Respiratory Diseases Associated With Organic Dust Exposure

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Learning objectives:

1. Define the important components representing organic dust exposure and mechanisms mediating airway disease consequences.
2. Recognize the spectrum of airway disease and the at-risk populations associated with various organic dust exposures.
3. Describe preventative and therapeutic approaches to mitigate airway disease associated with organic dust exposures.

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Organic dusts are complex bioaerosol mixtures comprised of dust and par ticulate matter of organic origin. These include components from bacteria, fungi, pollen, and viruses to fragments of animals and plants commonplace to several environmental/occupational settings encompassing agriculture/farming, grain processing, waste/recycling, textile, cotton, woodworking, bird breeding, and more. Organic dust exposures are linked to development of chronic bronchitis, chronic obstructive pulmonary disease, asthma, asthma-like syndrome, byssinosis, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis. Risk factors of disease development include cumulative dust exposure, smoking, atopy, timing/duration, and nutritional factors. The immunopathogenesis predominantly involves Toll-like receptor signaling cascade, T-helper 1/T-helper 17 lymphocyte responses, neutrophil influx, and potentiation of manifestations associated with allergy. The true

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Abbreviations used
ACO- Asthma-COPD overlap
AHR- Airway hyperresponsiveness
BALF- Bronchoalveolar lavage fluid
COPD- Chronic obstructive pulmonary disease
FeNO- Fractional exhaled nitric oxide
FEV1- Forced expiratory volume in 1 second
FVC- Forced volume capacity
HP- Hypersensitivity pneumonitis
Ig- Immunoglobulin
IL- Interleukin
IPF- Idiopathic pulmonary fibrosis
LPS- Lipopolysaccharide
MyD88- Myeloid differentiation factor 88
OA- Occupational asthma
ODTS- Organic dust toxic syndrome
Th- T-helper
TLR- Toll-like receptor
TNF- Tumor necrosis factor
WRA- Work-related asthma

prevalence of airway disease directly attributed to organic dust, especially in a workplace setting, remains challenging. Diagnostic confirmation can be difficult and complicated by hesitancy from workers to seek medical care, driven by fears of potential labor-related consequence. Clinical respiratory and systemic presentations coupled with allergy testing, lung function patterns of obstructive versus restrictive disease, and radiological characteristics are typically utilized to delineate these various organic dust—associated respiratory diseases. Prevention, risk reduction, and management primarily focus on reducing exposure to the offending dust, managing symptoms, and preventing disease progression. **(J Allergy Clin Immunol Pract 2024;12:1960-71)**

Key words: *Organic dust; Asthma; Obstructive lung disease; Hypersensitivity pneumonitis; Fibrosis; Occupational*

INTRODUCTION

Organic dusts refer to a complex mixture of dust and particulate matter of organic origin including components from bacteria, fungi, pollen, and viruses to fragments of animals and plants.[1] Organic dust exposures have been linked to development of chronic occupational airway diseases such as chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, asthma-like syndrome, byssinosis, hypersensitivity pneumonitis (HP), and idiopathic pulmonary fibrosis (IPF). Establishing the true prevalence of airway disease directly attributed to organic dust, especially in a workplace setting, remains challenging. The diagnostic confirmation of occupational respiratory diseases can be difficult and complicated by hesitancy from workers to seek medical care, driven by fears of potential labor-related consequences.[2] Workers with worsening symptoms tend to leave their jobs, and those without immediate symptoms remain in the workplace, which has been referred to as "the healthy worker effect."[3] This review addresses risk factors contributing to disease development, immunopathogenesis, disease entities, diagnostic approaches, and management strategies.

EPIDEMIOLOGY

Industries commonly affected by organic dusts include agriculture and food production with high variability in concentration exposure typically related to tasks performed rather than herd size.[3] In the dairy industry, milking and animal-handling activities provided a higher risk of concentration exposure.[3] In the avian industry, hatchery workers experience an increased prevalence of respiratory symptoms including cough and/or phlegm.[4] Furthermore, workers assigned to avian-sorting rooms also had a decrease of 11% in forced vital capacity (FVC) compared with those working in incubation rooms.[4] Moreover, in a Norwegian study of farmers, livestock farmers had increased risk of chronic bronchitis (adjusted odds ratio [aOR] 1.9; 95% confidence interval [95% CI] 1.4−2.6) and COPD (aOR 1.4; 95% CI 1.1−1.7) compared with crop farmers after adjustment for potential confounders including age, gender, and smoking status.[5] A meta-analysis by Guillien et al[6] demonstrated a positive association between farming exposure and airflow limitation or chronic bronchitis in 10 of 22 studies (odds ratio [OR] 1.77; 95% CI 1.50-2.08) with cattle, swine, poultry, and crop farming associated with either airflow limitation or chronic bronchitis.

In the waste and recycling sector, organic dusts and volatile organic compounds were the highest during the sorting of materials in compost stations.[7] In the textile industry, recognized to have high endotoxin exposure, byssinosis is an occupational respiratory disease due to exposure to cotton, hemp, or flax. Hinson et al[8] reported a prevalence of byssinosis of 44% among workers directly exposed to cotton dust in a textile company in Benin, West Africa. In the wood-processing sector, Neghab et al[9] observed that 35% of Iranian sawmill workers experienced a 5% cross-work shift decrease in forced expiratory volume in 1 second (FEV_1). This occurred despite the existence of recommended occupational exposure limits and precautions offered by occupational safety organizations.[9]

IMMUNOPATHOGENESIS

Organic dusts are bioaerosols composed of a diverse and wide array of organic particles, encompassing fragments from both animal and plant sources, alongside pro-inflammatory mediators such as gram-negative endotoxins or lipopolysaccharides (LPS), gram-positive peptidoglycans, and fungal (1−3) b-D-glucans, among others.[10,11] These exposures induce release of pro-inflammatory cytokines/chemokines that typically drive the recruitment and activation of neutrophils, induce airway hyperresponsiveness (AHR), generate free radicals, and promote lymphocyte activation.[12,13] With repetitive exposures, airway remodeling and chronic disease develop.[14] Whereas LPS is a notable element within organic dust, it is the "whole" composition (as opposed to 1 isolated agent) of organic dust mixtures that drive pathogenesis. For example, individuals exposed to pig barn dust had a more pronounced inflammatory response as evidenced by elevated levels of interleukin (IL)-6, IL-8, and total cell counts in sputum samples compared with exposure to LPS alone, despite the concentration of LPS being several-fold higher than what is encountered in pig barns.[15]

Organic dust engages innate signaling pathways, mainly through the recognition of pathogen-associated molecular pattern molecules typically by Toll-like receptors (TLRs). The TLR2, TLR4, TLR9, and the common adaptor protein myeloid differentiation factor 88 (MyD88) have been implicated in the

acute inflammatory response to agricultural-related organic dust exposures.[16-21] In murine studies, swine confinement facility organic dust extract—induced acute airway inflammatory responses (ie, neutrophil influx, release of tumor necrosis factor [TNF]-α, IL-6 and neutrophil chemoattractants, and AHR) were nearly completely abrogated in MyD88-deficient mice.[18] Furthermore, striking reduction in airway inflammatory responses remained after daily exposure for 1 week in MyD88-deficient mice,[22] but there was enhanced airway mucous cell metaplasia.[23] Correspondingly, acute organic dust exposure in humans is also associated with cellular infiltration and increased cytokine production ascribed to TLR signaling. Namely, Hedelin et al[24] demonstrated increases in nasal lavage total and blood neutrophils, monocytes, and basophils following a 3-hour exposure to swine dust with associated increases in monocyte expression of TLR2 and TLR4. This response was reduced following the installment of fine particle separators.[24]

Highlighting the importance of TLR signaling pathways, a missense mutation in *TLR4* (Asp299Gly) has been associated with hyporesponsiveness to inhalant LPS exposure with decreased nuclear factor kappa B activity, decreased IL-1α production, and decreased airway epithelial TLR4 receptor.[25] Single nucleotide polymorphisms in the *TLR10-TLR1-TLR6* gene cluster have also been associated with *ex vivo* whole blood IL-6 (but not TNF-α) hyperresponsiveness to organic dust and gram-positive components in agricultural workers.[26] The CD14 is a receptor for LPS, and the CD14/−159 T allele polymorphism has been associated with increased circulating levels of CD14 and increased prevalence of wheezing without association in lung function in farmers.[27] In this same study, there was no association between TLR4/Asp299Gly and lung function or wheeze in farmers.[27] Otherwise, there is a paucity of data understanding the role of genetic susceptibility in organic dust—associated respiratory diseases.

Compared with the robust acute inflammatory response to a 1-time organic dust exposure, repetitive exposures result in a comparative reduction in pro-inflammatory cytokines/chemokines levels but a persistence of lung neutrophils, lymphocytes, and recruited monocyte/macrophages in animals studies, which has been termed the chronic inflammatory adaptation response.[22,28] Similarly, a 1-time organic dust exposure induces an increase in AHR in mice, and this response is lost with repetitive exposures,[28] consistent with the adaptation response but differs from experimental allergy asthma murine models. Correspondingly, pig farmers demonstrated an attenuation of symptoms, lung function, bronchial responsiveness, and markers of airway inflammation compared with first-time exposed naive individuals.[15] Nevertheless, these pig farmers had markers of low-grade, persistent inflammation compared with never-exposed individuals.[15]

Organic dust exposures can induce the recruitment of $CD4^+$ T-helper (Th) 1 cells, Th2 cells, Th17 cells, innate lymphoid cells, airway epithelial cells, and monocyte/macrophage activation responses.[29-31] In animal models, organic dust extract exposure induces lung alarmin IL-33 release, Th1/Th17 responses, and increased serum immunoglobulin (Ig) E levels without evidence for a Th2-mediated response or airway eosinophil influx.[22,32] The Th17 cells and IL-17 are recognized to induce the recruitment of neutrophils and monocytes/macrophages, contributing to the pathogenesis of asthma and COPD.[33,34] In severe equine asthma syndrome, a naturally occurring chronic organic dust airway disease in horses that shares similarities with asthma in humans, a similar Th17 response has also been demonstrated.[35]

Regulators of organic dust—associated airway inflammatory response include the anti-inflammatory cytokine IL-10. In a cross-sectional study of 625 veterans with farming experience, higher baseline blood concentrations of IL-10 were associated with higher FEV_1/FVC and inversely associated with whole blood stimulated ΔTNF-α and ΔIL-6.[36] In IL-10—deficient mice, organic dust extract—induced airway inflammation, neutrophil influx, and lung pathology were elevated, and this response was reversed with IL-10 supplementation.[37] Furthermore, short-term, lung-delivered recombinant IL-10 favorably hastened airway inflammatory recovery processes following acute, high-dose inhalant LPS exposure in mice.[38] In addition, airway cathelicidin (LL-37), an antimicrobial and LPS-neutralizing peptide implicated in tissue repair,[39] was increased in farmers with and without COPD versus healthy urban persons.[40] In advanced stages of COPD, LL-37 levels have been found to decrease, possibly highlighting the role of this peptide in antimicrobial protection.[41]

RISK FACTORS

Cumulative exposure to organic dust represents an important factor in disease development. In a cross-sectional study in Ethiopia, there was a high incidence of chronic respiratory symptoms in flour mill workers.[42] The presence of chronic respiratory symptoms was associated with working in the mixing department (aOR 5.3; 95% CI 1.68−16.56), work experience of 6 to 9 years (aOR 5.1; 95% CI 2.05−12.48), work experience 10 or more years (aOR 2.5; 95% CI 1.01−6.11), and working 8 or more hours per day (aOR 2.4; 95% CI 1.16−5.10).[42] The degree of exposure is also important. Andersson et al[43] demonstrated that each year of high exposure to soft paper dust (defined as > 5 mg/m^3) was associated with a 0.87% predicted decrease in FEV_1 (95% CI −1.39 to −0.35) and a 0.54% decrease in FVC (95% CI −1.00 to −0.08).[43] In contrast, a Danish register-based cohort study did not find an association between the cumulative organic dust exposure and COPD in the farming or wood industry despite lagging their variables 10 years to consider the period of disease development of COPD and the healthy worker survivor effect.[44] Instead, they noted a decreased risk of COPD in the highest exposed group (adjusted rate ratio 0.63; 95% CI 0.56−0.70).[44] However, it was suggested that tobacco smoke may have confounded the results to suggest a need for additional longitudinal studies.[44] Indeed, the coinfluence of tobacco smoking is important. Guillam et al[4] demonstrated lower forced expiratory flow between 25% and 75% of vital capacity and forced expiratory flow at 50% of vital capacity in duck hatchery workers who smoked compared with nonsmoking workers.

The role of atopy as a risk factor is less clear. Dairy farmers who had persistent airflow limitation were more likely to have at least 3 positive tests for allergen-specific IgE compared with dairy farmers without persistent airflow limitation.[45] House dust endotoxin has been associated with atopic and nonatopic asthma in farming populations across the United States. In a large case-control study involving a cohort of farmers and their spouses, Carnes et al[46] demonstrated that increasing endotoxin levels was associated with higher odds of current asthma (unadjusted OR 1.30; 95% CI 1.14−1.47), and moreover, endotoxin was

TABLE I. Risk factors associated with development of organic dust–associated respiratory diseases

Risk factor	Respiratory disease
Cumulative exposure	COPD/chronic bronchitis
	HP
	IPF
Very high concentration, 1-time exposure	ODTS
	HP
Tobacco smoking	COPD/chronic bronchitis
	Byssinosis
Composition of organic dust (eg, endotoxin)	Atopic and nonatopic asthma COPD/chronic bronchitis
	Byssinosis
Age* (eg, young adults)	Obstructive lung disease
Atopy*	Asthma
Timing of exposure (eg, late- vs early-life exposure)	Atopic and nonatopic asthma
	COPD/chronic bronchitis
Micronutrient deficiencies* (eg, zinc deficiency)	COPD/chronic bronchitis

*Additional studies are needed to fully understand its impact in the development of respiratory diseases.

associated with atopic asthma (aOR 1.38; 95% CI 1.09–1.74) and nonatopic asthma (aOR 1.24; 95% CI 1.07–1.43) after adjustment for sex, smoking status, race, and season.

Timing of exposure may also be important. Exposing mice to Amish organic dust extracts prior to the onset of experimental allergen-induced asthma sensitization and challenge resulted in reduced airway inflammatory outcomes.[47] In contrast, when mice were exposed to swine confinement organic dust extracts after allergen-induced asthma sensitization and challenge phase, there was potentiation of airway inflammatory outcomes.[48] Among U.S. farmers, a nonlinear relationship between endotoxin and asthma was described, with higher endotoxin levels associated with current asthma (OR 1.30; 95% CI 1.14–1.47) and modifiable by early-life farm exposure.[46] Notably, the association between dust endotoxin and asthma was higher in individuals not born on a farm (OR 1.67; 95% CI 1.26–2.20) than in those who were (OR 1.18; 95% CI 1.02–1.37). This highlights that the "protective effect" of early-life farming exposure may be linked to endotoxin exposure.[46,47]

The impact of age as a risk factor for the development of organic dust airway disease has been difficult to establish. Earlier studies (1990s) demonstrated that a relative excess of respiratory symptoms and reduced lung function were higher among swine producers aged 26 to 35 years, which may have reflected more intense exposures.[49] It has also been demonstrated that "young (7–9 wk old)" mice had a more robust inflammatory response to swine confinement organic dust exposures than "older (12–14 mo old)" mice.[50]

Micronutrient deficiencies represent global health concerns[51] and may represent an additional risk factor. Nutritional zinc insufficiency has been associated with lower pulmonary function (FEV_1/FVC $P = .03$; trends for FEV_1 $P = .056$) among veterans with history of farm exposure in COPD individuals.[52] In animal studies, dietary vitamin D[53] and docosahexaenoic acid (omega-3 fatty acid)[54] supplementation demonstrated reduced airway inflammatory indices following exposure to organic dust extracts. Thus, nutritional approaches may potentially reduce organic dust–associated airway inflammation, but future studies in humans are necessary. A summary of the risk factors and respiratory disease(s) associated with organic dust exposure is shown in Table I.

RESPIRATORY DISEASES ASSOCIATED WITH ORGANIC DUST EXPOSURES

Organic dust toxic syndrome

Organic dust toxic syndrome (ODTS) is a complex disease entity that can develop acutely, usually occurring within hours of exposure to very high dust concentrations, also referred to as acute febrile syndrome or grain fever. The risk of its development increases with concentration and duration of exposure. Symptoms include fever with generalized malaise, myalgias, dyspnea, nonproductive cough, chest tightness, and nausea.[55] Laboratory testing typically reveals leukocytosis with neutrophilia. Chest imaging, oxygen saturation, and pulmonary function test may be unremarkable.[56] Most cases of ODTS are mild, with symptoms usually resolving within 24 hours, but can persist for 2 to 5 days.[55] In contrast to HP, ODTS lacks prior sensitization to antigens driving its pathogenesis. Furthermore, the role of corticosteroid therapy remains uncertain in ODTS.[57]

Asthma

Adult exposure to organic dusts in industries such as farming, soft paper, and cotton are associated with an increased risk of developing asthma.[58] A comprehensive meta-analysis revealed that exposure to dust from paper/wood, flour/grain, and textiles can raise the risk of asthma by 48%,[59] but information regarding preexisting asthma was not included. Reducing exposure also decreases the frequency of asthma exacerbations.[60] The term "asthma-like syndrome" refers to acute, nonallergic airway responses commonly seen in agricultural settings, characterized by chest tightness, wheezing, and/or shortness of breath. This syndrome may also manifest as a cross-shift decline in FEV_1, often linked to acute neutrophilic airway inflammation. Unlike classic asthma, this syndrome can occur upon first exposure, suggesting an inflammatory rather than an allergic reaction.

Byssinosis

Byssinosis refers to a specific respiratory disease directly caused by cotton dust (textile industry). Breathlessness, cough, and chest tightness are more severe at the start of the work week but may evolve to include productive cough and exertional dyspnea with repeated exposures.[61] Tobacco smoking is an additional risk factor.[62] Ocular and nasal irritation may also be present.[63] Disease progression has been categorized into distinct stages. Initially, there is a stage of irritation (0–5 y), which often improves upon cessation of exposure. The next phase is temporary incapacity, usually occurring after 10 or more years. The final stage involves complete disability, characterized by chronic bronchitis and emphysema.[64] Diagnosis is based on the World Health Organization grading system and Schilling criteria[65,66] that includes symptoms and the weekday affected.[8] The severity of byssinosis correlates with a more rapid decline in pulmonary function.[65,66] Note, swine confinement workers also report worsening respiratory symptoms with weekday exposure and improvement when away from work,[67] and these symptoms are rarely related to allergy to porcine proteins.[68-70]

TABLE II. Characteristics and diagnostic features associated with various organic dust–associated respiratory diseases

Organic dust–associated disease	Clinical symptoms	Causative agents	Diagnostic procedures	Lung function testing	Imaging
Asthma	Respiratory	Livestock and crop dusts, wood dust, cotton dust, mold, pollens, bacteria, chemicals	Possible eosinophilia ± specific allergen sensitivity	Variable obstructive pattern Cross-shift ↓ in FEV_1 > 10%	Normal, bronchial wall thickening, air trapping
Asthma-like syndrome	Respiratory	Grain and farming dust, mold, bacteria, chemicals	Allergen skin testing is typically negative ±Airway neutrophils	Variable obstructive pattern Cross-shift ↓ FEV_1, < 10%	Normal, bronchial wall thickening, air trapping
Byssinosis	Respiratory	Cotton dust	Allergen skin testing is typically negative	Variable airflow limitation Across workday variability	Normal, bronchial wall thickening to opacities
ODTS	Respiratory and systemic	High concentrations of organic dust	Leukocytosis, specific IgE and IgG testing is typically negative	Normal with possible obstructive or restrictive pattern	Normal, ground-glass opacities possible
COPD, chronic bronchitis	Respiratory and systemic	Livestock and crop dust, wood dust, cotton dust, mold, bacteria, chemicals	±Skin testing, may be positive in ACO	Obstructive pattern with limited reversibility	Air-trapping, bronchiectasis, emphysema
HP	Respiratory and systemic	Mold, bacteria, avian proteins, vegetable and animal dust, chemicals	Specific IgG detection, ↑BALF $CD8^+$ T cells, airway neutrophils	Restrictive pattern, reduced DLCO	Mosaicism, ground-glass opacities, centrilobular nodules, reticulation, traction bronchiectasis
IPF	Respiratory and systemic	Vapors, gases, dust, fumes, metal dust, wood dust, silica dust	Allergy skin testing typically negative, UIP lung biopsy	Restrictive pattern (irreversible at late stage), reduced DLCO	Honeycombing, ground-glass opacities, traction bronchiectasis, reticulation

DLCO, Diffusing capacity of carbon monoxide; *UIP,* usual interstitial pneumonia.

COPD/chronic bronchitis

The prevalence of COPD/chronic bronchitis among nonsmokers varies between 2% and 4.2%[71] with a systematic review demonstrating associations between farming exposure (ie, cattle, swine, poultry, and crop farming) and airflow limitation or chronic bronchitis.[6] Livestock farmers were more likely to have chronic bronchitis (OR 1.9; 95% CI 1.4−2.6) and COPD (OR 1.4; 95% CI 1.1−1.7) than crop farmers.[5] Farmers with allergy have significantly lower FEV_1, and the effects of farming and specific agents on COPD were substantially greater in farmers with atopy.[5] Despite modernization efforts in the dairy industry that have reduced COPD prevalence,[72,73] traditional dairy farming remains a risk factor for COPD with additive smoking effects observed.[74] In poultry work, prevalence rates of COPD were higher in individuals with longer exposure regardless of smoking status.[75] In cotton work, particularly those workers exposed to both jute and hemp dust, the frequency of chronic bronchitis in retired workers who previously smoked was higher (20%) than currently smoking workers (17%).[76] Working in dense dust areas, active smoking, being older than 40 years of age, being an exsmoker, and working in the factory for a period exceeding 15 years were significantly associated with bronchitis and emphysema development.[76]

Asthma-COPD overlap

Asthma and COPD are prevalent respiratory conditions that can overlap in 15% to 20% of patients,[77] referred to as asthma-COPD overlap (ACO). Individuals with COPD displaying asthmatic characteristics, as well as asthma patients with a history of smoking who develop non–fully reversible airflow obstruction, fall into this ACO category.[78] Diagnosis of ACO in COPD patients typically reflects the presence of reversible airflow obstruction, type 2 inflammation with airway or peripheral blood eosinophilia, or a previous physician's diagnosis of asthma.[79]

The association of ACO with work-related asthma (WRA) or organic dust exposure is not well established. A U.S. Behavioral Risk Factor Surveillance Survey found that 51.9% of adults with WRA and 25.6% of those with non-WRA had also been diagnosed with COPD.[80] Those with concurrent WRA and COPD experienced more severe asthma exacerbations and outcomes than those with non-WRA and no COPD. In a study identifying ACO in an occupational asthma (OA) cohort of 304 subjects by Ojanguren et al[81] in Montreal 86% were diagnosed with OA alone and 14% with occupational ACO. The occupational ACO group was older, required higher doses of inhaled corticosteroids, had longer exposure to offending agents, was more frequently exposed to low molecular weight agents, and showed less atopy

TABLE III. Exposure reduction and environmental controls for management and prevention strategies of organic dust exposure–associated lung disease

Focus area	Description
Environmental risk assessment	Applicable to agriculture, textile, woodworking, and construction industries
	Avoidance of high dust and endotoxin exposure tasks. However, this may not be socioeconomically feasible[124]
Environmental monitoring	Regular air quality monitoring
	Use of air sampling devices to measure the concentration of organic dust particles
Environmental controls	Implementation of engineering controls
	Improving ventilation systems[125]
	Incorporating dust extraction and collection systems.
	Using mobile recirculating ventilation systems[126]
	Ensuring that machinery and equipment are well-maintained
Work practice controls	Modification of task execution to reduce dust exposure
	Wetting down surfaces to prevent dust from becoming airborne
	Using tools and machinery that produce less dust
	Ensuring proper cleaning and maintenance procedures
	Adopting newer, cleaner technologies[127]
PPE: education and training	Incorporation of PPE: masks, respirators, and protective clothing.
	Proper training and education are required
	Workers should be educated on
	Risks of organic dust exposure
	Recognizing hazardous conditions
	Proper use of control measures and PPE
	Regular training sessions can reinforce this knowledge and keep workers informed about new practices or equipment
Policy and regulation compliance	Compliance with local and international health and safety regulations
	Adherence to occupational exposure limits for different types of dust
	Implementation of recommended safety practices
Worker health surveillance and education	Baseline/prework health examinations
	Regular health examinations, including lung function tests, chest x-rays, and allergy testing
	Education on trigger avoidance and proper medication use
	Support groups and counseling can also be beneficial
	Smoking cessation because smoking represents an additive effect
	Medical plan with rescue inhalers, bracelets as necessary

PPE, Personal protective equipment.

compared to the OA group.[81] In Finland, a study highlighted the significant association between the risk of ACO and the presence of mold odor in the workplace.[82] A Finnish study demonstrated that asthma patients exposed to vapors, gases, dust, or fumes in their occupation were more likely to develop ACO than those without such exposures.[83]

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a complex syndrome caused by a non–IgE-mediated allergic reaction to organic particles or low molecular weight agents involving type III (immune complex–mediated) and type IV (delayed-type hypersensitivity) reactions.[84] Symptoms can vary widely depending on the duration and intensity of exposure and typically include cough, fever, chills, dyspnea, and fatigue. These symptoms can appear acutely, often 4 to 8 hours after exposure, or develop insidiously, particularly if the exposure to the antigen persists. Lung inflammation is characterized by lymphocytic and frequently granulomatous features that can result in lung fibrosis.[84] The occupational causes of HP, been recently described in a systematic review,[85] includes farmers (farmer lung) and bird breeders or pet bird owners (bird fancier lung) as well as woodworkers, cheese manufacturers, and textile workers. Diagnosing HP involves a combination of clinical evaluation, lung imaging, lung function tests, and sometimes lung biopsies.[86] The primary treatment for HP is avoidance of the offending antigen. Corticosteroids are often used. In advanced fibrotic stages, management is more complex, requiring additional intervention including possible lung transplantation.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause, primarily occurring in older adults. It is defined by the presence of radiological and/or histological usual interstitial pneumonia and has a poor prognosis with a median survival of 2.5 to 4 years.[87] Although organic dust exposures have been proposed in the development and/or exacerbation of IPF, their direct link to IPF remains unclear.[88] An international collaborative review

TABLE IV. Key areas of future research and development to advance knowledge and care of individuals with organic dust–associated respiratory disease

Focus area	Comment
Mechanism of disease	• In-depth understanding of the cellular and molecular pathways involved to aid in developing targeted therapies and interventions • Research into understanding resolution and recovery following organic dust exposure to develop novel targeted approaches • Further evaluation of the role of organic dust in the pathogenesis of IPF because little is known. Understanding and differentiating IPF from other forms of ILD that are directly caused by organic dust exposure, such as HP, which can present with fibrosis but has a distinct pathogenesis and clinical course from IPF
Long-term health effects	• Longitudinal studies to track the long-term health impacts of organic dust exposure • Understanding the progression of diseases over time and identifying any late-onset effects
Genetic and environmental interactions	• Understanding how genetic predisposition interacts with environmental exposure to organic dust • Deciphering why some individuals are more susceptible than others to developing airway diseases
Improved diagnostic tools	• Developing more sensitive and specific diagnostic tools for early detection of airway diseases related to organic dust • Tools needed range from biomarkers, imaging techniques, and lung function tests
Better exposure assessment methods	• Advancing methods for assessing and quantifying organic dust exposure in different environments • Improving the understanding of dose-response relationships and knowledge of accurate exposure limits
Preventive strategies and interventions	• Developing more effective preventive strategies and interventions, including improved personal protective equipment, workplace modifications, and educational programs
Treatment modalities	• Exploring new treatment options, including pharmacological and nonpharmacological therapies • Assessing the efficacy of existing treatments in managing symptoms and slowing disease progression
Impact of climate change	• Understanding how climate change might influence the generation and distribution of organic dust and the subsequent impact on airway disease
Public health policies	• Developing and evaluating public health policies and guidelines to protect workers in high-risk industries • Assessing the economic impact of such diseases on individuals and health care systems
Global perspectives	• Considering the global diversity in types of organic dust and varying workplace standards • Developing a global consensus and applicable guidelines through international collaborative research

ILD, Interstitial lung disease.

and meta-analysis assigned an attributable fraction for occupational exposures to the burden of IPF of 26%, calculated from 11 studies.[89] In this study, several exposure categories (vapors/gases/dust/fumes, metal dust, wood dust, silica dust) but not agricultural dust were significantly associated with IPF.[89] However, a U.S. multicenter, case-control study identified several occupations that were associated with IPF, including farming, livestock raising, hairdressing, raising birds, stone cutting/polishing, and jobs with exposure to metal dust and vegetable/animal dust.[90] Awadalla et al,[91] in a multicenter, case-control study in Egypt, demonstrated that the risk of IPF was higher in women working in farming, raising birds, and with occupational exposures to animal feeds, dust, and pesticides. Moreover, a case-control study in Italy found that farmers, veterinarians, and gardeners had a particularly high risk of developing IPF, and the risk increased with increased lengths of exposure.[92]

The issue of incorrectly diagnosing chronic HP as IPF has been raised. A 2013 study revealed that, out of 46 patients initially diagnosed with IPF following established guidelines, 20 were later found to have HP.[93] Many of these cases were associated with bird-related antigens, particularly from feather bedding.[93] De Sadeleer et al[94] studied 244 patients with IPF to demonstrate that IPF patients with a history of exposure to mold or birds had improved survival rates compared with those without such exposure, although survival was less than that of HP.

DIAGNOSTIC STRATEGIES

Presentation

Organic dust exposure generally triggers symptoms of cough, chest tightness, wheezing, mucus production, and shortness of breath, even in healthy individuals. In asthma and COPD, exposure can further exacerbate symptoms, reduce lung function, and increase in AHR.[95] Flulike symptoms can be found in ODTS and HP, and progression to irreversible pulmonary fibrosis, restriction, and diminished diffusing capacity of the lungs for carbon monoxide can be seen in HP and IPF.[84,87] Clinical, functional, and radiological characteristics of organic dust–associated respiratory disease are summarized in Table II.[96]

Testing

Lung function. Lung function testing is recommended in exposed, at-risk persons because spirometry is particularly valuable for workers with preexisting obstructive diseases or smokers[49,97] to monitor lung function over time and establish a dose-response effect.[98,99] For example, swine-confinement workers often exhibit an accelerated loss of lung function, evidenced by a decrease in FEV_1 during a work shift.[100,101] Changes in lung function (FEV_1) across a work week, particularly in textile workers, aid in predicting disease.[102] A restrictive ventilatory defect may also be observed in HP or IPF, as well as impaired gas exchange (reduced diffusing capacity of the lungs for carbon monoxide) and/or hypoxemia during exercise.[86]

Measuring fractional exhaled nitric oxide (FeNO) may also be warranted. Exhaled nitric oxide increased from baseline value of 7.5 (range 5.7−13.7) to 13.4 (range10.5−17.5) parts per billion after swine facility exposure.[103] In addition, the rise in FeNO post−work shift, along with diminished pulmonary function, established across-shift FeNO as an effective, noninvasive method to assess airway inflammation in textile workers.[104] Serial FeNO measurements at home versus work settings can further validate a dose-response relationship.[105]

Laboratory tests. The detection of serum-specific IgE and IgG antibodies of organic dust components can be beneficial to establishing causation. For example, patients with grain dust−induced symptoms may be sensitized to dust mites or cereal flour proteins (ie, wheat, rye, and barley).[106] However, the presence of specific IgE antibodies may not be indicative of symptomatic exposure, as in individuals exposed to corn dust, in whom specific IgE, IgG, and IgG4 antibodies were identified in both symptomatic and asymptomatic subjects.[107] Conversely, a cohort study of workers with asthma-like symptoms following grain dust exposure, confirmed through inhalation challenges, lacked evidence for specific serum antibodies.[108]

The identification of antigen-specific IgG antibodies is a key diagnostic criterion for HP (Table I). Elevated antibody titers following exposure, or a decrease in levels after avoiding exposure, can further support this diagnosis. However, the absence of these antibodies does not rule out the disease, and their presence alone is not definitive because they may merely indicate exposure in asymptomatic individuals.[84] In a study involving asymptomatic swine-confinement workers, the presence of IgG antibodies to specific porcine proteins was noted, whereas IgE-mediated reactions to these proteins were rare.[70]

Skin testing. Allergy skin prick testing may also be useful. Over 15% of grain handlers exhibiting airway symptoms demonstrated sensitization by skin testing to storage mites (*Lepidoglyphus destructor* and *Acarus siro*) and molds (*Candida*).[109] In addition, skin test sensitization to wheat and rye has been linked to a decrease in lung function during a work shift in grain workers.[98] However, the relationship between asthmatic response and symptoms with positive grain dust−extract skin testing remains unclear.[108,109] An improvement of quality and standardization of these complex allergen extracts may potentially increase diagnostic accuracy.[106]

Bronchoalveolar lavage. Bronchoscopy with bronchoalveolar lavage fluid (BALF) analyses represents an additional tool to characterize the pattern of airway inflammation. The BALF from workers recently exposed to swine environments demonstrated increased levels of neutrophils, lymphocytes, and macrophages compared with those exposed for longer durations.[110,111] Moreover, higher BALF concentrations of IL-1β, IL-6, IL-8/CXCL8, and TNF-α were demonstrated in exposed versus nonexposed individuals.[112] Notably, swine workers with at least 1.6 years of exposure demonstrated increased levels of IL-6, whereas TNF-α was not detected following acute exposure.[113] In chronic stages of exposure, BALF may reveal an increased concentration of total cells, neutrophils, albumin, fibronectin, and hyaluronan[100] and striking increases in BALF cell mRNA for IL-17A.[114]

In HP, the BALF cellular profile is typically characterized by marked lymphocytosis (>50%) and a predominance of $CD8^+$ T cells (also reflected in a low $CD4^+/CD8^+$ ratio).[84] This pattern is common in the acute and subacute stages of the disease. Following intense exposure or during resolution stages, a significant increase in neutrophils may also be observed.

The BALF can be used to distinguish between exposed workers who develop HP or alveolitis and those who remain asymptomatic. This distinction is based on a low $CD4^+/CD8^+$ ratio for HP and elevated levels of hyaluronan for alveolitis.[84,111] Despite these indicators, limited data have been demonstrated for significant differences in cell counts within BALF between farmers exhibiting respiratory symptoms and those without symptoms.[115] This highlights a need for further research to validate the efficacy of BALF in differentiating symptomatic from asymptomatic exposed workers because most studies compare exposed workers (including symptomatic and asymptomatic workers) with unexposed controls.[100,111]

Inhalation challenges. Inhalation challenges have confirmed the capacity of organic dust to induce respiratory symptoms and enabled analysis of lung function and inflammation profiles.[116,117] Inhalation tests using extracts from durum wheat and corn dust have proven particularly useful in demonstrating AHR in grain handlers.[118] These challenges have also been useful in assessing the impact of endotoxins and dust mites in triggering airway inflammation in sensitized patients, although the results have been mixed.[108,109,119] In cases of suspected HP, inhalation challenges are recommended to help identify the specific causative agent. The effectiveness, applications, and safety of allergen challenge tests in respiratory disorders have been recently reevaluated.[120] These tests are predominantly viewed as tools for research purposes. In the United States, inhalation challenges to identify the cause of HP are generally not performed, primarily owing to regulatory constraints.

Imaging

Chest imaging, notably high-resolution computed tomography, can assess the disease activity and aid in diagnosis (Table I).[96] Chest radiograph findings are often nonspecific, including patterns like ground-glass or interstitial opacities, consolidations, or micronodules, but may appear normal in many patients.[84] High-resolution computed tomography is recommended for symptomatic individuals with abnormal lung function tests, and it is valuable in determining the necessity and location for lung biopsy.[121] In the active or early stages of disease, transient pulmonary infiltrates, isolated diffuse ground-glass opacities, mosaicism, and centrilobular nodules may be observed.[122] Bronchial wall thickening and air trapping can be identified in obstructive diseases like asthma and COPD/chronic bronchitis.[123] In HP, mosaicism and diffuse ground-glass centrilobular nodules may indicate small airway involvement. During the fibrotic stages of HP and IPF, features such as reticulation, traction bronchiectasis, and architectural distortion are observed, signaling irreversible disease.[122]

MANAGEMENT AND PREVENTION

The management of airway diseases caused by organic dust involves both supportive care and standard medical interventions. The primary focus is on reducing exposure to the

offending dust, managing symptoms, and preventing disease progression (Table III).[124-127] Industries that have adopted newer-built buildings with modern and presumed cleaner technologies have shown better respiratory health outcomes than older counterparts.[127] Although personal protective equipment such as respirators are recommended and can reduce airway inflammatory consequences in swine barn workers,[128] The personal protective equipment has not been shown to reduce swine barn air—induced AHR.[128] Moreover, lung function decline occurs in cotton textile mill workers despite use of a face mask.[61]

Pharmacological treatment

Pharmacological treatment can be dependent upon the severity and type of airway disease. Available therapies include bronchodilators, corticosteroids, and antihistamines; however, there is no evidence that the use of inhaled bronchodilators alleviates symptoms or slows disease progression.[96] Biologics, including the anti-IgE monoclonal antibody omalizumab, have been successfully used in cases of severe occupational asthma caused by cereal allergens[129-131] and low molecular weight agents.[132] Given that workers exposed to organic dust typically exhibit a neutrophilic asthma phenotype/endotype (as opposed to an eosinophilic phenotype), there may be theoretical benefit with treatments effective in type-2-low asthma, such as tezepelumab.[133] However, this therapy has not been specifically explored in symptomatic workers.

In severe HP or IPF, immunosuppressant agents including azathioprine and mycophenolate mofetil may be used. Antifibrotic agents pirfenidone and nintedanib have also been utilized to slow the progression of IPF and lung function decline.[134]

Pulmonary rehabilitation

Pulmonary rehabilitation may be necessary for those with significant respiratory impairment. This includes exercises to strengthen the respiratory muscles, improve lung function, and help with breath control.

FUTURE DIRECTIONS

The future research directions in the field of airway diseases associated with organic dust exposure are broad and multifaceted (Table IV). Advancements are necessary to improve the prevention, early detection, and effective management of airway diseases associated with organic dust exposure, ultimately leading to improved health outcomes for affected individuals.

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