5b.03 Occupational Immunotoxicology

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Abstract

Individuals working in a variety of occupational industries and sectors are potentially exposed to biological, chemical, and hazardous agents with dermal and respiratory being the two most common routes of exposure. These exposures can potentially result in numerous diseases and can adversely affect an individual's health and capacity to perform at work resulting in significant economic losses. Occupational immune diseases are some of the most common illnesses that affect workers including inflammation, allergy, respiratory disease, autoimmunity, or other immune modulation resulting in suppression following exposure in the work environment. Due to the complexity of the immune system, the identification of agents that induce immunotoxicity requires specific assays. Various organizations have proposed different approaches to immunotoxicity testing that include validated immune testing protocols that measure diverse immunological biomarkers and endpoints. This chapter provides descriptions of the most commonly recognized occupational immune diseases

5b.03.1 Introduction

The importance of occupational health and medicine was recognized by the early 1900s. Alice Hamilton was a leading expert in the field of occupational health and a pioneer in the field of toxicology, studying occupational illnesses and the dangerous effects of industrial metals and chemical compounds on the human body. In 1908, she was appointed by the governor of Illinois to the newly formed Illinois Commission on Occupational Diseases, the first such investigative body in the United States. For the next decade she investigated a range of issues for a variety of state and federal health committees. She focused her explorations on occupational toxic disorders, examining the effects of substances such as aniline dyes, carbon monoxide, mercury, tetraethyl lead, radium, benzene, carbon disulfide, and hydrogen

sulfide gases. She pioneered occupational epidemiology and industrial hygiene in the United States. Her findings were scientifically persuasive and influenced sweeping health reforms, changing laws and general practice to improve the health of workers.

Individuals working in a variety of occupational industries and sectors are potentially exposed to biological, chemical, and hazardous agents with the skin and the lung being the two most common sites of exposure. The Environmental Protection Agency (EPA) estimates that approximately 86,000 chemicals are registered for industrial use with an estimated additional 2000 new chemicals being introduced annually. The Occupational Safety and Health Agency (OSHA) estimates that more than 40 million workers in the United States have the potential for exposure to hazardous chemicals. Occupational exposures can result in numerous diseases and can adversely affect an individual's health and capacity to perform at work resulting in significant economic losses including decreased productivity, medical expenses, and loss of work due to illness, with associated costs estimated to exceed $1 billion annually in the United States alone (Moscato and Rampulla, 2003; Mancini *et al.*, 2008; Cashman *et al.*, 2012). Occupational immune diseases are some of the most common illnesses that affect workers in the United States. Occupational exposures can cause inflammation, allergy, respiratory disease, autoimmunity, or other immune modulation following exposure in the work environment. During 2011–2015, total annualized medical expenditures among U.S. workers were $7 billion ($901 per person) for asthma and $5 billion ($681 per person) for Chronic Obstructive Pulmonary Disorder (COPD) (Syamlal *et al.*, 2020).

5b.03.2 Identification of Occupational Hazards

Increasing scientific, regulatory, and Congressional concerns about the human health effects of biological and chemical agents in our environment gave rise to many different agencies with focuses on decreasing or eliminating exposures to those chemicals in an effort to reduce disease and disability. Potential occupational hazards must first be identified, and their toxicity understood before exposure to these agents can be regulated. The National Toxicology Program (NTP) is an interagency program whose mission is to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology. The program maintains an objective, science-based approach in dealing with critical issues in toxicology and is committed to using the best science available to prioritize, design, conduct, and interpret its studies. Through a formal open nomination and selection process, potential chemical hazards can be identified and selected for investigation. Agents considered appropriate for study generally fall into two broad, yet overlapping, categories: (1) agents judged to have high concern as a possible public health hazard based on the extent of human exposure and/or (2) suspicion of toxicity and agents for which toxicological data gaps exist and additional studies would aid in assessing potential human health risks. NTP is continually evolving to remain at the cutting edge of scientific research and to develop and apply new technologies. NTP plays a critical role in providing needed scientific data, interpretations, and guidance concerning the appropriate uses of data to regulatory agencies and other groups involved with health-related research. Through its interactive relationship with regulatory agencies, NTP plays an indirect, but important role in shaping public health policy (see "Relevant Websites" section).

The National Institute for Occupational Safety and Health (NIOSH) and the Agency for Toxic Substances and Disease Registry (ATSDR) have a primary emphasis to protect workers from toxic chemical exposures. Employees, union officials, or employers can ask NIOSH through their Health Hazard Evaluation (HHE) Program to investigate potential health hazards present at their place of work. NIOSH can provide assistance by assessing exposure and employee health. Based on their findings, NIOSH will recommend ways to reduce hazards and prevent work-related illness. The evaluation is done at no cost to the employees, union official, or employers (see "Relevant Websites" section). NIOSH is also involved in basic science research related to hazard identification, methods development, and understanding the mechanisms of occupational exposure-induced immune disease.

ATSDR is directed by Congressional mandate to perform specific functions concerning the effect on public health of hazardous substances in the environment including public health assessments of waste sites, health consultations concerning specific hazardous substances, health surveillance and registries, response to emergency releases of hazardous substances, applied research in support of public health assessments, information development and dissemination, and education and training concerning hazardous substances (see "Relevant Websites" section).

5b.03.3 Regulation of Occupational Hazards

Numerous agencies including the CDC, Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA) are involved in the regulation of occupational exposure in the United States (Boeniger and Ahlers, 2003). Congress created the OSHA with the Occupational Safety and Health Act of 1970 to assure safe and healthful working conditions for working men and women by setting and enforcing standards and by providing training, outreach, education, and assistance. OSHA sets enforceable permissible exposure limits (PELs) to protect workers against the health effects of exposure to hazardous substances, including limits on the airborne concentrations of hazardous chemicals. Most OSHA PELs are 8-h time-weighted averages (TWA). Ceiling and peak limits may also be set, and chemicals may be given a skin designation to warn against skin contact. Approximately 500 PELs have been established. However, many limits are outdated, and there are also many substances for which OSHA does not have workplace exposure limits (see "Relevant Websites" section).

The Occupational Safety and Health Act of 1970 also established NIOSH. NIOSH is part of the CDC, in the U.S. Department of Health and Human Services. It has the mandate to assure "every man and woman in the Nation safe and healthful working conditions and to preserve our human resources." NIOSH is a very diverse agency that employs experts in epidemiology, toxicology, biological sciences, medicine, nursing, industrial hygiene, safety, psychology, chemistry, statistics, economics, and many branches of engineering. NIOSH works closely with OSHA and the Mine Safety and Health Administration in the U.S. Department of Labor to protect American workers and miners. Recommended exposure limits (RELs) for hazardous substances in the workplace are established by NIOSH to protect worker health. In developing RELs and other recommendations to protect worker health, NIOSH evaluates all available medical, biological, engineering, chemical, and trade information relevant to the hazard and transmits its recommendations to OSHA for use in developing legally enforceable standards (PELs). NIOSH also publishes its recommendations in publicly available sources such as the NIOSH Pocket Guide to Chemical Hazards, Criteria Documents, Current Intelligence Bulletins, Alerts, Special Hazard Reviews, Occupational Hazard Assessments, and Technical Guidelines (see "Relevant Websites" section).

The American Conference of Governmental Industrial Hygienists (ACGIH) is a private, nonprofit, nongovernmental corporation. Its objective is not to develop standards but develop recommendations or guidelines to assist in the control of occupational health hazards. Two examples are threshold limit values (TLVs) and biological exposure indices (BEIs). TLVs refer to airborne concentrations of chemical substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed, day after day, over a working lifetime, without adverse effects. BEIs are guidance values for assessing biological monitoring results (concentrations of chemicals in blood, urine, etc.). BEIs represent the levels of determinants that are most likely to be observed in specimens collected from healthy workers who have been exposed to chemicals at the TLV. TLVs and BEIs are health-based values and are not intended to be used as legal standards (see "Relevant Websites" section).

Efforts to control workplace exposures to hazardous agents by the above-mentioned agencies have typically focused on inhalation rather than skin exposures. As a result, assessment strategies and methods are well developed for evaluating inhalation exposures in the workplace; however, standardized methods are currently lacking for measuring and assessing skin exposures (Dotson *et al.*, 2011). Currently, the EPA utilizes a direct method to measure the chemical concentrations at the interface between the person and the environment as a function of time, resulting in an exposure profile. There are currently no occupational exposure limits (OELs) set for dermal exposures. However, chemicals with dermal penetration risk are given a skin notation assignment (S) as a guidance to warn against potential for increased risk of systemic toxicity due to dermal penetration in addition to inhalation exposure. NIOSH has 142 skin notations assigned to chemicals; OSHA lists 159 notations in the Pocket Guide and over 219 chemicals have a skin notation assigned by the ACGIH. Historically, the main goal of the skin notation is to communicate the potential for dermal absorption; however, the criteria and protocols for the assignment of skin notations vary among the different agencies and have many limitations. In 2017, NIOSH updated a strategy (NIOSH Skin Notation (SK) Profile) intended to address many of the limitations in the historic approaches applied to establishing skin notations (NIOSH, 2017). The NIOSH SK Profile uses a unique tiered approach to provide information about systemic and direct effects including dermal absorption, corrosivity, irritation and sensitization, systemic toxicity specific for the chemical, and ultimately determination of a substance's hazard potential, or its potential for causing adverse health effects as a result of skin exposure (Dotson *et al.*, 2011) (see "Relevant Websites" section). The NIOSH SK assignment incorporates scientific data on the physicochemical properties of a chemical, epidemiology, toxicology, data from mechanistic studies, and computational techniques, including predictive algorithms and mathematical models by means of analytical or numerical methods. Skin Notation Profiles are intended to inform occupational health practitioners, researchers, employers, and workers in potentially hazardous workplaces about potential health effects associated with dermal exposures with the ultimate goal of better protecting workers from the risks of skin contact with hazardous chemicals.

5b.03.4 Immunotoxicity Testing

Occupational exposures can often result in adverse effects on the immune system. Due to the complexity of the immune system, the identification of agents that induce immunotoxicity requires specific assays. Establishing a direct link between exposure and disease manifestation for immunotoxicity in humans remains difficult because of the inherent limitations of epidemiological studies to draw causal conclusions. Various organizations [Organization for Economic Cooperation and Development (OECD), NTP, Dutch National Institute of Public and the Environment (RIVM), U.S. FDA, and the EPA] that conduct testing for immunotoxicity have proposed different approaches to immunotoxicity testing that include validated immune testing protocols that measure diverse immunological biomarkers and endpoints, mainly in laboratory animals but also in humans (WHO, 2012). Typically, before any conclusions can be made, a battery of tests evaluating immunotoxicity must be conducted. Testing schemes, organized in stepwise protocols (Tiered) with increasing complexity, have been successfully used as a standardized approach to identify and characterize immunotoxic agents. These tests are designed to detect a change in lymphocyte subpopulations or cellularity, hematology, histopathology, weight of an immune system organ, or to evaluate altered immune system function. Tier 1 is comprised of a series of preliminary screening assays intended to identify suspect immunotoxicants. Tier 2 tests are projected to identify the specific immune target responsible as well as evaluate effects on host resistance, and Tier 3 tests are focused on identifying mechanism of action. The development and adoption of experimental methods for the evaluation of immunotoxicity

has been a primary focus of the field for years. For some effects such as autoimmunity and respiratory allergy, efforts are ongoing but remain a challenge. This chapter provides information about some of the most common skin, lung, and systemic immunological occupational diseases.

5b.03.5 Occupational Immune Diseases

5b.03.5.1 Lung Diseases

5b.03.5.1.1 Work-related asthma

Millions of people suffer from allergic conditions, such as asthma, characterized by exaggerated immune responses. Asthma can cause recurrent attacks of symptoms such as wheezing, chest tightness, shortness of breath, and coughing. In severe cases, these symptoms can be disabling or lead to death. Fortunately, when potential hazards are recognized, work-related allergies and asthma can often be prevented, or their effects minimized. Work-related asthma (WRA) which includes occupational asthma (OA) and work-exacerbated asthma (WEA) are recognized as the most prevalent work-related lung diseases in the industrialized world (Vlahovich and Sood, 2021). It has been estimated that up to 20% of adult-onset asthma is caused by occupational factors and that roughly 90% of these cases involve immunological mechanisms (Mapp *et al.*, 2005). Irritant-induced OA accounts for less than 10% of cases of OA. OA is asthma caused by workplace conditions and is typically subdivided into allergic (sensitizer) and nonallergic (irritant) asthma. Allergic OA is caused by sensitization to occupational allergens (low- and high-molecular weight) and has a latency period during sensitization before the symptoms begin. Irritant-induced OA includes both an acute onset form (reactive airways dysfunction syndrome (RADS)) which begins within 24 h after a single high-dose (usually accidental) exposure and a delayed onset form which occurs after repeated lower-level exposure over days to months.

Diagnosis of WRA is difficult and has been the subject of many studies and articles over the past several decades. Diagnostic guidelines for OA rely primarily on pulmonary function tests (PFTs) including specific inhalation challenge (SIC) testing, serial peak expiratory flow (PEF) rate measurements, methacholine challenge tests or other diagnostic tests such as skin prick tests (SPT), and serologic antibody evaluation (Lau and Tarlo, 2019). A complete clinical and work history related to asthma symptoms is necessary for diagnosis, and even in combination with diagnostic tests, it can be difficult to determine the specific type of WRA (Friedman-Jimenez *et al.*, 2015; Lau and Tarlo, 2019). It is thought that genetics may play an import role in the development of these diseases (Mapp, 2001; Vandenplas, 2011).

There are over 600 documented agents associated with WRA, 400 involve sensitizing mechanisms (Friedman-Jimenez *et al.*, 2015; Roio *et al.*, 2021). Common occupational agents that induce WRA exist in almost every sector affecting workers including bakeries (wheat, cereals, and enzymes), health care workers (latex and biocides), laboratory workers (animal proteins, enzymes, or other pharmaceuticals), manufacturing (diisocyanates), electronic workers (amines, acrylic glues), woodworkers (wood dust and formaldehyde), metal workers (complex platinum salts, nickel, cobalt, chromium compounds), hairdressers, and cosmetologists (biocides, acrylates, persulfate salts).

Based on the Work-Related Lung Disease Surveillance System (eWoRld), NIOSH published the 10 most frequently reported agent categories associated with cases of WRA (2009–11). Listed in the order of percent of cases these include miscellaneous chemicals and materials (21%), cleaning materials (17%), minerals and inorganic dusts (16%), pyrolysis products (12%), indoor air pollutants (10%), molds (7%), plant and tree materials (6%), ergonomics (5%), solvents (4%), and animal/insert material (3%). Based on these agent classifications, the highest percent of OA and WRA are due to chemicals, cleaning materials, and minerals and inorganic dusts. While the cases of OA are not broken down specifically into allergic and irritant, the percent cases of RADS consisted of a relatively small portion ($<2\%$) of the total overall cases. Although most cases for each agent category are WRA the specific asthma type has not been classified, further emphasizing the difficulty in diagnosing these respiratory diseases. Animal models are often utilized for the hazard identification of agents that can cause asthma; however, no method has been standardized and validated for this purpose (Pemberton and Kimber, 2021; Meek *et al.*, 2023).

5b.03.5.1.1.1 Allergic occupational asthma

The majority of OA is immunological in nature. Research into various aspect of OA with humans and using animal models continues to be an active pursuit in immunotoxicology, with current focus on further clarification of environmental, genetic, cellular, and molecular mechanisms that participate in the response. Typically, agents that induce allergic OA are classified as high- or low-molecular weight (HMW $>$ 5 kDa; LMW $<$ 1 kDa), and their size is thought to play a significant role in their allergenicity and mechanism of action. Typically, protein allergens are HMW, innately immunogenic, and act as complete antigens. Detection of specific antibodies (e.g., IgE or IgG) is commonly employed for the assessment of HMW allergies, and screening of exposed individuals can be accomplished through SPT or immunoassays (Tiotiu *et al.*, 2020). Several challenges exist in the diagnosis and identification of HMW allergy. HMW allergens in some compounds such as wheat and latex have been better characterized than others. While most recombinant proteins are available for testing, in some products multiple proteins may be allergenic and individuals may have different sensitivities to different proteins which may present a challenge for the identification of the suspect agent(s).

In contrast, LMW allergen exposures that result in allergic OA are not always associated with detection of circulating specific antibodies, discrepancies exist between human and animal studies, and not as much is known about the mechanisms of immunological diseases that they induce. Diisocyanates and acid anhydrides are groups of chemicals that are most characterized with respect to allergic asthma. However, due to inconsistent findings and poorly understood mechanisms, there is a need for additional research and standardized methods for the evaluation of LMW agents that can cause OA (Arts, 2020).

5b.03.5.1.1.1.1 HMW occupational asthma

Exposure to HMW agents that cause OA is common among every occupational sector. Occupations with high risks for exposure include farmers and individuals who work with animals, food production and bakery workers, printers, laboratory workers, individuals in manufacturing, and health care workers. Latex allergy has been one of the better-characterized occupational allergies (Toraason *et al.*, 2000). While exposure to latex gloves is the most common cause, contact with latex-containing articles including catheters, oxygen masks, syringes, and tracheal tubing have also been reported to induce latex allergy (Kahn *et al.*, 2016). Though the incidence of latex allergy has decreased, sensitized health care workers still suffer from this allergy. Latex contains an array of cellular proteins, lipids, and amino acids. Inhalation of airborne allergens bound to substances such as glove powder are commonly reported to result in allergic reactions; however, direct contact is also a common mode of exposure. The incidence of sensitization depends on the latex allergen content of gloves and the amount of aeroallergen, which is influenced by the use of glove powder. While all potential allergens in latex have not been fully characterized, a list of 15 allergens (Hev b 1–Hev b 15) has been established with Hev b 5, Hev 6, and Hev b 7 identified as the most common occupational latex allergens (Yip *et al.*, 2000; Raulf-Heimsoth *et al.*, 2007). While some allergens are specific for latex, other latex allergens have been found to share IgE epitopes and cross-reactivity with plant-derived proteins from foods such as avocado, banana, kiwi, tomato, and mango. This phenomenon is referred to as latex-fruit syndrome (Beezhold *et al.*, 1996). While latex allergy is most often associated with OA, it can also manifest as urticaria, rhinitis, conjunctivitis, allergic contact dermatitis (ACD), and anaphylaxis (Sussman and Beezhold, 1995). Allergic diseases (predominately ACD) may also result from exposure to LMW chemicals that are added during the manufacturing process of latex products (Kahn *et al.*, 2016).

Flour is another very common HMW occupational allergen. Cereal flour is one of the basic materials used in the food industry and animal feed production. Occupationally, the highest exposure to flour dust is usually observed in bakeries and grain mills with significant exposure also occurring in pasta factories, pizza bakeries, confectioneries, restaurant kitchens, malt factories, animal feed plants, and agriculture (Stobnicka and Gorny, 2015). Baker's asthma is one of the most frequently occurring forms of OA, and most studies indicate that wheat and rye flour proteins are allergens for 60–70% of bakers with workplace-related respiratory problems (Page *et al.*, 2010). The main grain used in the bakery industry is wheat, and wheat flour has been identified to contain at least 40 allergens which have been shown to cause adverse health effects in exposed workers (Sander *et al.*, 2001). Flour dust usually contains various other components which play an important role in dough improvement, such as a variety of enzymes (α-amylase, cellulase, hemicellulase, malt enzymes), additives (baker's yeast, egg powder, milk powder, sugar), flavorings, spices, and chemical ingredients (preservatives, antioxidants, bleaching agents). The enzyme α-amylase (added to improve baking characteristics), thioredoxin, plain lipid transfer proteins, and serine proteinase inhibitor are among the main factors associated with baker's asthma, and studies have found that the highest frequency of specific IgE measurements were identified for α-amylase inhibitors Tri a 28 and Tri a 29.01 (Stobnicka and Gorny, 2015). The risk of adverse health outcomes including morbidity, cough, wheeze and asthma, is closely related to the flour dust exposure levels (Jeebhay and Baatjies, 2020).

Exposure to laboratory animals can also result in occupational allergy and is commonly observed among technicians, animal caretakers, physicians, and scientists who work in pharmaceutical industries, university laboratories, and animal breeding facilities (Feary and Cullinan, 2016). Due to the increased use of rodents such as mice and rats in animal research, sensitization is increasing in laboratory animal technicians. It is estimated that between 5% and 8% of this population develops laboratory animal allergy with some estimates suggesting an increase of up to 23% over a 2-year period in the United States. Urine is the main source of the allergenic protein, but allergens can also be found in dander, hair, saliva, and serum of mice and rats. The major inhaled allergens resulting from exposure to mice and rats are lipocalins (Mus m 1 and Rat n 1, respectively); these allergens share 64% homology in their amino acid structures. Mouse urinary protein has shown IgE cross-reactivity with rat urinary protein and Equ c 1 (a major horse allergen) (Saarelainen *et al.*, 2008).

In addition to the extensively-characterized occupational HMW allergens mentioned above, allergens from indoor fungal bioaerosols, soy and cannabis are beginning to be identified. Fungal bioaerosols are ubiquitous in the environment and human exposure can result in a variety of health effects ranging from systemic, subcutaneous, and cutaneous infections to respiratory morbidity including allergies and HP (Baxi *et al.*, 2016). In general, outdoor fungi are more abundant and well-associated with allergic disease; however, exposure to indoor fungi is gaining increased scientific interest due to increased public awareness that exposure can cause a variety of health effects. Evident dampness in building and indoor settings, including office buildings and schools, has been associated with increased respiratory symptoms (Haleem Khan and Mohan Karuppayil, 2012; Cho *et al.*, 2016; Wu *et al.*, 2018). Increased exposure to indoor fungi can also be the result of natural disasters such as hurricanes or flooding, water damage following infiltration/leaks and new construction methods (Sylvain *et al.*, 2019). While there are currently no federal standards or recommendations, for airborne concentrations of fungi or fungal spores, scientific research on the relationship between fungal exposures and health effects is ongoing.

With the legalization of hemp through the US Farm Bill and increased medical and/or recreational legalization of marijuana or cannabinoid compounds in many US states and Canada, an entire industry focused on hemp or cannabis production has emerged over the last several years in North America. With this new industry comes exposure of workers to plant pollens, allergens, organic and inorganic dusts, and bioaerosols generated during planting, harvesting or processing of plant material for consumer use. NIOSH conducted an HHE at an outdoor cannabis farm to identify potential health and safety hazards and found endotoxin or fungal contamination of cannabis as potential irritants or allergens (Green *et al.*, 2018; Couch *et al.*, 2020). Consistent with this, there have been reports that cannabis sensitization can produce rhinoconjunctivitis, asthma, pruritis, contact urticaria and angioedema (Decuyper *et al.*, 2017). Moreover, it has been demonstrated that workers in the hemp industry in other countries have compromised lung function and develop byssinosis, similar to cotton workers (Zuskin *et al.*, 1994). The possibility exists that allergies to marijuana, and not only hemp, also occur and could be due to reactions against the cannabis lipid transfer protein, Can s3 (Gamboa *et al.*, 2007).

Although well recognized as a common food allergen, exposure to soy has more recently been identified as the causative agent of OA and asthma epidemics resulting from soy dust inhalation exposure. At least 16 soy allergens, including Gly m1–8, have been identified some of which are more specifically related to respiratory sensitization (L'Hocine and Boye, 2007). Studies were conducted to identify suspect allergens (Green *et al.*, 2011). Immunoblotting revealed IgE against multiple soy antigens with the prominent proteins identified to be the soybean storage proteins, β-conglycinin (Gly m5), and Glycinin (Gly m6). Soy processing workers with IgE specific to soy reacted most commonly with soybean storage proteins compared with soy hull allergens identified in community asthma studies.

5b.03.5.1.1.1.2 LMW occupational asthma

Similar to HMW allergens, the potential for exposure to LMW allergens exists in almost every occupational sector. Toluene diisocyanate (TDI) is one of the most common occupationally relevant LMW chemicals shown to induce OA. TDI is a highly reactive chemical utilized in the automobile industry and in the manufacture of polyurethane foams, paints, elastomers, and coatings. In addition to OA, exposure to TDI can cause rhinitis and ACD (Mapp, 2001; Bello *et al.*, 2007). The incidence of OA related to occupational TDI exposure has been estimated at up to 5.5% for the total workforce (Diller, 2002). Although exact worker exposure numbers are currently unknown, NIOSH has estimated that 280,000 U.S. workers are potentially exposed to isocyanates (NIOSH, 1996), and this number has likely increased due to the recent increased industrial use of isocyanates (Bello *et al.*, 2007). Both the respiratory tract and skin are documented sites of diisocyanate exposure, which can occur following exposure to aerosols, liquids, or vapors (Redlich and Karol, 2002). Worker exposure has been confirmed via TDI adducts in the plasma and urine; toluene diamine, a hydrolysis product of TDI, has been measured in the plasma of exposed workers as an alternate marker of exposure (NTP, 2011). It is difficult to monitor and control occupational TDI exposures due to the mixed species of TDI commonly used in workplaces along with the lack of well-defined exposure data (Redlich and Karol, 2002). Despite gaps in the literature regarding TDI exposure it is clear that reduced exposure levels lead to lower cases of TDI-induced asthma. TDI sensitization is a difficult response to fully characterize due to the difficulty of performing appropriate human studies and the variation observed between human and mouse models. Accordingly, the clinical pathogenesis of TDI-induced asthma is not fully understood beyond observational data collected from patients with this condition. The contested role of IgE in TDI sensitization and asthma is a poignant example of the lack of understanding of basic mechanisms involved in these conditions. The apparent importance of IgE in murine models of TDI allergy is contrasted by the inconsistent appearance of this antibody (both total and specific) in human patients. The fact that IgE is associated with other chemical allergens and the pathogenesis of allergic asthma caused by these agents further complicates this question. When present, TDI-specific IgE serves as a predictive tool, but this antibody is not detected in many TDI asthmatics who frequently exhibit normal IgE levels (Liu and Wisnewski, 2003). It is possible that IgE-independent mechanisms of sensitization and asthma are integral in the pathogenesis of TDI allergy. Regarding the IgE conundrum along with general mechanisms of disease, it is evident that additional understanding of the immunologic mechanisms of sensitization and elicitation will better enable the development of appropriate hazard identification strategies and therapeutic targets relevant to TDI sensitization and asthma.

The current TDI OEL set by OSHA is 0.02 ppm (approximately 140 μg/m3), and 2.5 ppm is considered immediately dangerous to life and health. However, workplace air concentrations can range from < 1 to > 1000 μg/m3, based on various reports (NTP, 2011). Typically, limits are set by risk assessors based on experimental data and human health studies (covering effects and exposures) encompassing carcinogenesis, portal of entry irritation, and systemic effects (Dotson *et al.*, 2015). Frequently OELs are not adequate for protecting workers from chemical-induced allergy due to limited human data and the complexity of the sensitization response. Several of the key challenges associated with setting OELs for chemical allergens are selection of sensitization or elicitation to serve as the basis of the OEL, temporal factors involved in the allergic response, individual susceptibility to and reaction to sensitization, and examination of the relevant routes of exposure (Dotson *et al.*, 2015). Furthermore, once sensitization has occurred, exposure to very low levels of TDI (below the accepted OELs) may cause symptoms, making regulation extremely difficult (Redlich and Karol, 2002). Asthmatic responses have been demonstrated in sensitized workers following inhalation challenge of $\leq$ 1–5 parts per billion (ppb) TDI, which is at or below the current ACGIH TLV TWA of 5 ppb (Dotson *et al.*, 2015). Clearly, prevention of sensitization is the ideal outcome of regulation; however, if this is not feasible, early diagnosis and removal from any exposure would be the best course of action for a sensitized worker. In addition to diisocyanates, other LMW chemicals have been reported as common causative agents in

allergic OA. These include but are not limited to acid anhydrides (phthalic anhydride, maleic anhydride, and TMA), acrylic monomers, complex platinum salts, metals (nickel and chromium), biocides (glutaraldehyde and chlorhexidine), phenol-formaldehyde resin, persulfates, and aliphatic amines.

While the majority of LMW chemicals associated with allergic disease have been linked to ACD, only a very small fraction of those have been associated with OA. Currently there is no validated method for the hazard identification of LMW chemicals that can induce OA. The development of methods for hazard identification is complicated by the uncertainty about the clinical characteristics of LMW-induced OA along with knowledge related to the immunological mechanisms of the disease.

5b.03.5.1.1.2 Irritant occupational asthma

Irritant occupational asthma has been shown to result from a single massive exposure or lower dose chronic exposures and represent 4–14% of all cases of OA (Lemiere *et al.*, 2022). Over 70 agents have been identified to induce irritant OA, and these include acids, cleaning agents, ammonia, diesel exhaust, chlorine, cement, welding fume, construction dust, solvents, sulfur dioxide, smoke, spray paint, and dinitrogen tetraoxide (Lemiere *et al.*, 2022) Typically, this type of asthma is not associated with acquired immunity, and while the mechanism is not completely understood it is thought to be a result of epithelial cell damage and bronchial wall inflammatory changes with infiltration of lymphocytes (Tarlo and Lemiere, 2014). The best-defined subset of irritant-induced asthma was caused following high-level irritant exposure and initially described in 1985 by Brooks, using the term RADS (Brooks *et al.*, 1985). The criteria for this diagnosis include the exclusion of preceding airway disease, onset of asthma-like symptoms within 24 h after an evident single, very high (usually accidental) exposure, persistence of symptoms for at least 3 months, and objective changes consistent with asthma on spirometry and/or documentation of airway hyperresponsiveness. Patients who appeared to have a similar new-onset of asthma related to irritant exposure but did not meet all of the RADS criteria were categorized as having irritant asthma. This could result from irritation due to relatively low chemical concentration or a delay in onset of symptoms. An example of irritant-induced OA (not categorized as RADS) resulted from exposures following the World Trade Center collapse of 2001 (de la Hoz, 2011). One remarkable characteristic of the irritant-induced asthma observed among emergency/first responders and clean-up workers at this site was the slow onset of symptoms and long delay in clinical diagnoses. Workers were exposed to extremely high levels of inhaled alkaline calcium oxide dust which did not typically induce asthma-like symptoms until weeks after exposure. There is also evidence that agents which are classified as allergic sensitizers (grain, diisocyanates, TMA, and platinum salts) can also cause irritant-induced asthma. It has been suggested that a very high initial exposure which results in an irritant response can also initiate sensitization (Boulet, 1988).

5b.03.5.1.1.3 Work-exacerbated asthma

WEA, also termed work-aggravated asthma, is asthma that worsens at work but was not initially caused by workplace environmental conditions (Friedman-Jimenez *et al.*, 2015). Most patients with WEA experience symptomatic worsening at work with improvement away from work, and/or need to increase their use of asthma medications to treat worsening of their asthma due to workplace exposures. WEA is common and estimated to affect around 21.5% of adult asthmatics (Henneberger *et al.*, 2011). WEA has been defined based on the following criteria: preexisting or concurrent asthma, asthma–work temporal relationship, conditions exist at work that can exacerbate asthma, and occupational asthma was unlikely as a diagnosis. Agents identified to induce WEA include ammonia, engine exhaust fumes, metal fumes and dusts, silica dust, mineral fibers, organic chemicals, heat, and humidity (Tarlo, 2016). Dusts is most commonly implicated in WEA in health care and education settings, while smoke is more commonly associated with in-service jobs (Lim and Chung, 2014). The diagnostic tests for WEA are the same as those for OA. In the context of preexisting asthma, prior to the work exposures, and/or an absence of a specific sensitizer at work, the findings of work-related worsening of asthma documented by serial PEF recording, symptoms, and need for medications are supportive of WEA. However, the symptoms may mimic OA, and the diagnosis can often be difficult for those patients who have the concurrent onset of asthma while working and/or have exposure to a known respiratory sensitizer at work.

5b.03.5.1.2 Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is characterized by increased numbers of interstitial T-cells and macrophages, as well as noncaseating granulomas that can lead to significant alveolar destruction and parenchymal fibrosis. It is caused by the inhalation of a variety of agents that are usually organic and antigenic. The acute phase of HP can be summarized as an inflammatory process characterized by nonatopic neutrophilic inflammation caused by small organic particles. Generally, nonspecific airway hyperreactivity and mucus production are not observed during this reaction as is typically the case with allergic asthma (Bogaert *et al.*, 2009). The chronic symptoms of HP are associated with interstitial pneumonitis, lymphatic bronchiolitis (primarily CD8 + T-cells), and granulomas along with fibrosis of the alveoli and bronchioles (Bogaert *et al.*, 2009). More than 200 agents are associated with the development of the disease and include plant products, animal products, aerosolized microorganisms, and chemicals. Occupational exposures may occur in agricultural, manufacturing, industrial, and office settings (Churg, 2022; Walters and Huntley, 2023) . Most individuals develop HP through exposure to agriculture or industrial environments, but HP can also occur in home and offices through forced-air heating, humidification, or air-conditioning systems. HP is relatively common (5–15%) among workers exposed to significant concentrations of allergen and/or exposed for prolonged periods of time (Hirschmann *et al.*, 2009). There are many different forms of HP and new etiologies of the disease continue to be reported as changing agricultural and industrial practices lead to new types of exposures. Based on a mortality surveillance survey,

between the years of 1980 and 2002, the total number of deaths reported from HP were 814, with 68.4% being males (Bang *et al.*, 2006). HP due to unspecified allergic alveolitis and pneumonitis and unspecified organic dust accounted for 55.5% of all HP deaths, while farmer's lung was reported in 37.3%. All other sub-classification of HP accounted for less than 8% of the total HP deaths (Bang *et al.*, 2006). Agricultural workers are at a high risk for HP because they are potentially exposed to various organic dusts, animal proteins, avian proteins, insect products, and vegetable derivatives (Greskevitch *et al.*, 2007). Manufacturing is also an industry with a high number of reported cases of HP. HP due to LMW agents, including TDI and TMA, has occurred in workers during the manufacture of paints and epoxys (Wiszniewska and Walusiak-Skorupa, 2015). It is also recognized that machinists exposed to aerosolized metal working fluids that are contaminated with microorganisms may develop HP (Barber *et al.*, 2014). If diagnosed early, some types of HP are treatable by exposure avoidance and with medicines that reduce inflammation. If the condition goes untreated or is not well controlled over time, the chronic inflammation can cause irreversible scarring of the lungs that may severely impair function. Diagnostic techniques include high-resolution computed tomography (HRCT), bronchoalveolar lavage, and transbronchial lung biopsy (Richerson *et al.*, 1989).

5b.03.5.1.3 Bronchiolitis obliterans

Bronchiolitis obliterans (BO) refers to a rare but serious condition resulting in progressive and irreversible airway obstruction (Nett *et al.*, 2020). The histopathological features of BO suggest that injury and inflammation of small-airway epithelial cells and subepithelial structures lead to excessive fibroproliferation. This is due to aberrant tissue repair, including ineffective epithelial regeneration, in response to tissue injury (Gutor *et al.*, 2023) . This syndrome is typically the result of injury to the respiratory and terminal bronchioles (most often due to exposure to toxic chemicals) but can also results from transplant surgery and infection (Aguilar *et al.*, 2016). In 2000, cases of fixed obstructive pulmonary disease were identified among employees of a microwave popcorn production facility (Kreiss *et al.*, 2002). According to comparisons with the national data, the 117 workers who were examined had 2.6 times the expected rates of chronic cough and shortness of breath and twice the expected rates of physician-diagnosed asthma and chronic bronchitis. Overall, the workers had 3.3 times the expected rate of airway obstruction, and those who had smoked had 10.8 times the expected rate. Workers directly involved in the production of microwave popcorn had higher rates of shortness of breath on exertion and skin problems that had developed since they started work than workers in other parts of the plant. This was the first study to link exposure to the butter flavoring, diacetyl, to BO. Since the initial study, several additional cases of flavor-related lung disease have been diagnosed among workers of microwave popcorn facilities along with other flavoring manufacturing production (snack food, pet food, and coffee roasting) (Nett *et al.*, 2020). Animal inhalation exposures studies provide further evidence for workplace flavor-related lung disease (Morgan *et al.*, 2008; Palmer *et al.*, 2011; Hubbs *et al.*, 2019, Wang *et al.*, 2021). Damage to the very small airways (bronchioles) can occur with inhalation of certain flavoring chemicals, like diacetyl, resulting in chronic airflow obstruction that can progress to airway scarring and severe obstructive lung disease. Diacetyl (2,3-butanedione) is a diketone and an ingredient of butter flavoring used to intensify food flavor and aroma; it is present in many different food products including snack cakes, cookies, pretzels, candy, and dairy products (Pierce *et al.*, 2016). Recently, diacetyl has been detected in e-cigarettes; which are also being associated with the development of BO (Cao *et al.*, 2020; Eshraghian and Al-Delaimy, 2021). In addition to diacetyl, other structurally similar flavoring compounds including 2,3-pentanedione are also associated with BO in both human and animal studies (Flake and Morgan, 2017; Hubbs *et al.*, 2016, 2019). Polymorphisms in innate immune system genes may be associated with BO that develops in response to organ transplantation. Recent results revealed 57 differentially expressed genes associated with BO and validated four novel BO biomarkers (Wu *et al.*, 2023). Studies have also found the presence of circulating antibodies specific for donor-human leukocyte antigen (HLA) suggesting that antibody-mediated rejection has a causative role. In addition, regulatory T-cells and autoimmune responses to specific airway proteins (collagen and K-alpha 1 tubulin) have been identified as having potential importance in the pathogenesis of BO (Tiriveedhi *et al.*, 2012; Barker *et al.*, 2014).

The main symptoms of BO include progressive shortness of breath on exertion, chronic cough (usually nonproductive), and wheezing. Symptom onset has been reported to be gradual, with progressive shortness of breath occurring following months or years of exposure (Gutor *et al.*, 2023). The most obvious clinical finding in affected workers has been the presence of severe airway obstruction on spirometry that is not responsive to bronchodilator administration. After exposure cessation, affected workers have generally experienced stabilization of their disease although some workers continued to have lung function declines for up to 2-year postexposure. Because treatment with oral corticosteroids and bronchodilators generally does not lead to any significant improvement, lung transplant is the best option for complete treatment of the disease (Aguilar *et al.*, 2016). In 2013, NIOSH published its draft REL for diacetyl, with an 8-h TWA of 0.005 ppm and a 15-min short-term exposure limit (STEL) of 0.025 and for 2,3-pentanedione, 0.0093 and 0.031 ppm, respectively. Effective exposure controls can limit exposure and risk of morbidity from this preventable lung disease, and a better understanding of mechanism may help to aid in treatment.

5b.03.5.1.4 Chronic beryllium disease

Beryllium is a light-weight element that is processed into beryllium copper alloy, pure beryllium metal, and ceramic for use in highly specialized applications, such as defense, aerospace, and electronics industries. Downstream from manufacture and primary machining jobs there are a wide variety of occupations including dental technicians, jewelers, precious metal reclamation workers, welders, plumbers, and electricians which have the potential for beryllium exposure. It has been estimated that more than 134,000 workers in the United States are involved in the manufacture, machining, or manipulation of beryllium or beryllium-containing materials. In 2017, the inhalation PEL for 8 h was lowered from 2.0 $\mu g/m^3$ to 0.2 $\mu g/m^3$. The prevalence of beryllium sensitization

among exposed workers ranges from less than 1% in aluminum smelters where exposure is low to 20% in workers in highly exposed processes (Schuler *et al.*, 2008; Taiwo *et al.*, 2010). Beryllium exposure can result in delayed-type hypersensitivity in susceptible workers which can develop into chronic beryllium disease (CBD). The proportion of workers with beryllium sensitization that develop CBD ranges from 9% to 100% typically developing between 10 and 20 years following the first exposure (Mayer and Hamzeh, 2015). Although initial sensitization does not necessarily require a long-term exposure to beryllium, once someone is exposed there is a lifelong risk of developing CBD. In CBD, immune responses to inhaled beryllium lead to lung damage which can manifest into symptoms such as fever, cough, and shortness of breath. In addition to inhalation exposure, skin exposure is also suspected of being an important route for beryllium sensitization (Day *et al.*, 2006; Virji *et al.*, 2019). The key pathological manifestations of CBD are similar to sarcoidosis and include granulomas composed of epithelioid cells along with lymphocytic alveolitis (MacMurdo *et al.*, 2020). The beryllium lymphocyte transformation test (BeLPT), which demonstrates in-vitro proliferation of peripheral blood or bronchoalveolar lavage cells following beryllium stimulation, is used to help establish a clinical diagnosis (Rossman, 2001). Beryllium sensitization is determined based on a history of beryllium exposure and abnormal BeLPT. Diagnosis of CBD includes PFTs, chest radiographs, and transbronchial biopsies. Corticosteroids are typically used for treatment of CBD symptoms, but most of these patients will require lifelong treatment. The risk of developing sensitization to beryllium and CBD depends on genetic factors, including polymorphisms in antigen-presenting genes Human leukocyte antigen (HLA) Class II molecules involved in antigen presentation including HLA DPB1, with glutamic acid at position 69 (Glu69), have been identified in the majority of patients with beryllium sensitization or CBD (Fontenot, 2018).

5b.03.5.1.5 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a common inflammatory disease of the airways characterized by chronic obstruction of airflow that is not fully reversible. It refers to chronic bronchitis, emphysema, and combined presentations of these two diseases. The pathogenesis of COPD is based on innate and adaptive inflammatory responses to inhaled toxic particles and gases. The immunological changes associated with COPD are associated with tissue repair and remodeling that result in increased mucus production and emphysematous destruction of the gas-exchanging surface of the lung (Murgia and Gambelunghe, 2022). The nature of the antigens driving the immune response observed in the lungs of persons in the advanced stages of COPD is poorly understood but most likely includes antigens from noninfectious and infectious particles and may involve an autoimmune mechanism. An increase in mature lymphoid follicles with a germinal center and separated T- and B-cell zone observed in the airways of smokers with severe and very severe COPD (25–30%) provide support for a role for the adaptive immune system in this disease. Although the exact reason for this increase in not known, it has been attributed to a large antigen load, autoimmune mechanisms, and increased exposure to neoantigens in the damaged extracellular matrix (Hogg and Timens, 2009).

COPD is a leading cause of morbidity and mortality in the United States and worldwide, and this burden continues to grow (Bang, 2015). COPD was the sixth leading cause of death in the US in 2020 (Syamlal *et al.*, 2022). The CDC estimates that cigarette smoking is the single most important risk factor for COPD across the world, and it is associated with 80–85% of all cases. However, recent studies suggest that inherited COPD risk factors also effect the development of the disease (Bang, 2015). It is well recognized that COPD is also caused by occupational exposures. Estimates show that 15% of COPD is attributable to occupational exposures, and the fraction of COPD attributable to occupation ranges from 20% to 53% of nonsmoking workers (Bang, 2015). Coal mine dust and crystalline silica encountered in industries such as mining and construction are commonly known risks for COPD. In addition, among agricultural workers and farmers, the disease has been attributed to exposures to dust and biological agents (Sigsgaard *et al.*, 2020). Newly identified occupations with elevated COPD prevalence include machine operators, construction trades, financial record processing, cotton workers, farm machinery workers, construction workers, and bus drivers. Chronic exposure to inhaled mineral dusts, metal fumes, organic dust (wood, grains, etc.), diesel exhaust fumes, and/or chemical gases or vapors can lead to COPD. COPD manifests numerous ways from fever, or fatigue on exertion, to multiple respiratory symptoms (dyspnea, cough, and increased sputum production). COPD is diagnosed with PFTs that allow determination of the extent of airflow obstruction and monitoring of disease progression. Treatment for COPD ranges from oral and inhaled medications to reduce dyspnea and improve exercise tolerance in patients with stable disease to long-acting bronchodilators, cardiopulmonary rehabilitation, and long-term oxygen therapy for patients with more severe disease.

5b.03.5.1.6 Silicosis

Silicosis is an occupational fibrotic lung disease, caused by inhalation of crystalline silicon dioxide (quartz and cristobalite), resulting in progressive impairment of lung function. Lung injury typically occurs when inhaled silica particles reach the alveoli and are ingested by alveolar macrophages. The direct cytotoxic effects of silica cause macrophage death with subsequent inflammatory cascade resulting in fibrosis (Pollard *et al.*, 2021; Chen *et al.*, 2022). Aside from pulmonary fibrosis, it is well established that patients with silicosis often have a higher incidence of autoimmune diseases (Maeda *et al.*, 2010; Krefft *et al.*, 2020). The effect of silica on the immune system is thought to be a result of its potential adjuvancy activity. In addition, the increasing extracellular presence of various autoantigens such as DNA, RNA, and organelles released from apoptotic macrophages that phagocytized silica particles may increase the likelihood for activation of the immune system (Maeda *et al.*, 2010; Adamcakova and Mokra, 2021).

Silicosis can be categorized as simple (nodular) silicosis, progressive massive fibrosis, silicoproteinosis, or diffuse interstitial fibrosis. Crystalline silica occurs naturally in rock (quartz) and sand and in products such as concrete, ceramics, bricks, and tiles. OSHA estimates that more than 2 million workers are exposed to silica dust. Applications and occupations with a high risk for

silica exposure include foundries, brick making, painting, glass, concrete, china, pottery, plumbing, construction, silica sand blasting, and coal mining (Cohen *et al.*, 2008). While exposure limits have been set, studies have shown the development of significant respiratory disease in workers with exposure to crystalline silica at levels of 0.1 mg/m3, the current OSHA PEL is 0.05 mg/m3 (Cohen *et al.*, 2008). Silicosis has a latency period of approximately 10–30 years, although the disease can develop earlier in workers exposed to high quantities of fine silica dust over a shorter period. In addition to causing silicosis, crystalline silica exposure has been associated with pulmonary function impairment and COPD. Silica is classified by the International Agency for Research on Cancer (IARC) as a known human carcinogen. Silica-induced diseases can be prevented by reducing exposures. Due to increased hazard awareness, deaths from silicosis fell more than 70% between 1968 and 2005 (Weston, 2011) and continue to decrease (Bang *et al.*, 2015; Chen *et al.*, 2022).

5b.03.5.1.7 Coal workers pneumoconiosis

Coal production in the United States has continued to increase since the 1930s. Coal worker's pneumoconiosis (CWP), or black lung, results from exposure to washed coal or mixed dust consisting of coal, kaolin, mica, and silica. CWP is an interstitial lung disease (similar to silicosis) that affects the tissues and gas-exchange surface of the lung (Sirajuddin and Kanne, 2009; Liu and Liu, 2020). Although the exact mechanisms leading to CWP are unknown, evidence suggests that the disease is characterized by chronic pulmonary inflammation and fibrotic nodular lesions that usually lead to progressive fibrosis resulting from processes including inflammation, fibroblast proliferation, generation of reactive oxygen species, upregulation of antioxidants, and synthesis of extracellular matrix (Liu *et al.*, 2021). CWP is divided into two categories based on disease severity: simple pneumoconiosis (fibrotic lesions remain limited) and progressive massive fibrosis (severe alternations in lung functions due to extensive fibrosis and emphysema). Development of CWP is associated with immune system activation and increases in a biochemical marker of cell-mediated immunity; neopterin has been shown to be increased in the bodily fluids of individuals with the disease (Ulker *et al.*, 2007).

CWP usually develops slowly, taking 10 years or more from initial exposure to onset of disease, and most often onset of disease is associated with the extent of exposure. CWP is characterized by aggregates of coal dust and fibroblasts which present as small black opacities. Workers with CWP can be asymptomatic in the early stages, but progression can result in dyspnea as pulmonary function declines. Severe cases can cause shortness of breath, loss of pulmonary function, and even death (Weston, 2011). In the United States, the Coal Mine Health and Safety Act of 1969 (42 CFR Part 37) mandated a comprehensive set of measures to prevent CWP. Enactment was followed by a marked reduction in the prevalence of CWP in long-term coal miners. In the period 1970–74, about 32% of miners with 25 or more years of tenure in coal mining who participated in a national X-ray surveillance program had evidence of CWP. By the period 1995–99, prevalence in this group had dropped to about 4%. Unfortunately, in the recent period 2005–06, prevalence increased to 9%. In addition, advanced cases have recently been detected in miners in their 30s and 40s. In view of the increasing use of coal as an energy source and the predicted growth of coal mining, protecting coal miners from respiratory disease continues to be an important and ongoing priority. As a result, NIOSH recently cut the PEL in half to a REL of 1 mg/m3. The Mine Safety and Health Administration (MSHA) in conjunction with NIOSH conducts the Coal Workers' X-Ray Surveillance Program (CWXSP) for underground coal miners, and the Miner's Choice Program (MCP), for surface miners. These programs offer chest X-rays for coal workers at the beginning of their employment and then again, every 5 years.

5b.03.5.1.8 Asbestosis and mesothelioma

Asbestos is a commercial term that refers to six types of fibrous minerals, including one serpentine (chrysotile) and five amphiboles [crocidolite (riebeckite), amosite (cummingtonite–grunerite), anthophyllite, tremolite, and actinolite]. Asbestos mineral fibers are flame and heat-resistant, pliable, strong, refractory to corrosive chemicals and provide insulation. Because of their heat-resistant properties, asbestos has been widely used as a building material. It has also been woven into fabric to make fireproof, protective textile products, used in brake liners and pads, tiles, bricks, lining of furnaces and ovens, and used to make filters in the chemical industry (Weston, 2011) (see "Relevant Websites" section). The deleterious effects of asbestos exposure have been recognized for decades. Although its use in the United States has largely disappeared, exposure continues to occur due to renovation or demolition of existing building stock or through exposure to asbestos-containing products that continue to be imported. Despite its ban from use and manufacture in 55 countries, asbestos continues to be mined and formulated into new products in many countries including Russia, China, Brazil, and Kazakhstan. The World Health Organization (WHO) estimates that there are approximately 125 million people who are currently exposed to asbestos in the workplace and more than 107,000 people die each year on a global basis from asbestos-related occupational exposures. Inhalation of asbestos fibers can have many adverse health effects. Fibrous asbestos particles can exert their biological effects in several ways. The particle may result in elevations in oxidative stress along with excessive inflammation resulting from macrophages trying to clear the particles from the body (Gaudino *et al.*, 2020; Fiorilla *et al.*, 2023). It has been suggested that asbestos exposure may influence immunocompetent cells and ultimately results in a reduction of tumor immunity (Kumagai-Takei *et al.*, 2020). Studies have found that natural killer cells (obtained from cell lines and healthy donors exposed to asbestos for extended periods have reduced cytotoxicity and decreased activation). In addition, decreased extracellular signaling activity and production of granzyme and perforin have been reported (Kumagai-Takei *et al.*, 2021).

The symptoms associated with asbestos exposure develop slowly, usually presenting a decade or more after exposure. Therefore, asbestos-caused diseases remain an important problem. Asbestos exposure can result in numerous lung conditions including pleural effusion, pleural plaques, diffuse pleural thickening, asbestosis, mesothelioma, and lung carcinoma. These risks increase

multiplicatively if an exposed person also smokes (Sirajuddin and Kanne, 2009; Markowitz *et al.*, 2013). The pleura is most frequently affected by asbestos exposure, with localized pleural thickening or pleural plaque occurring in up to 80% of exposed workers. Pleural plaque typically forms 15–30 years after exposure and increase in frequency with exposure duration (Seaman *et al.*, 2015). Asbestosis is an interstitial lung disease resulting from pulmonary fibrosis caused by asbestos exposure and is almost always associated with pleural plaque (Seaman *et al.*, 2015). Mesothelioma, which arises in the pleura or peritoneum (lining of the abdominal cavity) as a result of asbestos exposure, has a high fatality rate (Markowitz, 2015). Approximately one-half of all occupational-related deaths due to cancer are caused by asbestos, and it is estimated that 28,000–43,000 deaths due to mesothelioma occur per year (Markowitz, 2015) with 26,278 deaths in 2020 (Sung *et al.*, 2021).

5b.03.5.2 Skin Diseases

5b.03.5.2.1 Occupational contact dermatitis

Occupational contact dermatitis (OCD) is one of the most common types of illness accounting for approximately 90–95% of all occupational skin disorders in the United States. Common symptoms of dermatitis include itching, pain, redness, swelling, and/or formation of a rash with the potential for chronic changes including alteration in pigmentation, skin thickening, and cracking following repeated or prolonged exposure. The severity is highly variable and depends on many factors including chemical properties of the hazardous agent, exposure concentration, duration and frequency of exposure, environmental factors, and condition of the skin. Individual risk factors such as atopy, age, environment, and sex have also been shown to influence OCD.

Occupations with a high incidence of OCD include health care workers, cleaning staff, metal workers, food industry workers, construction workers, painters, and hairdressers (Diepgen, 2012). Thousands of different products including medicines, antioxidants, preservatives, antiseptics, biocides, pesticides, disinfectants and cleaning agents, metals, constituents of plastic and rubber materials, oils, pigments and dyes, cosmetics, depilatory waxes, Peru balsam, rosin, turpentine, and plant and animal proteins may cause OCD (Li and Li, 2021). The most common occupational contact allergens include carbamates and thiuram mix (rubber accelerators, pesticides, herbicides, fungicides), epoxy resins, formaldehyde and glutaraldehyde (preservatives, disinfectants), and nickel (Lampel, 2015). Contact dermatitis can be classified as subjective irritancy, acute irritant contact dermatitis, chronic irritant contact dermatitis, ACD, phototoxic, photoallergic, and systemic contact dermatitis (Wiszniewska and Walusiak-Skorupa, 2015). The most common forms of OCD include ACD and irritant contact dermatitis (ICD).

ACD is an inflammation of the skin caused by an immunologic reaction triggered by dermal contact with a skin allergen. In ACD, the cytotoxic damage to the skin produced by the inflammatory mediators and the cell infiltrates leads to the clinical symptoms of ACD which may occur within 24 h of exposure in a previously sensitized individual and reach its maximum response between 48 and 72 h (Wakem and Gapari, 2000). ICD is a nonimmunologic reaction that manifests as a local inflammation of the skin caused by direct damage to the skin following exposure to a hazardous agent. The reaction is typically localized to the site of contact. Available data indicate that ICD represents approximately 70–80% of all cases of OCD (Bains *et al.*, 2019). ICD may be caused by acute exposures to highly irritating substances such as acids, bases, and oxidizing agents; high frequency of wet work; or chronic cumulative exposures to mild irritants such as soaps and detergents, solvents, glove use, and weak cleaning agents.

The symptoms and presentation of ICD and ACD are similar which often make it difficult to distinguish between the two without clinical testing such as patch testing. Epicutaneously applied patch tests representing a standard series of allergens are the standardized diagnostic procedure to confirm ACD. For accurate diagnosis of OCD, it is essential to assess the exposure to the relevant allergen. Therefore, the patch testing may include the patient's own products as well as test articles based on chemical analysis of the products from the workplace. The reading and interpretation of patch tests should conform to principles developed by the International Contact Dermatitis Research Group and the North American Contact Dermatitis Research Group (2006). Once the allergen has been identified, management of OCD includes medical treatment and workplace interventions, with avoidance of contact with the offending agent(s) being key to the success of treatment.

Hairdressers and cosmetologists represent a large occupational group with a high incidence of OCD (Lyons *et al.*, 2013; Anderson and Meade, 2014) such as ICD and ACD with higher incidences reported for hairdressers compared to cosmetologists. The rates for ACD and ICD identified from epidemiology studies range between 27.3% and 72.7% and 20.0–51.1%, respectively, with the hand being the most common body site of involvement (Krecisz *et al.*, 2011; Warshaw *et al.*, 2012; Lyons *et al.*, 2013). In several of the studies, ACD was more prevalent than ICD which is somewhat unique to this industry (Warshaw *et al.*, 2012; Lyons *et al.*, 2013). The most common exposures that result in ICD and ACD are to detergents/surfactant/colors/fragrances present in shampoos (isopropyl myristate and triethanolamine), additives such as preservatives or biocides (formaldehyde, dibromosalicylanilide, methyldibromoglutaronitrile, methylisothiazolinone), permanent wave solutions (cysteamine hydrochloride, glyceryl monothioglycolate, diglyceryl thioglycolate), bleaching agents (persulfate salts), fragrances or dyes present in other hair product formulations (*p*-toluene diamine, para-phenylenediamine, 4-aminoazobenzene, pyrogallo), acrylates used for nail art acrylic products, and nickel sulfate used in the cosmetology equipment (Uter *et al.*, 1998; Landers *et al.*, 2003; Krecisz *et al.*, 2011; Hougaard *et al.*, 2012; Warshaw *et al.*, 2012; Chu *et al.*, 2020).

Persulfate salts (ammonium, potassium, and sodium) are inorganic salts used as oxidizing agents in hair bleaches and hair-coloring preparations at concentrations up to 60% (Symanzik *et al.*, 2023). They have been reported to cause ICD, ACD, urticaria, rhinitis, and asthma (Hougaard *et al.*, 2012; Anderson and Meade, 2014; Symanzik *et al.*, 2023). Allergies to hairdressing chemicals such as persulfates are enhanced by detergents or other irritants present in shampoos. Chronic exposure to irritants in these

products can enhance allergic contact sensitization to dyes, waving solutions, and other chemicals. Frequent wetting and drying of the hands that occur in these professions may further enhance these effects. Although well characterized to induce ICD and ACD in industries such as painting, printing, and health care, the use of acrylates (materials formed by the polymerization of monomers derived from methacrylates) in the cosmetology sector is increasing (Kolar and Ljubojević Hadžavdić, 2022). Cosmetologists working with artificial nails were identified as 80% of all occupational cases of ACD in a 7-year study with 2263 patients evaluated for dermatitis caused by acrylates (Ramos *et al.*, 2014).

Health care workers also have a high incidence of OCD (Aalto-Korte *et al.*, 2021). Some of the most common chemicals encountered in the health care profession include biocides (glutaraldehyde and *Ortho*-Phthalaldehyde (OPA)) commonly used for applications such as the sterilization of medical devices which are sensitive to normal heat or steam sterilization processes and the disinfectants used on surfaces (such as quaternary ammonia compounds) (Suneja and Belsito, 2008). Medical gloves containing certain rubber accelerators (carbamates, 2-mercaptobenzothiazole) and antibacterial hand sanitizers and soaps (chloroxylenol and cocamide diethanolamine) have also been identified as common sources of allergens (Anderson and Meade, 2014). There are increased rates, in general, for ACD to the majority of the above-mentioned agents among health care workers compared to non-health care workers (Kadivar and Belsito, 2015). Quaternary ammonium compounds including benzalkonium chloride (BAC) [alkyldimethylbenzylammonium chloride (ADBAC)], benzethonium chloride (BEC), and didecyldimethylammonium chloride (DDAC) are known sensitizers in humans (Bernstein *et al.*, 1994; Shaffer and Belsito, 2000; Suneja and Belsito, 2008; Kadivar and Belsito, 2015). A study evaluating 142 patients with suspected allergies to BAC and BEC confirmed sensitization by patch test to these compounds in 20% of the patients and identified potential co-reactions between the two quaternary ammonium compounds in 85% of the subjects who tested positive (Dao *et al.*, 2012). Animal data typically describes these compounds as irritants and/or sensitizers and suggest that exposure duration and concentration may influence the type of immune response induced (Manetz and Meade, 1999; Gerberick *et al.*, 2002; Shane *et al.*, 2019). Healthcare workers have very high frequencies of hand washing (70–100 times per shift) and glove use (1.5 h per shift), and repetitive exposure to wet work and frequent glove use are significant factors in development of occupational ICD (Malik and English, 2015). The development of ICD, or simultaneous exposure to other chemicals, may predispose these individuals to induction of sensitization and subsequent ACD because the skin is more susceptible to chemical penetration and/or immune alterations (Visscher and Randall Wickett, 2012; Callahan *et al.*, 2013; Baur *et al.*, 2021).

Occupational exposure to metals results in a high frequency of ACD with 10–15% of the population estimated to have allergies to at least one species of metal (Kurt and Basaran, 2020). Numerous metals including gold, chromium, cobalt, platinum, nickel, palladium, and mercury are known to induce allergic responses resulting in ACD (Zug *et al.*, 2009; Anderson and Meade, 2014; Karagounis and Cohen, 2023). Following patch testing of 4454 patients (not all due to occupational exposure), nickel sulfate (19.0%), cobalt chloride (8.4%), potassium dichromate (4.8%), were found to be among the most common allergens with nickel being identified as the most frequent positive allergen (Zug *et al.*, 2009). Sources of occupational metal allergen exposure include releases from dental tools and alloys (Kettelarij *et al.*, 2014), scissor and nail instruments used by cosmetologists and nail technicians (Warshaw *et al.*, 2012), coin handling operations (Gawkrodger *et al.*, 2012), and metal processing (Henneberger *et al.*, 2001). Recently the increased occupational use of metal nanomaterials has raised concerns about exposure and allergic disease (Roach *et al.*, 2019). High incidences of OCD have also been observed in cleaner workers using hydrochloric acid and dust mop products. Hand dermatitis was reported by 28% of the current workers (Mirabelli *et al.*, 2012). In addition, the rates of ICD and ACD in food service workers were reported to be 30.6% and 54.7%, respectively, with the use of rubber gloves identified as the most common source of responsible allergen (Warshaw *et al.*, 2013).

The connection between skin and the respiratory systems in occupational allergic disease has recently gained interest (Suzuki *et al.*, 2011; Segaud *et al.*, 2022). Some research has suggested that the early signaling events in the skin including: barrier breakdown, irritation caused by excessive hand washing, exposure to chemical irritants, glove usage, genetics, and wet work may be necessary for sensitization and may manifest in dermal and respiratory allergic disease. Additionally, dermal exposure may be a determinate or prerequisite in allergic pulmonary responses (Ainscough *et al.*, 2013). Select common occupational contact allergens including epoxy resin, nickel sulfate, potassium dichromate, formaldehyde, glutaraldehyde, and isocyanates are established or possible causes of OA (Arrandale *et al.*, 2012). Inhalation and dermal exposures to these agents should be controlled, and both OA and ACD should be considered as possible health outcomes.

The human repeat insult patch test (HRIPT) is still used in many countries as a confirmatory test for skin allergens; however, ethical concerns and the existence of reliable alternative testing procedures have largely eliminated the justification for the HRIPT. Animal models have also been developed to identify sensitizing chemicals and to distinguish between ICD and ACD (Chipinda *et al.*, 2021). Historically guinea pig tests (GPT; i.e., the Guinea Pig Maximization (GPMT) and the Buehler assay (BA)) were used for this purpose. The murine local lymph node assay (LLNA) was developed in 1989 (Kimber, 1989) as an alternative method for the evaluation of the sensitizing potential of LMW chemicals. The LLNA has been evaluated extensively in the context of both national and international interlaboratory trials and validated in the
United States by the Interagency Coordinating Committee on the Validation of Alternative Methods (Dean *et al.*, 2001), and in Europe by the European Center for the Validation of Alternative Methods (ECVAM) (Spielmann and Liebsch, 2002) resulting in the LLNA becoming the preferred method for assessing skin sensitization potential by various regulatory authorities. In 2002, the LLNA was adopted by the Organization for Economic Cooperation and Development (OECD) as a stand-alone method (OECD,

2010). The LLNA has been designated as the initial requirement for sensitization testing with the new Registration, Evaluation, Authorization, and Restriction of Chemical substances (REACH) regulation in the European Union.

5b.03.5.2.2 Urticaria and other skin disease

Although not as common, other skin conditions may occur as a result of occupational chemical exposures. These comprise <10% of occupational skin disease and include nonallergic urticaria, eczema, folliculitis, and skin cancer (Anderson and Meade, 2014). In addition to skin disorders, dermal exposure to many commonly used occupational chemicals, such as solvents and pesticides, may result in systemic effects such as acute poisonings, neurotoxicity (Ma, 1994), lung, liver, and kidney toxicity (Peiro *et al.*, 2007); cardiovascular and respiratory toxicity (Pirson *et al.*, 2003); reproductive toxicity; carcinogenicity (Kaerlev *et al.*, 2005); and potentially death (Lin *et al.*, 2009). Dermal exposure can also result in system immune dysfunction (see below).

5b.03.6 Systemic Immune Modulation

Chemical exposures may also induce systemic immune abnormalities including immune suppression and autoimmunity. In contrast to allergic reactions which are generally clinically apparent and well understood by the general public, immune suppression, and autoimmunity may manifest in symptoms which are more difficult to directly correlate with exposure. Immune suppression may manifest as an increased susceptibility to infectious disease and cancer, and autoimmunity can manifest as target organ dysfunction or more generalized systemic disease.

5b.03.6.1 Immunosuppression

Decades of research has resulted in the development of specific assays and endpoints to identify immunosuppressive agents and using these many regulatory agencies have developed specific immunotoxicity testing guidelines. These assays include evaluation of antibody production, enumeration of lymphocyte subpopulations, natural killer cell assays, and host resistance studies (Anderson and Shane, 2018; Burleson *et al.*, 2018). The humoral immune response including the production, release, and increase in circulating levels of antigen-specific antibodies is important for protection against infectious agents and for prevention or reduction of severity of influenza, respiratory infection, cold, and other diseases. Reduced antibody production is an indication of decreased immune function or immunosuppression that may indicate a greater risk of disease. Antigen-specific IgM to a T-cell-dependent antigen is considered one of the most predictive measures of overall immune function because proper response requires cooperation between T-cells, B-cells, and antigen-presenting cells to develop an antibody response (Luster *et al.*, 1992). Antibody responses can be examined by measuring antigen-specific antibody levels after challenge with specific antigens in laboratory animals and after vaccination in humans. Following exposure, epidemiological studies, often with limitations, can also provide information about potential health outcomes of which the most commonly observed pathologies include i certain cancers and common infections (Kramer *et al.*, 2012; Corsini *et al.*, 2013).

The earliest classes of immunosuppressive chemicals studied included: heavy metals (lead, cadmium, arsenic), halogenated aromatic hydrocarbons (2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)), polychlorinated biphenyls (PCB), polybrominated biphenyls (PBB), aromatic hydrocarbons (benzene and toluene), pesticides (trimethyl phosphorothioate), carbofuran, chlordane, aromatic amine (benzidine, acetylaminofluorene), and particulates (asbestos, silica, beryllium) (Luster and Rosenthal, 1993; Veraldi *et al.*, 2006). More recently the chemical, perfluorooctanoic acid (PFOA), a per- and polyfluoroalkyl substance (PFAS), has been identified as immunotoxic by the NTP. PFOA is a synthetic, highly stable chemical that is used in manufacturing of protective coatings for carpets, stain- and grease-resistant clothing, paper coatings, and nonstick pans (OECD, 2005). Because of its high stability and extremely low surface tension, it is used in numerous consumer and industrial applications. While PFOA was identified in all serum samples tested for perfluorinated compounds from the general U.S. population in the 1999 National Health and Nutrition Examination Survey (NHANES, 1999–2000) (Calafat *et al.*, 2007), serum PFOA levels for individuals who had occupational exposure were typically ~ 4–5 times greater than the general U.S. population (Steenland *et al.*, 2010). A relatively recent cohort of workers exposed to PFOA at a DuPont chemical plant in Parkersburg, West Virginia, has provided information about the immunotoxicity of this chemical. In addition to occupational exposures, these workers were also exposed to PFOA in drinking water contaminated by production facilities. Reduced antibody titers to influenza vaccine were associated with increased serum PFOA levels in individuals in this area (Looker *et al.*, 2014). An increased incidence of kidney and testicular cancer was correlated with increased serum PFOA levels for individuals who worked at this plant (Barry *et al.*, 2013). In addition, occupational exposure to PFAS has been linked to health effects such as prostate cancer and non hepatitis liver disease, malignant and nonmalignant renal disease, diabetes mellitus, chronic renal disease, hypothyroidism, and immune dysfunction (Steenland *et al.*, 2010; Steenland and Woskie, 2012; von Holst *et al.*, 2021). More recently, firefighters exposed to PFAS through firefighting foam have been recognized as an occupational group with an increased incidence of certain types of cancer, suggesting that in addition to immunotoxicity, the skin may be an important route of exposure (Franko *et al.*, 2012; Ragnarsdóttir *et al.*, 2022). Supporting the epidemiological findings is consistent evidence that PFOA exposure results in suppression of the primary antibody response, as determined by antigen-specific IgM antibody production to single

challenge with T-cell-specific antigens in PFOA exposed mice following multiple routes of exposures (Yang *et al.*, 2002; Dewitt *et al.*, 2008; Shane *et al.*, 2020). Although PFOA has been phased out of production in the US, it is still detected in the environment and the majority of the human population due to its stability and biopersistence. Additionally, alternative PFAS are currently being produced, used, and presumed to be safer, although studies support the potential for immunotoxicity (NTP, 2019; Weatherly *et al.*, 2021; Weatherly *et al.*, 2023). There are still knowledge gaps which complicate hazard identification and risk assessment (Woodlief *et al.*, 2021; Ehrlich *et al.*, 2023).

5b.03.6.2 Autoimmune Disorders

Autoimmune diseases represent a heterogeneous group of disorders that affect specific target organs or multiple organ systems. These diseases are initiated by the loss of immune tolerance and are mediated through lymphocyte activation that leads to tissue damage by self-reactive lymphocytes and autoantibodies, resulting in debilitating symptoms and potentially death when vital organs are affected (Anaya *et al.*, 2018). Although autoimmune disorders encompass a wide spectrum of diseases, they share clinical signs and symptoms, physiopathological mechanisms, and genetic factors. Systemic autoimmune diseases, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and rheumatoid arthritis (RA), appear to have complex etiologies, and the manifestation of these effects in a given individual may depend on other environmental factors or differences in genetic susceptibility (Pisetsky, 2023).

The events initiating an autoimmune response are largely unknown; however, intrinsic and extrinsic factors associated with the induction, development, and exacerbation of autoimmunity include genetics, hormones, age, and lifestyle. A recent study suggests, autoimmune diseases affect approximately 10% of the population (13% in women and 7% in men) (Conrad *et al.*, 2023) and additional evidence suggests that autoimmune disease numbers continue to increase (Miller, 2023). Silica exposure has been linked in numerous studies to an increased incidence of SLE, dermatomyositis, vasculitis, renal disease, and rheumatoid arthritis (Cohen *et al.*, 2008; Go and Cohen, 2020; Woo *et al.*, 2022). In high-level silica exposure, SLE is 10 times higher than the expected sex-specific prevalence in the general population, but the strength of this association falls in both men and women as exposure is reduced (Pollard, 2016). Silica exposure can also aggravate preexisting rheumatoid disease and is associated with an increased production of antinuclear autoantibodies in both mice and humans, possibly through production of excess cellular debris in a highly inflammatory environment. While the exact mechanisms by which exposure to silicate dusts drives autoimmune responses are not clearly elucidated, it is thought to relate to the finding that silica is a potent immune modulator that can act as an adjuvant to nonspecifically enhance the immune response, increasing proinflammatory cytokine production and inducing apoptosis and necrosis. However, whether this is a universal response to inhaled mineral dusts is unknown (Pollard *et al.*, 2021). Correlations between asbestos exposure and autoimmune disease also suggest a higher-than-expected risk of systemic autoimmune disease among asbestos-exposed populations. Although, in general this association is less compelling than that found with silica. There are limited reports of immune abnormalities and humoral indices consistent with autoimmune mechanisms, including a variety of autoantibodies, and RA has been the systemic autoimmune disorder most frequently associated with asbestos exposure (Lee *et al.*, 2017). Epidemiological assessments of systemic autoimmune diseases in asbestos-exposed cohorts have been relatively small studies that tend to suffer from problems with exposure assessment. There are also numerous studies that suggest an association with work-related solvent exposure, and various autoimmune or autoimmune-like diseases including systemic sclerosis, scleroderma, or connective tissue disorders. Research in this area began in 1957 when the first patients developing a scleroderma-like syndrome after exposure to vinyl chloride, epoxy resins, trichloroethylene, perchloroethylene, and other mixed solvents was reported (Barragan-Martinez *et al.*, 2012). While limited in number, exposure to hair dyes has also been associated with autoimmune disorders including primary biliary cirrhosis and SLE (Smyk *et al.*, 2013).

There are numerous factors that limit the research necessary to make the associations between occupational exposures and autoimmune disease. These include challenge in obtaining statistical power due to the low prevalence (i.e., 24 per 100,000 for SLE, 5 per 100,000 for system sclerosis) of autoimmune diseases, long, uncertain and variable, latency of autoimmune changes, limited animal models (Germolec *et al.*, 2012; Janssen *et al.*, 2022), and lack of accepted criteria for diagnosis or classification of autoimmune diseases. However, despite the difficulties in defining the risk factors that lead to immunopathology, the number of candidates proposed for specific autoimmune diseases is continuously growing as new evidence is reported for infectious agents, chemicals, physical factors, adjuvants, and hormones.

5b.03.7 Conclusions and Research Needs

Hundreds of biological and chemical hazards influence a variety of immunological disorders. While these diseases may be diverse in nature, the importance of understanding the mechanism that lead to disease is universal. As new occupational hazards continue to emerge and require characterization, it is critical that we understand the mechanism that can trigger or exacerbates immune-mediated diseases. As our understanding of immunology has advanced, the screening paradigms for immunotoxicology are continually being updated to include additional relevant and sensitive endpoints, such as enhanced histopathology and routine enumeration of lymphocyte subsets. Although immunotoxicology is continually evolving, scientists in the field recognize the need to identify the most efficient and sensitive approaches for advancement. One concern has been the realization that the traditional screening methods require

a very large number of animals and are inadequate to handle the number of chemicals that need screened. Due to these issues, along with the expense, time, animal welfare concerns, and the general push for the reduction of animal use, a recent focus has been placed on applying new approaches and technologies that would provide sensitive assays while reducing or replacing animal use. This effort has led to the development of more advanced in vitro methods to study immunotoxicology (Luebke, 2012). Specific understanding of mechanism has direct implications in developing appropriate intervention, prevention, and treatment strategies. In addition, there is also a need for the development of validated and standardized methods for the identification of these hazards. Evaluation of these compounds will allow for better risk assessment which will ultimately lead to the establishment of OELs and regulation to protect workers. Expansion of the immunological database for human exposure to chemicals in the workplace and the development and publication of regulatory guidance documents and materials are essential to educate exposed workers and the general public. In the future, the field of human immunotoxicology will greatly benefit from the widespread use of recognized testing protocols along with the use of sensitive biomarkers and clinical endpoints in humans. There is no doubt that the field of immunotoxicology will continue to advance as a science and will continue to benefit from the advancement of other disciplines. Guidelines and regulations will need to evolve within the field to reflect our current knowledge and provide the best predictions to reduce risk to human health.

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