
**NATIONAL OCCUPATIONAL RESEARCH AGENDA (NORA)**

# NATIONAL OCCUPATIONAL RESEARCH AGENDA FOR IMMUNE, INFECTIOUS AND DERMAL DISEASE PREVENTION (IID)

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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 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 is third decade in 2016 with an enhanced structure. The ten sectors formed for the second decade 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 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 Immune, Infectious, and Dermal Diseases Prevention (IID) Cross-Sector focuses on work-related immune diseases, such as irritant and allergic contact dermatitis, allergic rhinitis, asthma, or infectious disease, caused by work-related exposures. It also includes workplace exposures to chemicals that can be absorbed through contact with skin that may result in adverse health impacts.

## 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 have started the third decade by identifying broad occupational safety and health research objectives for the nation. These research objectives build from advances in knowledge in the last decade, address emerging issues, and are based on council member 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 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.

### Immune, Infectious, and Dermal Diseases Prevention Council

The NORA IID Cross-Sector Council brings together individuals and organizations to share information, form partnerships, and promote adoption and dissemination of solutions that work. Members were invited who had expertise or interest in one or more of the three broad but interrelated areas of focus of the cross sector: Immune, infectious, and dermal diseases. The IID Council was formed in 2016 for the third decade of NORA, and the initial web-based meeting was held Jan 26, 2017. The IID Council seeks to facilitate the most important research, understand the most effective intervention strategies, and learn how to implement those strategies to achieve sustained improvements in workplace practice. Members have come from universities and hospitals, government agencies, and private industry. Currently there are 15 active members of the IID Council who advanced six broad occupational safety and health research objectives for the current NORA decade.

## What does the National Occupational Research Agenda for IID represent?

The National Occupational Research Agenda for IID is intended to identify the knowledge and actions most urgently needed to identify occupational risk factors to prevent avoidable adverse health outcomes among workers. This agenda provides a vehicle for all stakeholders to describe the most relevant issues, research gaps, and safety and health needs for the cross-sector. It is meant to be broader than any one agency or organization. It identifies the priorities for the entire country and all of its research and development entities, whether government, higher education, or industry. Because the agenda is intended to guide national occupational health and safety efforts for IID, 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. Those who developed this agenda believe 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 as an input into the development of a NIOSH Strategic Plan. Programs will use the burden, need, and impact method 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 are to be separate but linked.

## Who are the target audiences?

Workers within broad and diverse occupational sectors are susceptible to immune, infectious, and dermal diseases. Ultimately, the intended beneficiary of IID research is the individual worker. The IID Council has identified an agenda that will require the efforts of researchers and physicians with expertise in these areas to achieve the objectives identified herein. For implementation of these objectives, the target audiences include partners in industry, labor, trade associations, professional organizations, and academia to reduce the incidence of immune, infectious and dermal diseases associated with work place exposures.

## How was the research agenda developed?

The agenda was developed collaboratively, with web-based meetings and e-mail discussions among the IID Council members. At the inaugural meeting of January 26, 2017, members were introduced to the vision of the Immune, Infectious, and Dermal Diseases Prevention Cross-Sector. Members were asked to consider using the burden, need, and impact method as a framework to guide the development of objectives, with the goal of maximum impact.

IID Council members were tasked individually with identifying evidence-based broad objectives informed by their areas of knowledge, expertise and concern. During subsequent meetings, each suggestion was discussed by the Council. These discussions led to refinement of the objectives and supporting language for justification. Ultimately, six objectives were agreed upon for the IID Agenda. These six objectives were reviewed and considered by all IID Council members, and all comments were discussed and incorporated. Meeting these objectives will require basic research to build upon a foundation of scientific knowledge so that future efforts to implement practices or technologies in the workplace will proceed from a sound, evidence-based foundation.

# THE OBJECTIVES

## Objective 1: Investigate effects of recurring low-level occupational exposures on dermal, immune, and infectious diseases

Workers who encounter chemical and biological agents at their jobs may typically be exposed to low levels over time which could result in immune dysfunction including hypersensitivity, immunosuppression, and/or autoimmunity[1]. Further, long-term cumulative absorption by the dermal route is expected to contribute to systemic and target organ toxicity (i.e, skin), especially when the skin barrier is impaired. Skin is constantly exposed to various endogenous and exogenous factors that may impact its barrier function at the physical, mechanical, immunological, and microbial levels. The barrier function of the skin depends upon a symbiotic relationship between resident microbial communities and host tissue[2]. Chronic alterations of barrier properties and skin microbiome may lead to changes in the potential for a chemical to be absorbed and metabolized by the skin[3,4], thus, increasing the ability of compounds and pathogens to enter the skin and systemic circulation causing adverse effects both locally and systemically.

Additional research is needed to better characterize the skin barrier functions, including the skin microbiome, and the impact of low-level occupational exposures received by skin. To advance our understanding on potential risks posed and to reduce the local and systemic effects of recurring low-level occupational exposures on dermal, immune, and infectious diseases, research is needed in the following areas:

- **Role of perturbations on skin microbiome in maintenance of skin barrier function**

In healthy adults, the skin microbial community has been shown to be dependent on the specific characteristics of the site of isolation[5]. Despite the skin's exposure to the external environment, its bacterial, fungal, and viral communities have been shown to be fairly stable over time[6]. However, the effect of either acute and/or chronic low-level exposures to occupationally relevant compounds on the skin microbiome composition and function has been examined only in a few studies. Acute exposure to antiseptic treatments was shown to result in a rapid, but short-term, depletion of the skin microbial community[7]. The potential health consequences of these types of effects are not well-documented or understood. In a recent study, the loss of a skin microbial community stability and decrease in immunoregulatory bacteria on the skin was shown to lead to cutaneous inflammation and potential infection[8]. Future studies are needed to investigate the impact of low-level chemical and/or biological exposures on the skin microbiome and the skin’s barrier function.

- **Toxicity resulting from xenobiotic metabolism by the skin and skin microbiome**

Microorganisms actively metabolize xenobiotic compounds, potentially creating toxic metabolites in the process that exacerbate the toxicity of a xenobiotic exposure. One example is low-level exposure of polycyclic aromatic hydrocarbons (PAHs) to the skin, which is toxicologically relevant due to their (pro-) carcinogenic potential[9]. A recent review of the state of the science regarding dermal absorption of carcinogenic polycyclic aromatic hydrocarbons (cPAHs) concluded that the aggregate available data do not provide a broad understanding of how different PAH source materials, PAH concentrations, or soil chemistries influence the absorption of cPAHs from soil[10]. PAHs are carbon and energy sources for commensal microbes, including the skin microbiome. Skin commensals were observed to transform benzo-a-pyrene into a range of highly cyto- and genotoxic metabolites that were excreted in toxicologically relevant concentrations leading to increased host toxicity[9]. Research on the potential

health impacts of the metabolism by the skin and skin microbiome is needed to better understand the development and risks associated with low-level occupationally-relevant xenobiotics.

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## Objective 2: Investigate the contributions of skin exposure to the overall body burden of toxic substances

Worker exposure to chemical agents may lead to organ-specific toxicity. The skin is a portal for entry of toxic substances into the body, and therefore skin exposures may contribute to systemic toxicity. Systemic absorption represents a broadly recognized but difficult to quantify burden[1]. The CDC estimates that more than 13 million workers in the United States, spanning a variety of occupational industries and sectors, are potentially exposed to chemicals that can be absorbed through the skin. Approximately 82,000 chemicals are in industrial use with an estimated additional 700 new chemicals being introduced annually resulting in a high potential for skin exposures to chemicals. While hundreds of chemicals (metals, cyanate

esters, epoxy and acrylic resins, rubber additives, and chemical intermediates) present in virtually every industry have been identified to cause direct and immune mediated effects such as contact dermatitis or urticaria, less is known about the number and types of chemicals contributing to systemic effects. Systemic effects resulting from skin exposure to chemicals have resulted in acute poisonings[2], neurotoxicity[3]; lung, liver and kidney toxicity[4]; reproductive toxicity[5]; carcinogenicity[6] and death[7]. Solvents are frequently used by numerous occupational sectors including manufacturing. In 1981, OSHA estimated that approximately 350 solvents were commonly used in the United States. Inhalation is the major route of solvent exposure due their vapor pressures but their physical properties also allow for ready absorption into and across the skin[8]. Solvents and other chemicals may also enhance the penetration of other chemicals by disrupting the protective lipid layer of the skin[9]. Studies have suggested that exposure to complex mixtures, excessive hand washing, use of hand sanitizers, high frequency of wet work, and environmental or other factors may enhance penetration and stimulate other biological responses altering the outcomes of dermal chemical exposure. Therefore, it is critical to understand how skin exposures contribute to total body burden of xenobiotics. In an attempt to raise awareness, skin notation assignments communicate the potential for dermal absorption, however; there is a need for standardization among agencies to communicate an accurate description of occupational hazards. Understanding the hazards of skin exposure is essential for the proper implementation of protective measures to reduce risk and ensure worker safety and health.

To improve understanding of the contributions of skin exposure to the overall body burden of toxic substances, research is required in several areas:

- **Advancements in skin permeation measurements.**

The importance of measuring the permeation of chemicals in contact with skin under conditions that are relevant to workplace exposures has recently been emphasized[10, 11]. Kinetics of xenobiotic skin permeation are chemical specific and also strongly depend on exposure conditions including mass loading and exposure duration. Both *in vitro* and *in vivo* studies of dermal absorption and systemic uptake of hazardous workplace chemicals are required. Studies should be designed to yield maximum data including absorption rates, kinetic aspects of absorption, and mass absorption under the range of exposures that are typically encountered in the workplace. Studies that enhance our understanding of mechanistic aspects of skin absorption are particularly desirable.

- **Advancements in skin permeation modeling.**

Because of the large number of chemicals in industrial usage, it is impractical to measure skin permeation rates for any but a small fraction. Therefore, mathematical modeling of skin permeation is an important tool to enable the prediction of systemic absorption of workplace chemicals in contact with skin. Refinement of mechanistic models that account for skin structure and function, as well as chemical-specific physical properties, are needed.

- **Refinement of skin exposure and risk assessment strategies.**

Well-reasoned assessments of exposure and risk following skin exposure are essential requirements for protecting workers. Current assumptions and rationales underling these assessments may lead to conclusions that do not provide adequate protection to workers exposed to toxic chemicals through skin[10]. Research that addresses the accuracy of current risk assessment strategies for skin exposures is required. Advances in skin permeation measurements and models should inform refinements in exposure

and risk assessments. Improved understanding of skin exposure and its contribution to overall body burden will provide insight and evidence-based data that can advance hazard identification and risk assessment.

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## Objective 3: Improve current skin exposure measurement methods

Inhalational exposures within the workplace are readily estimated based on well-established air and breathing-zone sampling methods combined with estimates of pulmonary uptake efficiency. In contrast, the estimation of systemic uptake through the skin route requires detailed chemical-specific characterization of workplace exposures including spatial distribution of contamination, source to skin transfer, efficacy of industrial hygiene controls, worker personal hygiene practice and decontamination efficiency, and rate of chemical absorption by skin from mass loads that are typical of the specific workplace conditions. Research to better characterize transfer to and from the skin within the working environment, as well as quantitative characterization of the efficacy of skin exposure controls, is needed[1,2]. Additional research is also needed to better characterize dermal absorption of finite doses of chemicals in scenarios and conditions that are relevant to the workplace[3].

To improve our understanding of skin exposures and the corresponding potential for impact on occupational health, research is required in several areas:

- **Quantification of chemical loading on the skin surface**

Without an appropriate understanding of the loading of a chemical on the skin surface, an accurate characterization of dermal uptake or absorption is not possible. Additional research is needed to examine the loading of chemicals on the skin for a number of specific scenarios, including with specific pressure or contact type, with repeated contacts, and under different skin conditions, such as hydration level.[4, 5] Information on transfer of chemicals to and from the skin surface is also needed, including, but not limited to, the transfer efficiencies from surfaces to skin, clothing to skin, personal protective equipment to skin, and skin to skin.[6,7]

- **Characterization of dermal absorption or permeation**

To properly characterize the effects of skin exposures in the workplace, the amount of permeation into the body following skin exposure must be understood. Methods for dermal absorption assessment include both chemical modeling and the use of biological monitoring techniques.[8,9,10] Further research is needed to define approaches for chemical specific skin permeation estimation and modeling, and to determine appropriate biological monitoring methods for chemicals with the potential for significant impact on worker health and safety.

- **Efficacy of workplace controls for dermal exposures**

The hierarchy of controls should be applied in the same manner to chemical skin exposures as to other types of exposures, such as those via the inhalation route.[11] Further research is needed to understand the effectiveness of skin exposure controls in the workplace, as well as the identification of most effective methods for controlling skin exposures in the workplace.[12]

- **Efficiency of skin and surface decontamination methods**

Better information is needed to characterize the effectiveness of skin and surface decontamination techniques used in the workplace to control and/or prevent skin exposures to workers and to mitigate the potential for systemic toxicity from skin absorption.[13]

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## Objective 4: Reduce the incidence and transmission of infectious disease in the workplace

Transmission of infectious disease in the workplace can contribute to substantial costs and loss of productivity[1]. In addition to traditional occupational infection concerns like bloodborne pathogens and tuberculosis, other respiratory, enteric, and dermally shed pathogens are being recognized as important sources of occupational illness. Influenza causes U.S. employees to miss approximately 17 million workdays, at an estimated $7 billion a year in sick days and lost productivity[2]. Transmission within the workplace is a real concern. Research is needed that will develop and utilize appropriate methods and models to advance knowledge relevant to infectious disease transmission by various exposure routes in the workplace[3]. This will facilitate better understanding of the influence of the occupational environment and worker susceptibility on disease transmission. Additional diseases now recognized to have an occupational risk of transmission include Norovirus[4], Methicillin resistant *Staphylococcus aureus*[5-6], *Helicobacter pylori*[7], and *Legionella*[8], among others. Still other emerging infectious diseases, such as Ebola or Middle East Respiratory Syndrome (MERS), in addition to antibiotic resistant strains of common bacteria, may pose a risk of occupational transmission.

Individuals working in the health care sector are at an increased risk for exposure to influenza and other pathogens. Among 8 different reports of nosocomial influenza outbreaks in healthcare settings, the infection rate of staff members ranged from 8-63%[9], with the additional economic burden of a single nosocomial influenza outbreak at a hospital estimated to cost $34,179[10]. In addition to health care, workers in the public safety sector (e.g. EMS workers, firefighters, police, prison guards) are exposed to a variety of infectious diseases. Livestock workers, veterinarians, and others working with animals are another class of workers for which infectious risks in the workplace exist and should be better studied

[5,6,15, 16]. Research is needed to assess exposure pathways, develop quantitative risk models, improve dissemination of effective interventions, and to improve the quality and availability of surveillance data.

To reduce the incidence and improve the understanding of infectious disease in the workplace, research is needed in the following areas:

- **Assessment of Exposure Pathways**

Depending on the specific pathogen and workplace environment, transmission may occur via one or more multiple routes, including direct contact with patients or animals, contaminated surfaces, or airborne bioaerosols. Development of methods for quantitative assessment of the exposure pathways and their relative importance is essential to improve our understanding on infection risks and prevention of disease. Data on exposure factors and individual behavior are needed in addition to assessment of the prevalence of pathogens within the workplace environment.

- **Quantitative Models**

Quantitative microbial risk assessment (QMRA) models have been widely used in the estimation of infectious risks from food and water[17,18]. These models have utility in policy development and decision making. There have been few QMRA models developed for the occupational scenarios[19]. Research is needed to develop QMRA approaches to assessment of occupational risks of infection. Experimental work to generate dose-response relationships for pathogens and development of dose-response models for dermal and respiratory pathogens that account for chronic low-level exposure are also a priority.

- **Surveillance**

To minimize the work-related risks of influenza infections and transmission of other infectious diseases, research is needed on development of clinical and environmental surveillance methods to identify transmission patterns and effective prevention strategies in the occupational setting.

- **Intervention and preparedness**

Various interventions exist to prevent transmission of infectious diseases (vaccination programs, barrier protection, droplet reduction, etc.), however few interventions have been evaluated for efficacy across different occupational settings, beyond healthcare settings. Research to evaluate relevance and impact of intervention strategies is greatly needed in order to effectively prevent occurrence of infectious diseases in the workplace.

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## Objective 5: Reduce the incidence of allergic disease in the workplace

The burden of occupational allergic disease is widespread and serious. An estimated 11 million U.S. workers are potentially exposed to agents which can manifest as allergic diseases such as occupational asthma and allergic contact dermatitis. Hundreds of chemicals (e.g., metals, epoxy and acrylic resins, rubber additives, and chemical intermediates) and proteins (e.g., natural rubber latex, plant proteins, mold, animal dander) present in virtually every industry have been identified to cause allergic disease and the incidence in the workplace is increasing[1]. Significantly, occupational exposures are responsible for approximately 9-25% of all adult onset asthma cases[2,3] while allergic contact dermatitis represents 20% of all work-related cutaneous disorders[4]. These diseases can adversely affect an individual's health and capacity to perform at work resulting in significant economic losses[5,6]. Due to the large number and diversity of chemicals and other agents used in the workplace, it is critical that potential allergens continue to be identified. Investigations are also needed to help better understand the mechanisms of allergic disease. Ultimately, research is needed to improve dissemination of effective intervention methodologies and to improve surveillance for allergic diseases in order to both improve awareness and develop effective controls.

To reduce the incidence and improve our understanding of allergic disease in the workplace, research is required in several areas:

- **Identification of Allergens**

Due to the environmental, occupational, and clinical significance of allergens, as new hazards continue to emerge, it is critical to successfully identify and classify them. Immunological assessment for occupational allergens is limited by the fact that standardized tests are not available for most workplace-relevant allergens and there are limitations to the ones that are currently available[7]. Therefore, the development and use of rapid and sensitive methods for the early identification of the hazard is necessary. In addition, although there continues to be progress made on the development of skin and respiratory sensitizer identification assays, many allergic reactions, especially those precipitated by chemical exposures, cannot be comprehensively defined within the constraints of the current classification system. This illustrates the need for increased research pertaining to the mechanisms behind sensitization and allergic disease as well as the development of updated hypersensitivity classifications.

- **Mechanisms of Allergic Disease**

Occupational allergic conditions are multifactorial and are the result of complicated immunologic events. The limited knowledge of the immunologic mechanisms of sensitization continues to confound the development of predictive and classification assays. Novel molecules and mechanisms involved in allergic disease need to be investigated in order to elucidate specific entities that can be utilized for the development of hazard identification assays for occupational allergens. Additionally, a better understanding is needed of: the influence of complex mixtures; the role of the microbiome on allergy; the interaction between the skin and lung and between the skin and gut; skin barrier integrity; and genetic predisposition in order to better identify, prevent, and treat allergic diseases.

- **Surveillance, Intervention and Dissemination**

Occupational allergy has significant social and economic implications for workers, their families, their employers, and government agencies. Numerous approaches that integrate risk assessment and risk management strategies have been developed to try control workplace exposures to prevent the induction

of allergic response[8-11]. However, additional research is needed in this area. While OSHA occupational exposure limits (OELs) are an important tool applied to characterize and aid in controlling workplace exposures to occupational hazards, few OELs are established on the basis of preventing sensitization because of data limitations and a lack of understanding of the biological processes that govern immune-mediated effects. The route of exposure, exposure intensity, and duration/frequency of exposure have all been identified as factors complicating this process[2]. Additionally, early detection of preclinical biomarkers of sensitization may help to prevent development of occupational diseases through the implementation of the proper administrative and engineering controls. Research addressing these challenges along with a better understanding of allergic disease mechanisms has direct implications in surveillance, intervention and dissemination, informing appropriate risk assessment and management decisions to facilitate interventions and prevention of occupational allergies.

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## Objective 6: Investigate autoimmune disease risk associated with occupational and environmental exposures

Autoimmune diseases are immune-mediated conditions with the unique characteristic that the underlying immune response is directed towards self. Normally, the immune system recognizes and does not respond to its own cells and tissues, a state known as self-tolerance. Genetics, environment, and life style may exert pressure on immune tolerance and can result in breakdown of this safe-guard leading to

the manifestation of autoimmune disease. Autoimmune disease burden in the workplace is increasing and is recognized as an important area of research for NORA.

NIH estimates that there is in excess of 23 million people with an autoimmune disease in the United States alone (incidence of approximately 8%), and the incidence is increasing[1]. This burden surpasses that of cancer and heart disease indicating the significance of autoimmunity to public health. Current estimates indicate that there are approximately 80-100 autoimmune disease conditions, some with overlapping symptoms and others with very unique immune pathologies[1]. Individually, each autoimmune disease may appear rare, however, collectively, autoimmunity represents a significant burden and contributor to morbidity and mortality, especially in women. Increasing evidence indicates that occupational exposures contribute to development of autoimmune diseases[2].

Selected examples of exposure and autoimmune disease associations (Adapted from[2]).

| **Occupational/Environmental Exposure** | **Autoimmune Disease** |
|---|---|
| Therapeutics | Lupus (Procainimide, penicillinamine, isoniazid), Hemolytic anemia (penicillin, methyldopa) |
| Metals | Mercury associated with lupus like syndrome |
| Particulates (silica) | SLE, rheumatoid arthritis, ANCA-associated vasculitis and glomerulonephritis, and scleroderma |
| Pesticides | increased ANA with carbamates, organochlorines, pyrethroids, phenoxyacetic acids – HCB data in rodents but less clear in humans |
| Solvents | TCE and lupus, vinyl chloride and scleroderma |

Substantial and growing evidence supports an association between occupational exposures and autoimmune disease. The strongest associations have been shown with exposure to silica, industrial emissions/pollution, industrial solvents, or pesticides as risk factors for autoimmune diseases, including, but not limited to, lupus, rheumatoid arthritis and systemic sclerosis[3]. Given adequate health follow-up, it is estimated that 47-77% of workers exposed to silica develop some degree of silicosis[4]. Research has shown hypergammaglobulinemia, anti-nuclear antibodies, and end stage renal disease can occur in 65%, 34%, and 5% of individuals with silicosis, respectively[4]. These pathologies are consistent with systemic autoimmunity and suggest a progression to autoimmune disease in a proportion of silica exposed individuals. Investigation of the underlying mechanisms associated with inhalation of silica suggest initial activation of innate immunity and inflammation and inappropriate stimulation of adaptive immunity leading to breakdown of immune tolerance associated with autoantibody production and tissue damage. A study conducted at NIOSH demonstrated that workers with certain polymorphisms in their TNF$\alpha$ and/or IL-1$\beta$ genes, known to be associated with increased cytokine production, were at higher risk of developing silicosis[5]. These genetic findings support the inflammatory pathogenesis of silicosis and may play an important role in the progression of autoimmune disease. Additional evidence suggests that inhalation of other inorganic dusts is also associated with rheumatologic autoimmune diseases as an independent risk factor from silica in occupationally-exposed individuals[6]. Epidemiological evidence suggests that occupational exposure to organic solvents represents a significant risk factor for autoimmune disease being associated with increased risk for systemic sclerosis, primary systemic vasculitis and multiple sclerosis[7].

Overall, there is substantial epidemiological evidence linking occupational exposures to autoimmune disease risk and a significant data gap in the mechanistic and diagnostic understanding of the relationship. Autoimmune diseases are complex inflammatory conditions in which the immune system recognizes self and mounts an inappropriate and destructive response. Each autoimmune condition has unique challenges for understanding etiology and pathogenesis and represents a significant knowledge gap. However, comprehension of the initiators, targets, and effector mechanisms is essential to improving prevention, diagnosis, and therapeutic approaches. Research efforts need to focus on improved surveillance and diagnosis in the workplace as well as on developing and improving basic models for studying disease pathogenesis. Enhanced exposure metrics and timely diagnoses will allow correlation between occupational exposures and disease incidence. In addition, improved diagnostic tools will help refine the burden of autoimmunity in the workplace. Such tools will also have the potential to contribute to detection and intervention earlier in the clinical course of disease. Meeting these data gaps is critical as pointed out in a recent study suggesting an association between occupational exposures and death resulting from systemic autoimmune disease[8].

To improve understanding of the potential risk posed by occupational exposures for the development and/or exacerbation of autoimmunity, research is needed in the following areas:

- **Increased workplace hazard evaluations with specific goals for autoimmune disease.**

Hazard evaluations in the workplace with specific emphasis on autoimmune diseases are not common. Increasing the surveillance for autoimmune diseases in the workplace and associating them with occupational chemical exposures will strengthen the body of evidence and potentially identify novel exposure risks for autoimmunity.

- **Development and improvement of animal models of autoimmune disease.**

Animal models that closely recapitulate human autoimmune disease pathogenesis will greatly improve our ability to characterize disease mechanism and develop diagnostic tools. Current animal models of autoimmune disease may not meet this goal and require in depth characterization, modification, improvement, and potentially replacement. Development of animal models that are predictive of human disease is critical.

- **Identification of biomarkers of disease.**

Health hazard evaluations in the workplace to identify risks together with mechanistic research using animal models will lead to the identification of novel biomarkers of autoimmune disease. Biomarkers are important for disease surveillance and provide opportunities for early diagnosis and intervention.

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# APPENDIX

## IID Council Membership

Co-Chair: Jennifer Sahmel (Insight Exposure and Risk Sciences, Inc.)
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