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The Emerging Spectrum of Respiratory Diseases in the US Cannabis Industry

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Abstract

While the cannabis industry is one of the fastest growing job markets in the United States and globally, relatively little is known about the occupational hazards that cannabis production workers face. Based on the closely related hemp industry and preliminary studies from recreational cannabis grow facilities, there is concern for significant respiratory exposures to bioaerosols containing microbial and plant allergens, chemicals such as pesticides, volatile organic compounds and other irritant gases. Components of the cannabis plant have also recently been identified as allergenic and capable of inducing an IgE-mediated response. Accumulating evidence indicates a spectrum of work-related respiratory diseases, particularly asthma and other allergic diseases. Disentangling causal relationships is difficult given the heterogeneity of mixed exposures, diagnostic challenges and confounding by personal cannabis use. Despite and because of these uncertainties, better regulatory guidance and exposure controls need to be defined in order to reduce the risk of work-related disease.

Keywords

cannabis; allergens; occupational lung disease; occupational exposure

Introduction

Over the past decade, the cannabis industry has become one of the fastest growing job markets in the United States. Much of this rapid expansion is attributable to the increased legalization and decriminalization of delta-9-tetrahydrocannabinol (9-THC) containing cannabis, also known as marijuana, for recreational and medicinal use. In 2021, the cannabis job market grew by more than 30% and currently there are approximately 420,000 employees in the United States involved in cannabis cultivation or the manufacture and sale

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of related products.[1,2] Globally, the legal cannabis market is valued at over $20 billion with anticipated high rates of growth.[3]

Due to cannabis' historic status as an illegal drug, relatively little is known about the occupational hazards and associated diseases in the cannabis industry. As of February 2022, 37 states, 3 territories and the District of Columbia permit either medical or recreational use of cannabis.[4] However, because cannabis is still classified as a controlled substance by the US federal government, there are significant challenges to research with few studies in occupationally-exposed cohorts. Additionally, characterizing exposures can be difficult given the wide variation in cannabis-related operations, including the persistence of many illegal grow facilities.

Much of what we do know about occupational health effects within the cannabis industry is inferred from other agricultural processes, specifically in the closely related hemp industry. This literature and expert opinion from state and federal public health agencies, indicates potential exposure to multiple airborne hazards, including bioaerosols containing microbial and plant allergens, chemicals such as pesticides, volatile organic compounds and other irritant gases.[5–7] Emerging evidence also demonstrates a spectrum of work-related respiratory illnesses affecting employees with cannabis exposure in forensic laboratories, law enforcement officials and some recreational cannabis grow facilities.

In this review, we provide an overview of the cannabis industry, identify potential inhalational exposures and examine the evidence for associated respiratory diseases. While this information is geared towards the practicing clinician, it provides insights into potential health effects in medicinal and recreational users of cannabis and has important implications for the protection of workers within this emerging industry.

Historical Perspective on Respiratory Disease in the Hemp Industry

In addition to producing THC, the psychoactive component of cannabis, the plant -- *Cannabis sativa* – has been cultivated for centuries as a source of food and the fiber-based material called hemp. In the United States, the term hemp refers to *C. sativa* that contains less than 0.3% THC, whereas "cannabis" or marijuana typically refers to strains of cannabis that contain greater than 0.3% THC. As an important contributor to the textile and rope industries, *C. sativa* was a major commodity crop in the United States from the mid-18th to early 20th centuries and widely grown throughout Kentucky, Missouri and Illinois. The crop was either harvested by hand or with traditional hay-making equipment, dried in the fields to help separate the fibers within the stem, and then processed in hemp mills.[8]

Pulmonary disease in hemp workers was first described by the Italian physician, Bernardino Ramazzini, in the 1700s.[9] Many workers presented with a systemic asthma-like syndrome, characterized by fever, malaise, chest tightness and dyspnea at the start of the work week with slow improvement on consecutive days of exposure throughout the week. Symptoms would flare on re-exposure after holidays, weekends and other prolonged periods away from work. This syndrome was initially called cannabosis and later categorized under the umbrella term of byssinosis with other textile-fiber related diseases, including those in

cotton, jute and flax workers.[10] Several studies in the late 20th century documented a high prevalence of respiratory disease among industrial hemp workers, with upwards of 40– 60% of workers exhibiting symptoms of byssinosis.[10–13]

Byssinosis is a dust-induced disease of airway inflammation and bronchial hyper-reactivity, distinguished by severe airflow obstruction on the first working day that improves with repeated exposures. Large reductions in pre- to post- shift FEV_1 have been documented in multiple studies of workers with byssinosis in the textile industry. Over time, disease can progress to permanent respiratory impairment, chronic bronchitis and emphysema.[14] Although byssinosis has been described after short-term exposures, most workers develop disease after a long latency period of more than 10 years of exposure.[15] While the exact pathophysiology is unknown, byssinosis is thought to be non-immunologically mediated and no specific IgE antibodies have been identified. The concentration of endotoxin in organic dust correlates strongly with disease onset and severity, and is hypothesized to play a major role in pathogenesis.[16,17]

Overview of Cannabis Production for Recreational and Medicinal Use

The modern cannabis industry has close parallels with historic hemp production, but differences in work processes and exposures may affect the frequency, severity and spectrum of associated respiratory diseases (Figure 1). Instead of maximizing production of the stem or seed, cultivars of *C. sativa* and the subspecies, *C. indica*, that are bred for medicinal or recreational use, maximize production of the trichromes, or resinous glands found on the flowering bud. These glands produce psychoactive cannabinoids, including THC and cannabidiol (CBD), as well as terpenes, flavonoids and other phenolic compounds which give cannabis a distinctive flavor and aromatic profile. The dried and cured cannabis inflorescence, consisting of the complete flower head of the plant, can be sold for consumption by smoking in bulk, finely divided and rolled, or further processed into tinctures, concentrates and other products.

C. sativa is an adaptable plant that can be grown in a variety of ecological conditions, including indoor and outdoor environments. While industrial hemp is almost always grown outdoors, cannabis cultivars with higher THC contents may be grown outdoors, in greenhouses or in modified warehouse spaces. Indoor grow facilities can increase crop yield by facilitating year-long production with tightly regulated light, temperature, humidity, carbon dioxide level, air circulation and pest control.[18] Female plants are typically propagated through cuttings, which allows for consistent quality and quantity of cannabinoids. This also reduces contamination of different strains through cross-pollination and has the added benefit of producing unfertilized, seedless buds which are generally preferred by consumers.[19]

In contrast to many other modernized agricultural processes, cannabis cultivation involves a number of tasks which require direct plant handling throughout the growth cycle. This includes tasks such as trimming, destemming, harvesting, drying and processing dried plant material. Flower buds are sifted through screens of different sizes to help separate out the undesirable stems from the rest of the biomass, a process which can aerosolize cannabis

particles.[20] Many legal grow operations are also coupled with a facility for manufacturing cannabis products, including extracting cannabinoids from plants, testing and packaging recreational or medicinal products. Job roles within the cannabis industry are still evolving and, particularly in smaller production facilities, there is often substantial overlap in tasks among employees.

While worker demographics are incompletely understood, several small studies in legal cannabis grow facilities in Colorado, California and Washington suggest that employees are generally young, and the majority are non-Hispanic White and have some college education.[21,22] These studies also report high rates of personal cannabis use among employees, with upwards of 90% of workers using cannabis products multiple times per day. It's important to note that these worker characteristics may not be generalizable across the cannabis industry, particularly in illegal grow operations. In addition to employees directly involved in cannabis cultivation, a number of other occupations are at risk of regular cannabis exposure, including forensic laboratory workers, law enforcement officers, firefighters, emergency medical technicians and first responders.

Inhalational Exposures Associated with Cannabis Production

Workers involved in cannabis production are exposed to multiple potential bioaerosols, irritant gases, chemicals and other respiratory hazards (Table 1). While many of these are similar to exposures in other agricultural processes, some are specific to the cannabis industry. Cannabis itself is increasingly recognized as an allergen with several identified high molecular weight antigens that are capable of inducing specific IgE- antibodies.[23] Disentangling the causative exposures in relationship to respiratory disease is often difficult, particularly since many of these exposures occur simultaneously and cannabis workers have high rates of recreational cannabis use that may contribute to symptoms.

Bioaerosols

Chronic inhalation of organic dust is a well-established cause of respiratory diseases in other agricultural workers, including byssinosis in hemp workers.[24] While composition varies by industry and geography, organic dust is enriched in respirable particulate matter (PM) with high microbial content, including endotoxins, peptidoglycans, beta glucan, bacterial wall components and fungi. These are thought to contribute to disease development through both allergen specific pathways and non-IgE dependent innate immune responses to pathogen- or microbial-associated molecular patterns.[25]

Quantification of exposure is typically described in terms of concentration of total inhalable dust. Specific regulatory requirements exist for different types of dust, but many agricultural processes – including cannabis production – fall under the nonspecific dust permissible exposure limit for particulates not otherwise regulated (PNOR) of 15mg/m^3.[26] Studies of PM concentrations during hemp manufacturing noted high personal exposure levels ranging from 10.4 to 79.8 mg/m^3.[27] In contrast, the few studies that measured organic dust in medicinal and recreational cannabis facilities have reported lower exposures on the order of 0.01 to 20.5 mg/m^3.[28,29] While these concentrations mostly fell below regulatory limits, they varied significantly according to task, with highest levels observed during grinding and

sifting of dried plant product. As yet, there are no published reports of airborne levels of specific cannabis allergens associated with different production tasks.

The sequential watering requirements of *C. sativa* promote fungal growth, and *Golovinomyces cichoracearum* (powdery mildew) and *Botrytis cinerea* (grey mold) are commonly encountered cannabis pathogens. Prior studies to determine fungal diversity in cannabis grow facilities have identified over 200 fungal species, including species of Penicillium, Aspergillus, Fusarium and Trichoderma – all of which are associated with respiratory disease in agricultural workers.[28,30,31] Fungal growth may be particularly problematic in indoor grow facilities where ventilation is suppressed to limit environmental release of cannabis odors, either to be in compliance with local regulations or, in the setting of illegal grow facilities, to help avoid detection. One study of law enforcement officers removing plants from an illegal grow operation measured fungal spore concentrations over 500,000 spores/m^3 – exposure levels that are equivalent to those associated with mold remediation processes.[18]

In addition to fungal contamination, a wide range of bacterial pathogens have been identified in cannabis cultivation facilities. The National Institute for Occupational Safety and Health (NIOSH) conducted bacterial sequencing of personal and area air samples at one outdoor cannabis farm, revealing a diverse bacterial population with ~ 640 operational taxonomic units. Most of the species were clustered around the phylum of gram-positive bacteria, Actinobacteria, that has been implicated in work-related respiratory symptoms in potato processers. A number of endotoxin-producing gram-negative organisms were also identified, although endotoxin concentrations were all below the recommended Dutch regulatory exposure limit.[28]

Chemicals

To combat contamination of products by micro-organisms and other pests, pesticides are commonly used during cannabis cultivation (Table 2).[32] In areas where cannabis use is legal, regulatory bodies typically limit the specific pesticides that may be used on cannabis, and may also require third-party testing of products to ensure that levels are safe for consumers.[33–35] Since cannabis remains illegal on a federal level in the United States, this falls under the purview of the states, leading to variable regulation across the country with no federal oversight. Furthermore, while these regulations may limit the quantity and kinds of pesticides used in legal grow operations, they have little impact on illicit growers where fungicides and pesticides may be applied in excess.

Workers may be exposed to a variety of insecticides and herbicides during application or handling contaminated products.[36] In addition to workers, intervention staff who are responsible for dismantling illegal grows and chronic cannabis users are at risk of exposure. A study of an illicit indoor grow operation in Belgium showed that approximately 65% of the plants and air filters sampled contained pesticides, including some highly toxic organophosphates and carbamates.[37] A recent survey of cannabis workers in legal grow operations in Colorado demonstrated that 35% of workers reported a range of adverse health complaints, including mucocutaneous or respiratory symptoms, after handling pesticides.[22]

Other potential chemical exposures include fertilizers, disinfectants and other cleaning products that are known respiratory irritants.

Volatile Organic Compounds and Other Irritant Gases

The odors emitted from cannabis facilities are caused by terpenes and other volatile organic compounds (VOCs) directly produced by the plant. The intensity and composition of the emission profile is influenced by numerous factors, including indoor air quality management, growing conditions, plant strain and life stage. More than 150 individual terpenes have been identified in cannabis, with the key contributors to the distinctive odor including myrcene (earthy), limonene (citrusy), terpinolene (woody) and pinene (grassy).[38] Reported airborne terpene concentrations in cannabis cultivation facilities range widely, from a low of ~ 20ppb to a high of ~3500ppb.[39,40] While these measurements exceed the European Commission recommendations for overall indoor terpene concentrations (40–400ppb), individual terpene components are generally below regulatory standards.[41]

While terpenes themselves are considered to be relatively safe, they are highly reactive with oxidant species, such as hydroxyl radicals, ozone and oxides of nitrogen. The heterogeneous products formed through these reactions include formaldehyde and ultrafine particles, which can act as upper and lower respiratory tract irritants and, in some cases, such as formaldehyde, as sensitizers. In addition to being an occupational hazard to cannabis employees, VOC emissions can also affect regional air quality by contributing to odors and ground level pollution. People living in communities near cannabis cultivation facilities have reported nausea and eye irritation due to the strong smells, although it is unclear whether these symptoms are related to physiologic versus psychologic effects.[41]

VOCs are also formed as byproducts of decarboxylation, a process in which plant material is heated in ovens to transform cannabinoids into activated 9-THC. In particular, 2,3 pentanedione and diacetyl – VOCs that have been shown to cause epithelial damage in laboratory studies and are linked to bronchiolitis obliterans in flavoring workers - have been detected in air samples near decarboxylation ovens.[42]

Many facilities allow employees to use cannabis products recreationally during work hours, which can result in exposure to secondhand smoke and aerosolized cannabinoids. While there are few measurements of airborne cannabinoid concentrations, studies of surface wipe samples demonstrate detectable levels of multiple cannabinoids throughout grow facilities and are highest near the decarboxylation ovens.[43] Skin contact with cannabinoids may contribute to dermal reactions among employees.[44]

Indoor grow facilities may also have increased concentrations of carbon dioxide (CO_2), carbon monoxide, ozone and other irritant gases. Ventilation is carefully controlled to foster plant growth through CO_2 enrichment, contain or neutralize odors, and prevent microbial contamination. CO_2 levels are typically below indoor air quality recommendations of 2000ppm, but during fumigation maneuvers, they may exceed concentrations of 40,000 ppm that are hazardous to life.[6]

Allergens in Cannabis

The allergenic potential of cannabis has been discussed in several recent reviews, including an international consensus overview.[23,45–47] Cannabis allergy may be caused by inhalation, ingestion or cutaneous exposures to plant material and was initially described in recreational users. Although a delayed, type IV allergenic response has been described, the type I allergy is more common with an immediate hypersensitivity reaction within 20–30 minutes of exposure.[45] Manifestations range from mild rhinitis and conjunctivitis to severe, generalized symptoms with angioedema or anaphylaxis. These symptoms may overlap and be mistaken with cannabis intoxication, including conjunctival injection, orthostatic hypotension and anxiety.[23]

Several high molecular weight compounds that are capable of inducing specific IgE antibodies have been identified in the pollen, oil, roots, buds and leaves of the plant. The four cannabis allergens that have been accepted by the WHO/IUIS Allergen Nomenclature Subcommittee (Table 1) include profilin (Can s 2), non-specific lipid transfer protein (nsLTP, Can s 3), the oxygen-evolving enhancer protein 2 (OEEP2, Can s 4) and pathogenesis related protein 10 homologue (Can s 5).[48] Sensitization to nsLTP is associated with cross-reactivity to a large variety of fruits, vegetables, cereals, wine and beer. Interestingly, these allergens appear to have geographic distribution, with sensitization to nsLPT most commonly found in European individuals.[45] Other potential allergenic proteins that have been sequenced include ribulose-1,5-bisphospate carboxylase/oxygenase (RuBisCO) and thaumatin-like protein (TLP). THC and other low molecular weight cannabinoids initially were suspected as the cause of cannabis allergy, and while this has not been demonstrated, more recent evidence suggests that some may act as immunomodulators.[49]

No standardized extracts to test for cannabis allergy are commercially available at this time, although several diagnostic tests have been developed for research purposes. Most clinical testing relies on unstandardized skin prick tests to the bud, leaves, or seed of the cannabis plant. Additional work is needed to identify pertinent allergens, develop standardized extracts, and characterize sensitivity and specificity of diagnostics.[46]

Respiratory Health Effects Associated with Cannabis Production

There have been few studies reporting respiratory health effects in workers in the modern cannabis industry. Most of the evidence to date is derived from case reports, small case series and a few cross-sectional studies. This emerging data raises concern for a significant burden of work-related respiratory symptoms and disease (Table 3). Specifically, there is evidence for an increased incidence of asthma and other allergic diseases, although the precipitating exposures and the underlying pathophysiologic mechanisms are as yet undefined.

Upper and lower respiratory tract symptoms

Multiple case reports have been published demonstrating that occupational exposure to cannabis can be associated with increased upper and lower respiratory tract symptoms, including sinus congestion, chest tightness, wheeze, cough and shortness of breath.[50–53]

In contrast to the respiratory symptoms associated with byssinosis, these seem to develop with a shorter latency period, manifest soon after exposure and do not diminish through the work week. Cutaneous symptoms have also been described, with affected workers reporting dermal irritation, pruritis, contact dermatitis, urticaria and even angioedema.[50,54–57]

While published case reports have primarily focused on occupations with infrequent cannabis exposure such as law enforcement officers and forensic technicians, the growth in legal cannabis production facilities should lead to further understanding of risks among workers with more frequent and sustained exposures. Preliminary observational studies suggest a high burden of symptoms among occupationally-exposed cohorts. A study of 81 Belgian police officers found that 42% reported respiratory and/ or cutaneous symptoms with occupational cannabis exposure.[58] Similarly, 73% (16/42) of employees at 2 indoor cannabis grow facilities in Washington State and 45% (4/9) of employees in an indoor cannabis grow facility in Minnesota reported work-associated respiratory symptoms.[21,42]

Work-related asthma

Work-related symptoms have largely been attributed to asthma, rhinosinusitis and other allergic disease. Occupational exposure to cannabis has been implicated both as a trigger for worsening asthma (work-exacerbated asthma) and as a cause of new onset asthma (occupational asthma). The relative importance of allergic versus irritant exposures and underlying disease pathophysiology are still uncertain. Further phenotyping of irritant-induced versus sensitizer-induced occupational asthma is critical in determining appropriate workplace accommodations and treatment.

Published case reports of cannabis-associated asthma include a bird breeder with occupational exposure to *C. sativa* seed and a series of ten cases published from the Washington Worker Compensation Claim Database from 2002 to 2019, four of which were classified as new onset occupational asthma.[54,59] A recent fatality in a cannabis cultivation worker who was exposed to ground cannabis dust while preparing pre-filled joints was attributed to occupational asthma per an OSHA investigation.[60]

The prevalence of asthma among cannabis employees is still uncertain. While only one of eight employees in a Minnesota indoor cannabis facility had abnormal spirometry, approximately 1/3 of the 21 employees tested in two Washington indoor cannabis facilities exhibited obstructive spirometry and/ or an elevated fractional exhaled nitric oxide (FeNO).[21,42] A follow up study of cross-shift and cross-week spirometry in ten employees with work-related symptoms in the Washington grow facility demonstrated that FeNO increased from Monday to Friday – suggesting worsening airway inflammation with repeated exposure through the work week.[21] Even though these results are only based on a small number of workers and may not be generalizable to the entire cannabis workforce, they raise concern for a high rate of work-related asthma.

Occupational cannabis allergy

Most published studies have focused on cannabis sensitization induced by direct handling or inhalation of plant material as the cause of health symptoms, although objective diagnosis of cannabis allergy has been variable. For instance, 33% of the 21 employees tested in the

Washington State indoor grow facilities exhibited a positive skin prick test to a slurry of cannabis dust collected from their workplace, while none of the 81 Belgian police force study participants tested positive to a basophil activation test with rCan 3 or a crude cannabis extract.

It is unclear whether the dramatically different findings in these studies are due to differences in the specific method of making the diagnosis of cannabis allergy, patterns of allergic reactivity or underlying precipitating causes. Skin prick testing using a crude slurry of plant material is less specific than testing for sensitization to isolated proteins, and study participants may have been responding to mold or other contaminants in the plant slurry. Alternatively, as some experts have hypothesized, the difference in allergic reactivity could be attributable to different routes of cannabis exposure: almost all of the indoor grow facility workers personally used cannabis recreationally, while none of the police officers did. This raises the possibility that cannabis sensitization is induced through inhalation, ingestion or topical application of cannabis products rather than the direct handling of plant material during occupational exposures.

In the Washington State study, many cannabis employees reported smoking as their main form of cannabis use, which results in combustion of allergenic plant proteins and inhalation of respiratory irritants or adjuvants as well as sensitizers. When the study authors compared the rate of cannabis sensitization in the indoor grow facility employees with a group of recreational cannabis users and non-users from the same community, they found that occupational exposure was associated with an 8-fold higher risk of sensitization (data unpublished). Ultimately, these results are based on small numbers of participants, and additional work is needed to characterize the role of exposure in mediating work-related allergic disease.

Spectrum of Respiratory Diseases Associated with Cannabis Production

The full spectrum of work-related respiratory disease in cannabis workers is likely to extend beyond asthma and allergic rhinitis, to other airway and parenchymal lung diseases (Table 2). As recreational use of cannabis has only recently become legalized, the impact of prolonged occupational exposure is unknown and may contribute to accelerated lung function decline, chronic bronchitis and COPD. Reports from cannabis cultivation facilities of exposure to diacetyl, the presumed etiologic agent of bronchiolitis obliterans in popcorn and flavor workers, raises concern for possible small airway involvement.[6] Fungal contamination of cannabis has been linked to the onset of invasive infections, allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis in recreational users.[61–63] While none of these disease entities have been described with occupational cannabis exposure, the widespread presence of fungal pathogens – particularly in indoor grow facilities – could be a cause of disease in susceptible workers. Clinicians should become familiar with occupational exposures and potential associated diseases in cannabis employees, in order to recognize the link with work.

Clinical Evaluation and Approach to Diagnosis

Much of what is known about the clinical presentation of respiratory diseases in cannabis workers comes from anecdotal reports and requires further characterization. Many work-related respiratory diseases begin with symptoms that worsen at work and improve away from work, but may progress to persistent respiratory complaints as disease advances. Thus, clinicians need to maintain a high index of suspicion to correctly recognize and diagnose exposure-related disease.

The evaluation of cannabis workers with respiratory symptoms should follow the general approach to occupational lung diseases, beginning with a comprehensive exposure and clinical history. The occupational history should include a detailed description of the patient's job duties, work site, any personal protective equipment worn, and the nature of cannabis exposure and other potential workplace hazards such as pesticide use. Review of safety data sheets (SDS) for chemicals used in the workplace helps supplement exposure assessment. Specific attention should be given to establishing a temporal relationship between exposure and symptom onset, including the presence of a latency period before symptom onset and whether symptoms improve during weekends or holidays away from the workplace. A relevant personal exposure history should include a thorough history of recreational or medicinal cannabis use and any home cannabis cultivation.

Clues that indicate a potential IgE-mediated response to cannabis include a latency period of months to years with exposure before symptoms begin, preceding or accompanying rhinoconjunctivitis, a lag between direct exposure and symptom onset (typically two to four hours), and/or a history of atopy. Symptoms related to respiratory irritants are more likely to begin immediately upon exposure without a latency period and less specific triggers. The pattern of symptoms across the work week is important in ruling out byssinosis, which would be expected to improve during consecutive work days.

When a work-related respiratory condition is suspected, it is important first to definitively diagnose the condition, before then establishing work-relatedness. This approach will guide clinical management and assist with the requirements needed to consider a possible worker's compensation claim. The choice of testing is determined by the clinical presentation. Asthma may be diagnosed by spirometry with bronchodilator testing or by methacholine challenge. While 2022 society guidelines define bronchodilator responsiveness as a change of > 10% relative to the predictive value for FEV_1 or FVC, it is important for clinicians to be aware that some worker compensation systems may still use prior guidelines to define a significant bronchodilator response (e.g. 12%/200mL improvement in FEV_1).[64,65] A strong clinical suspicion of asthma supports more specialized testing even if spirometry with bronchodilator is unrevealing, as otherwise healthy persons with asthma may have normal PFTs but a significant methacholine response. Chest imaging may be helpful in supporting a respiratory diagnosis beyond asthma such as ABPA or hypersensitivity pneumonitis. Rhinosinusitis may be diagnosed by sinus CT, and a nasal smear with >0.3 eosinophils/high power field is considered diagnostic for allergic rhinitis, although it is non-specific regarding the cause.[66] Skin prick testing to regional aeroallergens is useful to establish a diagnosis of atopy.

Once the diagnosis is established, objective testing should be used to document an association with workplace exposures. If an allergenic response is suspected, it is important, whenever possible, to evaluate immunologic reactivity to potential eliciting agents through skin prick testing or specific immunoglobulin E antibodies. Testing for fungal sensitization should include Aspergillus, Penicillium, *Botrytis cinerea*, Fusarium and Trichoderma. While these fungal pathogens are common in the environment, the clinical history combined with evidence for sensitization is helpful in assessing work-relatedness. There is, as yet, no standardized approach to the diagnosis of cannabis allergy, but skin prick testing with either fresh plant material or purified extracts is currently the most feasible option within the United States. The development of additional diagnostic testing to specific molecular mediators of sensitization is underway, but not commercially available at this time. Although the gold standard for occupational asthma is the specific inhalation challenge (SIC), this is rarely available due to lack of standardized protocols and to legal and ethical considerations. Peak flow monitoring obtained at least four times a day, on days at work and away from work, is a reasonable alternative. The patient should mark associated symptoms and job tasks to further elucidate any association between disease and exposure. The results should be plotted to determine whether there is a pattern of worsened peak expiratory flow rates (PEFR) during workdays in comparison to days or weeks off work. Increased variability in PEFR and a reduction of greater than or equal to 20% between maximal and minimal readings that occurs during working days has a high sensitivity and specificity for sensitizer-induced occupational asthma.[67]

Management and Prevention

Treatment of work-related respiratory diseases in cannabis workers should focus on exposure control and pharmacotherapy. The underlying disease pathophysiology guides whether the recommendation is for complete elimination versus reduction in exposure. For disease processes mediated by an allergenic response, such as sensitizer-induced occupational asthma or hypersensitivity pneumonitis, complete removal from exposure is recommended as even minimal exposures may precipitate a severe response or ongoing disease progression. Elimination of the exposure may be possible with job accommodations, but in other cases – such as cannabis allergy, the employee may not be able to return to the worksite. Unless the patient is being seen as part of a worker's compensation evaluation, the provider must obtain the patient's permission to speak to the workplace about removal from exposure or the job. In some instances, the worker may decline a job change due to financial reasons or lack of alternative employment. In that instance, the provider should discuss possible risks of ongoing exposure and recommend close clinical follow up and symptom monitoring to determine disease stability vs. progression.

Reduction of exposure at the workplace is guided by the hierarchy of controls.[68] Several agencies, including the Colorado Marijuana Health and Safety Work Group, have published initial recommendations to guide the reduction and elimination of potential hazards within the industry.[5,69] In general, engineering controls – such as improved exhaust ventilation – are preferrable to personal protective equipment as effective methods of reducing exposures. Use of respirators containing filtering facepieces (such as a N95) should be considered with the tasks that have highest exposure to aerosolized particulates, such as grinding dried plant

material. If respirators are to be used, employers should implement an OSHA-compliant respiratory protection program. In some cases, the provider may recommend use of a voluntary use N95 to an employee, even when it is not mandated by the employer. In addition, body protective clothing, including coveralls, safety boots and gloves, should be considered as dermal contact with direct handling of plant material, pesticides and other chemicals may be an important route of occupational sensitization.[5]

Conclusion

With a rapidly expanding cannabis workforce, there is a growing need to understand the occupational hazards and potential diseases associated with the modern cannabis industry. The cultivation requirements and job tasks associated with cannabis production increase the risk of exposure to a broad range of bioaerosols, irritant gases, chemicals and other respiratory hazards. Characterization of the specific components and concentrations of these exposures has been hindered by the wide variation in work practices within the cannabis industry and legal constraints that have limited research in occupationally-exposed cohorts. While much of the evidence reviewed above comes from expert opinion, case series or small epidemiologic studies, results suggest a risk of work-related respiratory disease. Although the existing literature has focused primarily on work-related asthma and other allergic disease, the full spectrum of respiratory diseases is likely to encompass other airway and parenchymal disease. Diagnostic algorithms and commercially available, standardized tests of cannabis allergy are needed to help inform treatment approaches and prevention strategies. Future research efforts should focus on exposure controls to prevent disease development.

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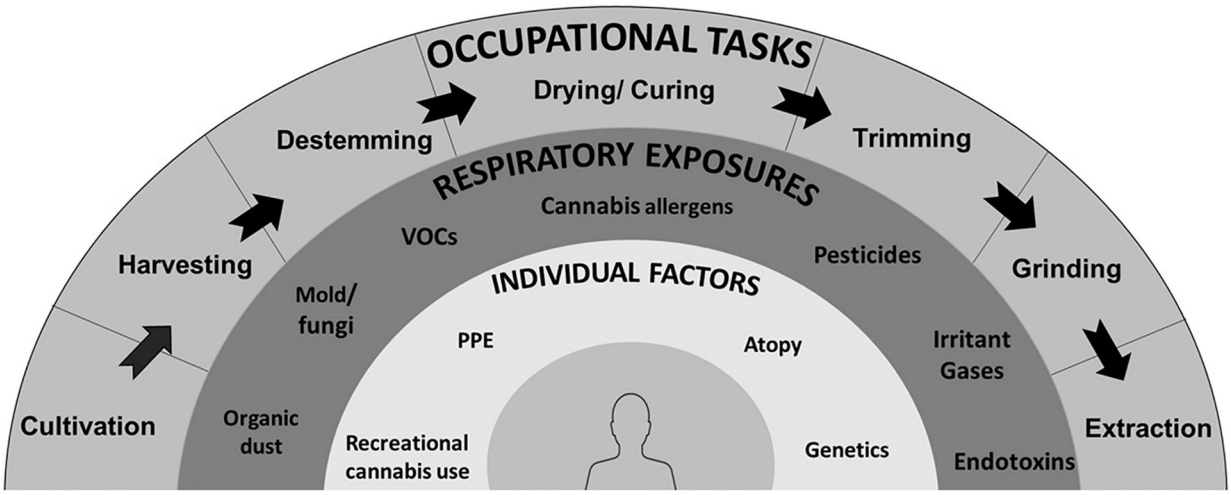

Figure 1. Occupational Respiratory Exposures in Cannabis Workers.

Representative figure demonstrating the potential respiratory exposures associated with modern cannabis production. The outer sphere represents the sequential work-processes involved in cannabis cultivation. Many of the respiratory exposures associated with specific job tasks are overlapping. Individual susceptibility and vulnerability factors may influence the development of disease. VOCs – volatile organic compounds, PPE – personal protective equipment.

TABLE 1.

Inhalation Exposures Associated with Cannabis Production

Bioaerosols	Organic dust Fungi and mycotoxins Bacteria and endotoxin Insects and mites
Chemicals	Pesticides and fungicides Fertilizers Cleaning products
Irritant gases and vapors	Cannabinoids Terpenes and other volatile organic compounds Carbon dioxide Carbon Monoxide Ozone
Cannabis allergens	Can s2: Profilin Can s3: Non-specific lipid transfer protein (nsLTP) Can s4: Oxygen-evolving enhancing protein 2 (OEEP2) Can s5: Pathogenesis related protein 10 homologue

TABLE 2.

Pesticides, Fungicides and Insecticides Identified in Legal and Illegal Cannabis Cultivation Facilities[32]

	Product	Symptoms of Exposure
Fungicides	Ferric sulfate	Eye, skin, respiratory tract, and digestive tract irritation
	Paclobutrazol	Eye, skin, and respiratory tract irritation
	Tebuconazole	Eye and skin irritation
Insecticides	Pyrethroids • Bifenthrin • Cyhalothrin • Cypermethrin	Eye irritation, respiratory tract irritation, skin tingling, burning, itchiness
	Carbamates • Carbaryl • Carbofuran • Methomyl • Propoxur	Cholinergic excess: fatigue, weakness, dizziness, confusion, nausea, vomiting, diarrhea, blurred vision, headache, sweating, tearing, drooling, tunnel vision, twitching, difficulty breathing
	Organophosphates • Diazinon • Malathion	Cholinergic excess: Fatigue, weakness, dizziness, confusion, nausea, vomiting, blurred vision, headache, sweating, tearing, drooling, tunnel vision, twitching, difficulty breathing
	Neem Oil	Eye and skin irritation, nausea, vomiting, headache
	Spinosad	Difficulty breathing, headache, eye and skin irritation
Miticide	Etoxazole	Eye, skin, respiratory tract, and digestive tract irritation, headache, dizziness, weakness, and nausea

TABLE 3.

Spectrum of Reported and Possible Respiratory and Skin Diseases Associated with Cannabis Production *

Respiratory disease	Upper Airway	*Allergic rhinosinusitis*
	Lower Airway	*Irritant induced asthma* *Sensitizer induced asthma* Byssinosis Allergic bronchopulmonary aspergillosis Chronic bronchitis COPD
	Parenchymal	Hypersensitivity pneumonitis
Dermal disease		*Irritant contact dermatitis* *Sensitizer contact dermatitis*

* Diseases in italics have been reported in workers with occupational exposure to cannabis