmonary function steadily declines and susceptibility to infections increases with age. What is less well known is whether the older worker is more susceptible to the impact of non-infectious occupational exposures, including sensitizing and non-sensitizing agents such as the vast array of occupational vapors-gases, dusts, and fumes. This is an opportunity for more basic/etiologic research and surveillance to document how workplace exposures impact older workers, including those with pre-existing occupational and non-occupational respiratory diseases.

Some industries are above the 2016 overall median age of 42.2 years for all employed persons: 44.7 years for coal mining, 46.7 years for nonmetallic mineral mining and quarrying, 44.5 years for manufacturing, 45.4 years for transportation and utilities, and 44.1 years for educational services (BLS, 2017b). Other industries are distinctly younger, with median ages of 30.0 years for accommodation and food services, and 39.3 years for wholesale and retail trade.

5.2.3 Investigate how over-weight/obesity interacts with occupational exposures to adversely impact respiratory health

Based on the National Health Interview Survey (NHIS) in the United States, the prevalence of obesity among all workers has dramatically increased over the past three decades, from 10% in 1986 to 28% in 2011 (Caban et al., 2005; Gu et al., 2014). The prevalence of obesity is not uniform across U.S. jobs, with the highest value of more than 41% in protective services, and also levels of 36% in community and social services, and only 20% among employees in real estate, rental, and leasing businesses. Obesity is associated with a greater likelihood of injuries, including chest wall injuries (Gu et al., 2016), and a greater rate of workers' compensation claims (Ostbye, Dement, & Krause, 2007). Obesity is also associated with greater self-reported respiratory symptoms such as wheeze and dyspnea (Lee et al., 2009); worse health status in smokers (Sood, Petersen, Meek, & Tesfaigzi, 2014); increased risk for incident asthma (Dixon et al., 2010); inadequate control of asthma symptoms (Dixon et al., 2010); worse quality of life in patients with COPD (O'Donnell, Ciavaglia, & Neder, 2014); greater odds of asthma-COPD overlap syndrome (Caillaud et al., 2017); increased risk for obstructive sleep apnea and obesity hypoventilation syndrome (Pierce & Brown, 2015); and increased risk for pulmonary embolism (Heit, Spencer, & White, 2016). There is limited literature on the potential interaction between obesity and occupational exposures on respiratory health. One study indicated that obese workers exposed to occupational asthmagens in a cable manufacturing company had disproportionately greater prevalence of asthma than other groups of workers (i.e., obese and non-exposed, non-obese and exposed, and non-obese and non-exposed) (Seyedmehdi et al., 2014).

Objective 6: Advance the understanding of the impact of occupational chronic low-level toxicant exposure on respiratory health, notably chronic low-level irritant exposure

Chronic exposure to inhaled irritants such as vapors, gases, dusts (organic and inorganic), and fumes (VGDF) has been associated with development of chronic obstructive pulmonary disease (COPD). COPD affects >5% of the population and is associated with high morbidity and mortality (NHLBI, 2012). An official statement of the American Thoracic Society estimated that 15% of the population burden of COPD is attributable to occupational exposures (Balmes et al., 2003). The population attributable fraction for occupational exposure is higher among never smokers, with a recent estimate of 48% (Würtz et al., 2015).

Chronic exposures to inhaled respiratory irritants at work have also been associated with worsening of asthma, termed work-exacerbated asthma. The prevalence of work-exacerbated asthma has been estimated at 21.5% for adults with asthma (Henneberger et al., 2011). Chronic moderate to low inhaled irritant exposures have also been suggested, from epidemiologic studies, to increase new-onset irritant-induced asthma (Vandenplas et al., 2014). The prevalence of asthma is increased in occupations with moderate to low irritant exposures, such as for cleaners, farmers, wood workers, aluminum smelter workers, and previously radiology technicians exposed to "dark room" chemicals. However, for many of these occupations there may be other mechanisms of new-onset asthma such as intermittent high level irritant exposures and sensitizer exposures, so this has been classified in a diagnostic algorithm as "possible irritant-induced asthma" (Vandenplas et al., 2014). In a previous evidence-based report, Baur et al. found the best evidence for causation of asthma or COPD related to irritants from 17 types of agents: benzene-1,2,4-tricarboxylicacid-1,2-anhydride, chlorine, platinum salt, isocyanates, cement dust, grain dust, animal farming, environmental tobacco smoke, welding fumes or construction work. Phthalic anhydride, glutaraldehyde, sulfur dioxide, cotton dust, cleaning agents, aluminum potrooms, various other farming environments, and foundries (Baur, Bakehe, & Vellguth, 2012).

Objective 7: Advance protection of the respiratory health of workers who respond to or are impacted by natural and unnatural disasters, including epidemics and pandemics

While it is not possible to anticipate all dangers, understanding the characteristics of airborne exposures typical of natural and unnatural disasters is essential to planning for implementation of preventive interventions including use of personal protective equipment (PPE) that will maximize the safety of workers potentially impacted by chemicals and infectious agents. The Emergency Preparedness and Response web site of NIOSH highlights the importance of understanding exposure to aerosols in disaster situations (NIOSH, 2017) : “Knowledge of distribution, re-suspension, and persistence of aerosol is extremely important in determining the risk from aerosol agents that are disseminated naturally (as in influenza), accidently, or purposely through terrorist events. Therefore, developing methods to evaluate the spatial and temporal distribution of biological and chemical aerosols is critical in identifying sampling strategies, predicting exposure-based risks, designing personal protective equipment and engineering controls, and identifying science-based clearance strategies for re-occupancy.” Additional basic/etiologic research is needed to inform these activities. In addition, there is a need for the development and validation of strategies for the timely evaluation of respiratory protection needs and for improvements in respiratory PPE that meets the needs of first responders.

OBJECTIVES 8-10: FUNDAMENTAL ACTIVITIES

Strategic Objective 8: Advance surveillance for occupational respiratory diseases and relevant exposures

8.1 Advance surveillance to improve the identification of emerging occupational respiratory diseases and relevant exposures

8.2 Advance surveillance for occupational respiratory diseases and relevant exposures by coordinating existing sources of surveillance data

8.3 Advance surveillance for occupational respiratory diseases and relevant exposures by identifying and validating new sources of surveillance data

There are several barriers to conducting meaningful public health surveillance for occupational respiratory diseases and relevant exposures. Traditional sources of data like the U.S. Bureau of Labor

Statistics conduct surveillance through systems that are much better at capturing data on work-related injuries than work-related illnesses. Common respiratory diseases like asthma can have both occupational and non-occupational causes, and the occupational etiology is often not considered by treating clinicians and, consequently, not recognized and reported through surveillance systems. Also, the workplace exposures responsible for long latency diseases like chronic obstructive pulmonary disease (COPD) could have occurred so far in the past that their work-relatedness is not recognized at the time of diagnosis and the disease is not labeled as related to work. Even if a long-latency disease is highly related to work, such as coal workers' pneumoconiosis, if diagnosis occurs after a worker has left their industry/occupation, cases are not routinely counted in current surveillance systems until they pass away and the death information is reported. This can be many decades after initial diagnosis. Hazard surveillance to track workplace exposures that cause or exacerbate respiratory diseases is often costly and uncommon. With these challenges, several surveillance research efforts are needed. Innovation is needed to make better use of existing sources of surveillance data, perhaps in combination, and to develop new sources of surveillance data. Also, new chemicals and new uses for known chemicals are introduced in workplaces each year, and surveillance techniques are needed to address these emerging exposures and diseases.

Objective 9: Advance the assessment of occupational exposures for the study of respiratory health

9.1 Develop new field equipment/strategies for the assessment of occupational exposures for the study of respiratory health

There have been several important improvements in the measurement of occupational airborne contaminants. Notably is the development and deployment of the continuous personal dust monitor (CPDM) for coal miners (https://www.cdc.gov/niosh/mining/features/CPDMhelpsminersavoiddust.html). Other improvements include the monitoring devices that can simultaneously measure a suite of different gases and dusts. For example, a hand-held real-time fourier-transform infrared spectrophotometer (FTIR) is commercially available that can function as a mobile-area sampler for several organic and inorganic chemicals. Additional equipment and strategies are needed to measure airborne exposures in a variety of occupational settings.

9.2 Develop new methods for the assessment of occupational exposures in epidemiologic studies of respiratory health

Field measurements often present a challenge to investigators attempting to conduct exposure assessment for epidemiology. The retrospective recreation of exposures when confronted with limited historical data has been a common problem. Now, with a surge in real-time continuous exposure monitors, investigators are presented with the challenge of how to summarize thousands of data points for dozens of different agents. In the past, this problem has received more attention from investigators of ambient air pollution who were dealing with data from stationary monitors of particles and gases like ozone. The large number of exposure data points is also very challenging for many occupational respiratory epidemiologists. There is a need to develop additional statistical methods for summarizing complex exposure data, guided by knowledge of the likely or known respiratory impact of the agents of interest.

Objective 10: Advance information dissemination, education, and positive changes in behavior for workers, patients, employers, policy makers, and health care providers about how to address the occupational contribution to respiratory health, including issues of impairment and disability

A healthy workplace is the result of efforts by a variety of stakeholders. Communicating what is necessary to protect the respiratory health of workers requires shaping the message to facilitate understanding and motivate action by the target audience. This is an ongoing challenge in preventing occupational respiratory diseases, and should take advantage of technological and communication options that are constantly evolving. There is a need for new communication and dissemination strategies that promote occupational respiratory health, including how to address respiratory impairment and disability due to occupational exposures.

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