Health Effects of Exposure to Cannabis in Workers in an Indoor Growing Facility

Niloufar Ghodsian

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Committee:
Christopher Simpson, Chair
Coralynn Sack
Nancy Simcox

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Abstract

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Niloufar Ghodsian

Chair of the Supervisory Committee:
Professor, Christopher Simpson
Department of Environmental and Occupational Health Sciences

Background: Legalization of recreational cannabis in multiple states, including Washington, has scaled up cultivation of this plant. This rise in cultivation also raises health and safety concerns for workers in this emerging industry. Limited research on occupational health hazards of working with cannabis has shown potential occupational exposures to volatile organic compounds, plant proteins, and microbial contaminants. Sensitization to different members of the *Cannabaceae* family like hemp and hops have been reported previously. Few reports are available about sensitization to cannabis in particular, but by evolving the legalization of cannabis, it is likely that this problem will increase in the future.

Methods: First, using a baseline questionnaire, our study characterized the prevalence of work-related allergic and irritant symptoms and their association with exposure in workers in an indoor cannabis growing facility (n=31). Second, for two weeks, lung function and airway inflammation were measured in a subset of workers with work-related symptoms to characterize acute and chronic changes in these two measures (n=10). Third, in the same subset of workers, a skin prick test was used to characterize the prevalence of cannabis sensitization.

Results: Among work-related symptoms, the prevalence of respiratory symptoms was the highest (65%), followed by ocular (39%), nasal (32%), and dermal symptoms (26%). Our findings suggested that workers with higher exposure to cannabis may have increased odds of having work related symptoms, although none of the associations were statistically significant.

Results of our analyses provided evidence for chronic decrease in pulmonary function and chronic increase in airway inflammation, but not strong evidence for acute changes in these two measures. Finally, 50% of participants in our sub-cohort of 10 workers with work-related symptoms were sensitized to cannabis.

Conclusion: The high prevalence of work-related symptoms, cannabis sensitization and impaired lung function observed in our study, raises the possibility that occupational exposures to cannabis are harmful to workers in this industry. Preventive measures are recommended to reduce worker exposure to cannabis, especially in areas with high concentration of dust.

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CHAPTER ONE: BACKGROUND AND SIGNIFICANCE

A Quick History of Cannabis

Rooted from the classical Greek word for hemp, *Cannabis sativa* which was first described in Europe, received its name from the Swedish father of botany, Carolus Linnaeus [1]. In contrast *Cannabis indica,* which is significantly different from the species found in Europe, was named after its country of origin, India. Hemp and cannabis share the same genus and species and are essentially the same plant, however, they differ because of their use and breeding [1]. Hemp, which is bred for strong and durable fiber, has been used in making ropes, textiles, and paper. Cannabis, which is bred for certain concentration of specific cannabinoids, has been used medicinally and recreationally across the world. Cannabinoids are bioactive components of the cannabis plant. The two main cannabinoids in cannabis are Δ-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), with the first one being the main psychoactive chemical of this plant [2].

When the psychoactive effect of cannabis was discovered, not surprisingly, cannabis became a magical plant in religious and ritualistic practices. The first documented medicinal use of cannabis dates back to the first century AD in China. The father of Chinese medicine, Shen Nung, believed that the "hemp elixir" – probably cannabis tea – treats a wide range of conditions from gout to malaria [1]. Despite these beliefs, the use of cannabis in China was only a passing phase because the use of drugs was seen as antisocial and was against Chinese (Confucian) cultural values. Similar reasons were true for many other societies and that is why the utilization of cannabis has been discouraged in many societies.

Because commercial utilization of cannabis has not been widespread, little attention has been drawn to the occupational health hazards of working in production of cannabis. Now that the recreational use of cannabis is legal, especially in the US and Canada, the production of this plant is skyrocketing to where in 2018, it was recognized as the fastest growing job market in the US by Consumer News and Business Channel (CNBC) [3]. With a 44% increase in workforce in 2018, this job market deserves more research in the area of occupational health and safety to cover 211,000 workers who are working in this nascent industry.

Cannabis Statistics

In November 2012, Colorado and Washington State legalized recreational cannabis. In 2019, 10 states plus the District of Columbia and Canada have legalized the recreational use of cannabis. Cannabis for medicinal use is legal in 33 states. For reasons such as substantial tax revenue, economic benefits, and regulation and product safety, it is predicted that more states will legalize production of cannabis for medical and/or recreational use in the next few years [4].

More legalization means more jobs and more workers exposed to unknown occupational health hazards of working in this industry. According to the 2018 Annual Report by the Washington State Liquor and Cannabis Board, there are 1,441 producer, processor, or producer/processor licensed cannabis businesses in Washington state alone [5]. A producer license allows the licensee to produce cannabis "for sale at wholesale to marijuana processor licensees and to other marijuana producer licensees" [6]. Producer licenses exist for plant canopy equal to two thousand square feet or less (Tier 1), between two thousand square feet and ten thousand square feet (Tier 2), and between ten thousand square feet and thirty thousand square feet (Tier 3). More than 80% of cannabis producer or producer/processor licenses in Washington state are Tier 2 and 3. A processor license allows the licensee "to process, package, and label usable marijuana and marijuana-infused products for sale at wholesale to marijuana retailers" [6]. Only 11% of all licenses are for processors only; the other licences for cannabis processing are combined with the producer license (Figure 1).

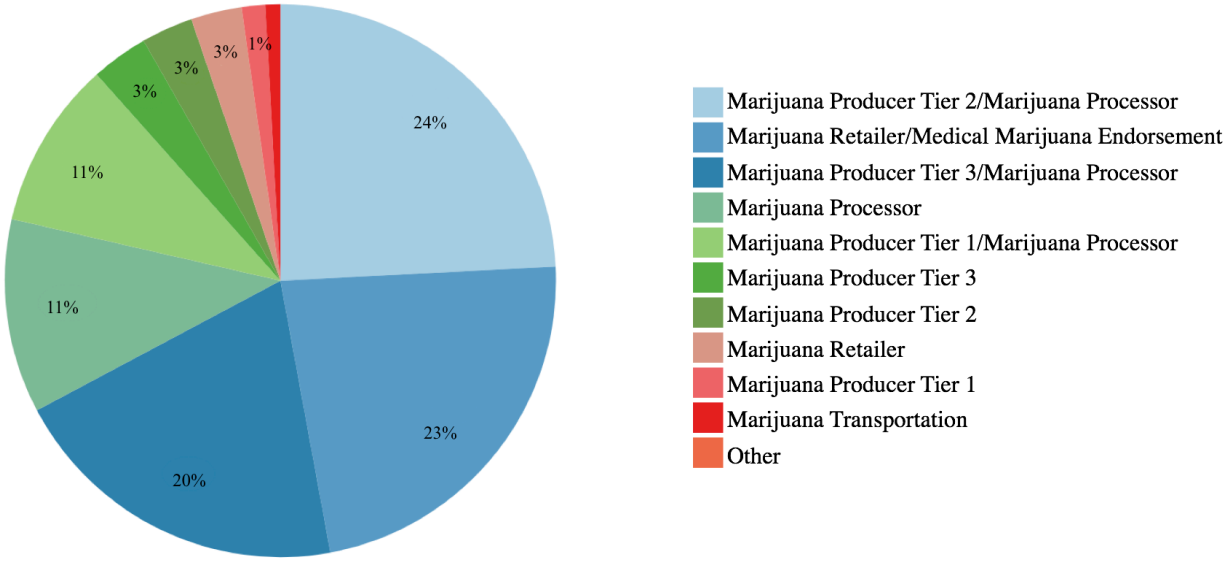

Figure 1: Distribution of marijuana licenses issued in Washington State [7]

These licenses are issued only for producing and processing cannabis. In addition, there are 505 retail licenses and 16 transportation licenses which still put workers in these jobs at potential risk for occupational exposure to cannabis.

Occupational Exposure to Hemp and Hops and Health Effects

As mentioned before, hemp and cannabis share the same genus [1], so it is possible that occupational exposure to cannabis impacts workers' health in the same way as hemp. Occupational exposure to hemp, which is well-studied [8], [9], is known to result in respiratory symptoms and diseases such as byssinosis, chronic bronchitis, and occupational asthma [10]. Bernardino Ramazzini, an Italian physician in the 17th century, was the first to recognize that workers exposed to organic dust of textile materials such as hemp suffer from asthmatic symptoms [11]. Today, byssinosis is known as the most likely occupational disease in hemp workers [12], [13]. Symptoms in early stages of the disease, which include fever, malaise, and chest tightness, were previously known as "Monday Fever" because they occurred on Mondays, after the weekend. Additionally, local irritations such as eye, nose, and skin symptoms are observed at a high rate in workers exposed to hemp and jute dust [10].

Exposure and health effect comparisons can also be made with hops. The current botanical classification of cannabis puts this plant together with the *Humulus* (hops) genus, in the small family of *Cannabinaceae* [14]. Because these two genera have many common characteristics, it is possible that the species in these genera may cause similar occupational health symptoms. Hops, however, do not contain the psychoactive cannabinoids present in cannabis [15]. Hops have been used in flavoring beer since the 12th century and this remains their major commercial application. Hops are primarily cultivated in outdoor farms. Various studies have reported links between working with hops and a variety of health issues, such as dry cough, dyspnea, chronic bronchitis, asthma [16], rhinoconjunctivitis [17], and contact dermatitis [18]. In a study of 23 hops farm workers in Poland, physical examination, interviews, lung function tests, and skin prick tests were performed in all workers. In this study, eight farmers reported symptoms of chronic bronchitis and five farmers reported occurrence of work-related symptoms including dry cough and dyspnea [16]. The overall result showed a potential risk of occupational respiratory illness in hops farmers. A case study of a 35-year-old brewery worker showed an allergic

response to hops after performing the skin prick test while a control group of 10 non-exposed individuals were all negative [17]. This worker who had worked in a brewery for three years, also produced an immediate nasal response after nasal challenge with hops extract. The study concluded that the worker's rhinoconjunctivitis was due to occupational exposure to hops in the brewery.

In another case study, occupational airborne contact and hand dermatitis was observed in a 57-year-old female hops farmer [18]. Her dermatitis which was of allergic nature, was confirmed both with the skin prick test and the patch test.

The described studies along with several other occupational hops studies [19], [20], provide strong evidence that long term occupational exposure to hops and hemp can lead to respiratory and dermal symptoms in workers. Since research is limited in establishing a relationship between health effects and cannabis exposure, studies on hemp and hops may be used to draw conclusions about outcomes of long term occupational exposure to cannabis.

Occupational Exposure to Cannabis

Although the cannabis industry has expanded exponentially in the last few years, the research on occupational hygiene in this industry remains underdeveloped. There are many areas of research that can be advanced, for example, quantifying exposure to biological agents such as molds, endotoxins, and plant proteins; exposure to chemical agents such as organic dust, volatile organic compounds (VOCs), and pesticides; and exposure to physical agents such as ultraviolet radiation and noise [21].

The Colorado Department of Public Health and Environment published a comprehensive guide in January of 2017 about worker safety and health in the cannabis industry [22]. This guide identifies many potential biological, chemical, and physical hazards of this industry. Mold, for instance, is a potential hazard because the production of cannabis requires high levels of humidity (up to 70%) which promotes the growth of mold. Martyny et. al evaluated levels of fungal spores in 30 indoor marijuana grow operations to determine potential exposures to first responders [23]. When compared to outdoor levels, 40% of grow rooms had at least a fivefold increase in levels of both viable and microscopic spores. Additionally, 57% of grow rooms had at least a fivefold increase in levels of viable *Penicillium* or *Aspergillus*/*Penicillium* mold

species.

In addition to mold, workers can also be exposed to dermal and respiratory allergens and sensitizers, such as plant material and endotoxin. Plant materials, such as thaumatin-like protein and non-specific lipid transfer protein, are proposed to be potentially allergenic in cannabis plants [24]. Endotoxin, a component of gram-negative bacterial cell walls, is correlated with inhalable dust in agricultural settings such as hemp processing factories [25], with mean concentrations reported to be 100 EU/m^3 in a jute and hemp factory in Turkey [10]. Occupational exposure to endotoxin is associated with development of byssinosis [26]. Previous studies have identified variations in levels of endotoxin by location and task [27], [28]. Endotoxin concentrations were found to be high during machine harvesting of vegetables and nuts, as well as during mowing of weeds [27].

Aside from biological hazards, chemical and physical hazards are also of concern. Examples of chemical hazards are carbon dioxide, carbon monoxide, VOCs, pesticides, and disinfectants which are not specific to the cannabis industry but inherent in the horticulture industry in general. VOCs and more specifically terpenes are found in abundance in the cannabis plant and contribute to its taste and odor [29]. While there are no health effects associated with terpenes, their byproducts of reactions with indoor oxidants such as ozone are suspected to cause respiratory symptoms [30].

Finally, some of the physical hazards associated with cannabis production include ergonomic hazards, noise, compressed gases, and extraction equipment.

The long list of biological, chemical, and physical hazards, along with increasing recent legalization of cannabis production, brings the cannabis industry to the forefront of research on occupational safety and health.

Health Effects of Exposure to Cannabis

One of the health concerns related to exposure to chemical and biological agents present in cannabis cultivation is respiratory illness. In Washington State, an increasing number of workers have complained about respiratory symptoms from occupational exposure to harmful substances in the cannabis industry [31]. The causes of respiratory illness could vary. For example, A Health

Hazard Evaluation by the National Institute for Occupational Safety and Health (NIOSH) in 2015 indicated that workers on cannabis farms were likely exposed to aerosolized bacteria and mold. Approximately, 40% of bacterial populations in this study were identified as endotoxin-producing gram negative bacteria that can increase the risk of hypersensitivity pneumonitis, chronic bronchitis, organic dust toxic syndrome, asthma, and allergic sensitization [32]. *Botrytis Cinerea* was identified as the major mold species in personal air samples which has been linked to hypersensitivity pneumonitis [33].

A study in Germany suggests an immunologic response to cannabis and hashish (a cannabis concentrate) in a laboratory technician and a physician who handled these two substances frequently for 25 and 16 years, respectively [34]. These two individuals did not have recreational exposure to cannabis, nor did they have a history of atopy, but they suffered from nasal congestion, sneezing, hand eczema, and mild asthma while working with cannabis. From 12 controls (8 atopic and 4 non-atopic), only two atopic individuals had a positive specific IgE test.

An article by Mayoral et al. describes allergic hypersensitivity to cannabis sativa pollen [35]. Mayoral's patients who worked in a laboratory handling *C. sativa* developed intense allergic rhinoconjunctivitis during two years of working there.

Three common approaches to cultivating cannabis are outdoor, greenhouse, and indoor. The advantages of indoor cultivation, which is the focus of this thesis, are security, low potential of cross contamination, and better yields [36]. However, indoor grow operations can potentially increase the risk of respiratory illness, especially if cleaning practices are not routinely undertaken and ventilation systems are not adequately designed [37]. In 2018, a survey study in Colorado investigated 214 cannabis workers in order to understand both physical and psychosocial hazards to worker health and safety [38]. In this study, in which 77% of the participants' organizations were indoor growing facilities, 17.6% of workers experienced skin irritation, 14.4% experienced headaches and dizziness, 13.4% experienced eye irritation, and 35.3% experienced other symptoms after handling pesticides used in cannabis production [38].

In addition, lack of regulations for adequate training and correct use of personal protective equipment adds to the potential hazards of working in this industry. The Walters et al. Colorado study cited above asked workers about health and safety training offerings. Results showed that

26% of participants never received such training on the job, 29% had a conversation about safety when hired, 27% had a more elaborate one-time training, and only 16% received structured, ongoing training programs [38].

Indoor Grow Description

Several stages are involved in production of cannabis plants indoors [30] and each stage is likely to correspond to a different combination of exposures. The process of cultivation begins with removing cuttings from a mature donor plant to create clones. Clones are new plants that share the same characteristics as the mature donor plant. This genetic consistency allows for more controlled experiments which eventually lead to increased crop productivity. Clones are vulnerable to mold at this stage, so employees monitor them closely and fertilize and water them by hand. When clones are mature, they are labeled and moved to a grow room where they are kept directly under grow lights [39]. When they reach the vegetative stage, they are replanted into larger pots and moved to another grow room in which they are watered and fertilized by a distribution system. At this stage, grow lights are controlled to induce flowering by regulating the light/dark cycle [39]. The stages described above, which involve the cultivation of the cannabis plants, are likely to expose workers to molds, fertilizers, pesticides, and VOCs such as terpenes [30].

A typical cannabis indoor growing facility harvests plants three to four times a year due to the ability to regulate the life cycle of the plants. Outdoor farms, on the other hand, harvest only once a year due to seasonal changes [30]. At the harvest stage, employees remove large stems from fully mature plants and hang them in another room to dry. Cutting stems releases a substantial amount of VOCs into the air, so workers are likely to exposed to high concentrations of VOCs, such as terpenes. It usually takes up to a week for cannabis plants to be dried. Employees then remove flowers from dried plants. Now that the plants are dried, in addition to VOCs, exposure to particulate matter is also likely.

Dried flowers are used in a variety of processes. Higher quality flowers (also called buds) are separated to be hand-trimmed for aesthetic reasons. Hand-trimming involves removing undesirable parts of the plants such as leaves and stems which again can release terpenes as well as particulate matter. Workers are likely to be exposed to high concentrations of these two

airborne contaminants in this process. The lower quality flowers are either mechanically trimmed or ground to a coarse powder to be used in pre-rolled joints, or extracted to create high THC concentrates and oils.

Summary

The described data on occupational hazards of handling the cannabis plant, although limited, has suggested adverse dermal and respiratory outcomes associated with repeated exposure to this plant. It is well warranted to bring more attention to occupational safety and health in this industry. The variations in exposure to irritants and sensitizers, such as mold, endotoxin, plant proteins, particulate matter, and VOCs, makes it more challenging to address these issues. Thus, it is evident that more research is needed to help establish clear guidelines to protect workers from exposure to chemical and biological agents specific to the cannabis industry.

Specific Aims

Due to the illegal status of cannabis in the past, limited research has been done to address health effects of exposure to potential contaminants in this industry. The current proposed study will investigate the association between cannabis exposure and health effects in workers in an indoor cannabis growing facility in Washington State.

The study will address 3 primary aims:

Aim 1: To characterize work-related dermal, nasal, ocular, and respiratory symptoms and their association with task amongst cannabis workers in an indoor growing facility.

> **Aim 1a**: To determine the prevalence of overall and work-related health symptoms.
>
> **Aim 1b**: To examine the association between workers' typically performed task and dermal, nasal, ocular, and respiratory symptoms.

Aim 2: To characterize cross-shift and cross-week changes in pulmonary function and airway inflammation using spirometry and exhaled nitric oxide respectively in a subset of cannabis workers with work-related symptoms.

Aim 3: To determine the prevalence of allergic responses to common Pacific Northwest molds and different strains of cannabis using skin prick testing in a subset of cannabis workers with work-related allergic symptoms.

This pilot study helps fill the existing gaps in occupational health research in the cannabis industry. The findings of this study can generate evidence on the association of occupational exposures to cannabis with dermal, nasal, ocular, and respiratory symptoms. In addition, it can be used to design future studies in this field in order to better understand the relationship between working in indoor cannabis production facilities and adverse health effects. The outcomes of this study will also be useful to develop and implement safety measures to reduce exposures amongst cannabis workers during growing, harvesting, and processing of this plant. These measures help mitigate harm and protect workers from being unduly exposed and consequently developing adverse health symptoms.

CHAPTER TWO: METHODS

Study Location

This study was conducted in an indoor cannabis producer/processor facility in Washington State from October 2018 through January 2019. This facility operates under a Tier 3 license (the largest size category) with a workforce of approximately 45 full time employees. Activities undertaken in this facility include cultivating the cannabis plant, harvesting, drying, curing, and fully processing it to a variety of consumer products including full buds, pre-roll joints and concentrates. The facility consists of several grow rooms for different stages of growth, a drying room for drying the plants after harvest, a large processing room to process the dry plants, and several smaller rooms for hand trimming, packaging/labeling, extraction and R&D as well as an office area for administrative tasks. In addition to growing its own product indoors, which results in three to four harvest cycles per year, the facility processes a large volume of outdoor grown product. The outdoor grown product is harvested only once per year, typically in October/November.

Study Design and Population

The study was reviewed and approved by the University of Washington Institutional Review Board (Study #: 04380).

Phase 1: The first phase of this research was a cross-sectional study of dermal, ocular, nasal, and respiratory symptoms in cannabis employees. Employees attended a group session (four to six workers) to go over the basics of the study to decide whether or not they want to participate. Upon their decision to participate, each employee was given a consent form to read and sign and they completed a baseline questionnaire. A total of thirty-one out of the forty-five full time employees at the grow facility participated in this phase of the research.

Phase 2: The second phase of this research involved repeated measures of cross-shift and cross-week changes in pulmonary function and airway inflammation. Study participants were also tested for a type I reaction to cannabis and molds using a skin prick test. Table 1 provides more details about Phase 2 data collection. For this phase of the study we recruited exclusively workers who had reported experiencing work-related symptoms in their baseline questionnaire. Employees who met the inclusion criteria were contacted and asked whether they were interested

in participating in the second phase. Figure 2 shows a flowchart of inclusion criteria which started with selecting the employees with the work-related wheeze. Our initial inclusion criteria was work related wheeze; however, the inclusion criteria were progressively broadened within the category of work-related respiratory symptoms until we had ten employees who agreed to participate in the sub-study. A total of five employees were unable to participate: two employees had left the company, one had a scheduling conflict, one never returned our call, and one was not interested in participating.

Table 1: Phase 2 Data Collection

	Instrument /material	**# Measurements per subject**	**Pre-shift**	**Post-shift**
Pulmonary Function	Spirometer	4	Yes	Yes
Airway Inflammation	FeNO	4	Yes	Yes
Questionnaire	Paper Survey	4	No	Yes
Skin Prick Test	Skin Applicator	1	N/A	N/A

Baseline Questionnaire: A baseline symptom questionnaire was administered to workers interested in participating in the study (n=31). This 45-question survey asked about basic demographics, occupational history, medical history, personal tobacco and cannabis use, typically performed tasks, use of personal protective equipment, and finally the presence of overall and work-related health symptoms (Appendix II). The health symptom component of the questionnaire was adapted from the European Community Respiratory Health Survey asthma questionnaire included items on work-related symptoms [40]. A total of four sessions were held to accommodate all employees who were interested in filling out the survey. For each session, there were at least two UW persons available to answer employees' questions and review the surveys at the end.

A simple symptom prevalence analysis was performed to identify employees with work-related symptoms. Answering "Yes" to any of the work-related symptom questions was considered to identify employees who had symptoms due to working in this facility. Questions, such as "does contact with certain materials, chemicals or anything else in your work makes your symptoms worse?" or "do your symptoms improve when you are away from your normal work?" were common work-related questions asked for each symptom. Table 2 provides more details on questions which were used to identify work-related symptoms.

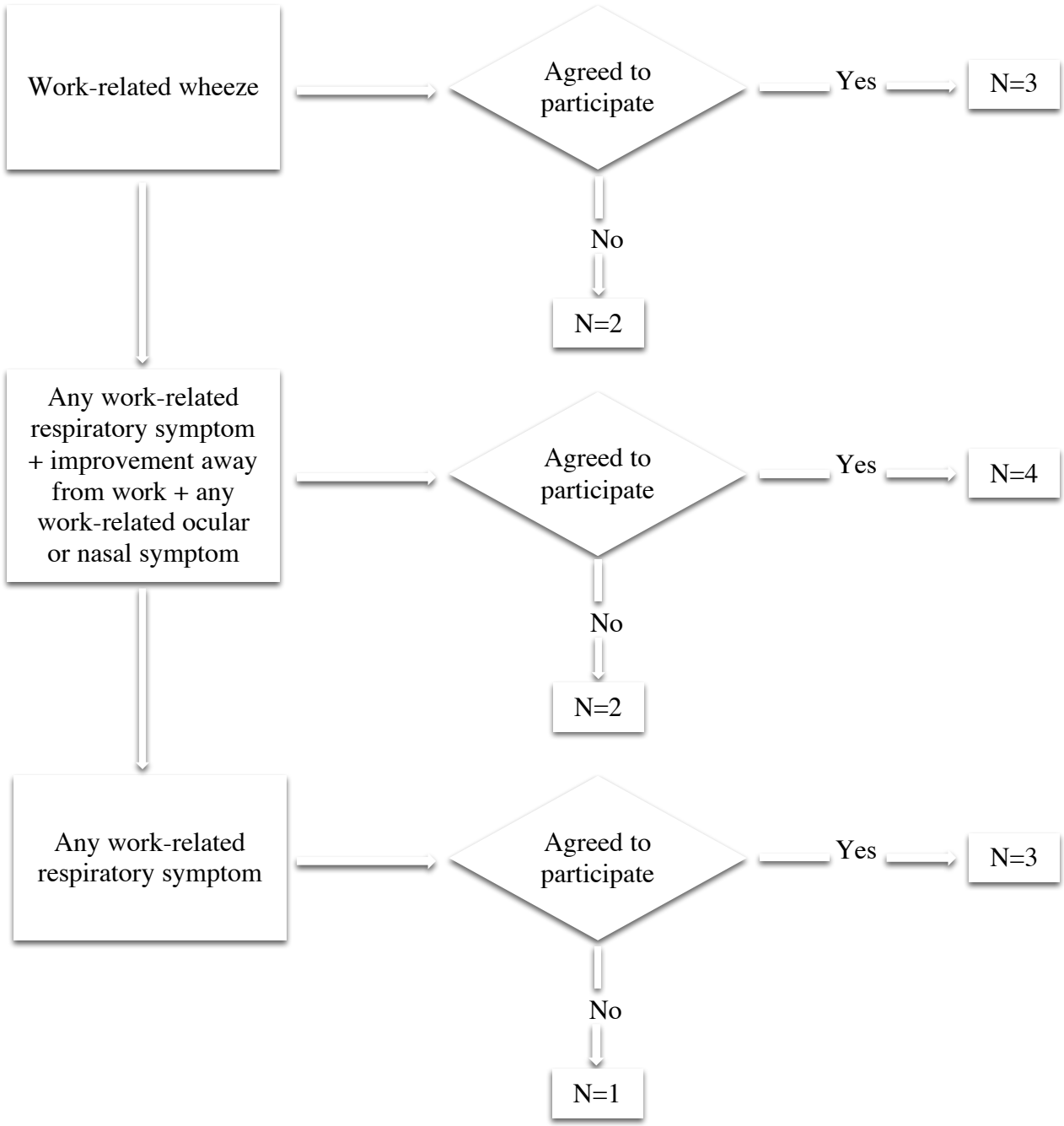

Figure 2: Criteria used for the recruitment of the sub-study cohort (Phase 2). All questions used in selection criteria were work-related symptom questions. The criteria were broadened until a desirable number of workers agreed to participate (n=10). A total of five participants were contacted but did not participate in the study.

Table 2: Questions in baseline questionnaire used to determine work-related symptoms (Appendix II)

Symptoms	Dermal	Ocular	Nasal	Respiratory
Question number	25, 26	28, 29, 30	33, 34, 35	43, 44, 45

Respiratory Health Measurements: Selected employees were followed for a period of two weeks to obtain measurements of airway inflammation and pulmonary function. These measurements were obtained pre- and post-shift for a total of four days, two Mondays and two Fridays (Appendix I, Table 1). Employees were asked to arrive 30 minutes before the start of their shifts to be able to conduct respiratory measurements before contact with any cannabis materials.

Before the start of respiratory measurements, a pulmonary physician, who was a part of the study team, trained other team members on operating the instruments. Quality Control (QC) procedures for each instrument were also reviewed and followed by the team to ensure that reliable measurements were obtained.

Airway inflammation was determined by measurements of fraction exhaled nitric oxide (FeNO)using a portable exhaled nitric oxide (NO) analyzer, NIOX VERO (Morrisville, NC). NO, which is present in the exhaled breath of all humans, plays a key role in all aspects of lung biology, including the pathophysiology of lung diseases such as asthma [41]. Employees were asked to empty their lungs, inhale through a personal mouthpiece to total lung capacity, and exhale slowly with a steady pressure. The instrument then analyzed the breath and displayed a result in approximately one minute. The same maneuver was performed by a staff member who was previously qualified for QC procedure by selecting QC ID on the screen. QC for was done the morning of each day of data collection following NIOX VERO User Manual [42]. FeNO results are expressed in parts per billion. Abnormal or borderline FeNO was determined based on American Thoracic Society Criteria (ATS) [41]. FeNO less than 25 ppb was considered normal, between 25 and 50 ppb was considered borderline, and more than 50 ppb was considered abnormal.

Pulmonary function tests (spirometry) were conducted using an NND EasyOne Air portable spirometer (Andover, MA). Spirometry assesses lung function by measuring the total volume of exhaled air as a function of time, and is commonly used in screening respiratory health [43]. Employees were asked to sit in a comfortable position, fill their lungs completely, seal their mouth around the instrument's mouthpiece, blast out as hard and as fast as possible, and continue until lungs are completely empty. A minimum of three acceptable maneuvers were obtained and the best maneuver, identified by the instrument, was selected. Attempts were acceptable when forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were within 5% of each other [44]. The displayed quality messages, rating from A to F, help the operator to assess the quality of a completed test (Appendix I). Both FVC and FEV_1 are expressed in liters and adjusted to percent predicted based on subjects' gender, height, and weight. We used ATS criteria to determine whether workers had decreased lung function. Any FVC or FEV_1 value less than 0.8 predicted was considered decreased lung function as well as any FEV_1 to FVC ratio of less than 0.7 [43].

Daily Symptom Questionnaire: On each day of data collection, a short questionnaire was also administered to each study subject at the end of the shift. The questionnaire asked about participants' tobacco and cannabis use in the last 24 hours as well as experiencing dermal, nasal, ocular, and respiratory symptoms during the past shift.

Skin Prick Test: Finally, a one-time skin prick test was performed on each employee to determine the prevalence of allergic responses to cannabis and mold in this sub-study cohort (n=10). Mold extracts were purchased from ALK-Abello, Inc. (Round Rock, TX, USA) and consisted of *Helminthosporium, Alternaria, Penicillium*, and *Aspergillus* which are commonly found in the Pacific Northwest. Cannabis slurries were prepared using two strains of cannabis, Durban Poison and Fruity Pebbles. For each strain, a mixture of leaves and flowers were ground to make a fine powder. The powder then was mixed with 1-2 ml of saline to make a slurry for the skin prick test. After application on the forearm, appearance of any wheal, erythema, pseudopodia, or itching after 20 minutes was considered an allergic reaction. A positive control with histamine was performed to rule out non-responsiveness. A negative saline control was also performed to rule out dermographism of the skin [24].

A pulmonary physician who was part of the study team prepared the cannabis slurries for the skin prick assay, and administered the skin prick tests to study subjects. The study physician also reviewed all pulmonary function and airway inflammation tests. The pulmonary function test was interpreted using the ATS/ERS criteria [45] and visually assessing the flow volume.

The study physician contacted all subjects with abnormal lung function, airway inflammation of allergic sensitization results to discuss the implications of these health measurements with the subjects.

Data Analysis

All relevant data from Phase 1 and 2 was entered into Excel sheets and a data dictionary was made for each data table. Flags were assigned to data values and an associated action was taken based on the flag type by the study team. Explanation of flagging variables can be found in Appendix IV. Data tables then were imported to R Version 3.5.1 for data analysis. Spreadsheets used include:

Baseline Questionnaire
Post-shift Questionnaire
Health Measurements

Aim 1a

The baseline questionnaire was used to calculate the prevalence of each work-related dermal, ocular, nasal, and respiratory symptom. Work-related symptoms were identified by specific questions about workers' symptoms at work (Table 2).

Aim 1b

Another piece of the first aim of the study was to evaluate the association between exposure and work-related symptoms. Because exposure measurements were not available, task categories were used as a surrogate measure of exposure. About 24 tasks were reported by workers, which then were placed into three main exposure categories, low, medium, and high, based on intensity of exposure to cannabis (Table 3). For example, dust-generating tasks such as sifting and grinding were placed into the high exposure category, and tasks with low exposure to cannabis such as office tasks were placed into low exposure category. In addition, conversations with the

workers and the facility manager about exposure were considered in determining these categories. Finally, we also used results from particulate matter and VOC measurements in another study which took place in the same facility to support our assignment of tasks to exposure categories. In this study, particle mass concentrations were the lowest for office task zones, 18.5 (IQR) = 13.8-21.1 μg/ m^3, and the highest for trim task zones, 59.2 (IQR = 43.5-78.2). The trend was the same for VOC terpene mass concentrations [46].

Table 3: Exposure (task) categories. Description of each task can be found in Table 3 of Appendix I.

Exposure Categories		
Low	**Medium**	**High**
Office	Packaging	Sifting
Inventory	Weighing	Grinding
Delivery	Hand-trimming	Knock Box
Internal Interview	Pre-roll	Harvesting
Picking Order	Tubing	
Order Fulfillment	Spraying	
Waste Disposal	Growing	
Labeling	Plant Survey	
Cleaning	Transferring Plants	
	Consolidating	
	Spinning	

For each employee, the percentage of time spent on each task was extracted from the baseline questionnaire. This information was then used to calculate the total percentage of time each employee spent in low, medium, and high. Figure 3 shows the maximum percent-time employees spent in a single exposure category. According to this graph, 97% (30 out of 31) of subjects spend at least 50% of their time in a single exposure category. Therefore, we assigned each employee to the single exposure category in which most of their time was spent. Eventually, we had 11 employees in low, 16 employees in medium, and 4 employees in high exposure (task) categories.

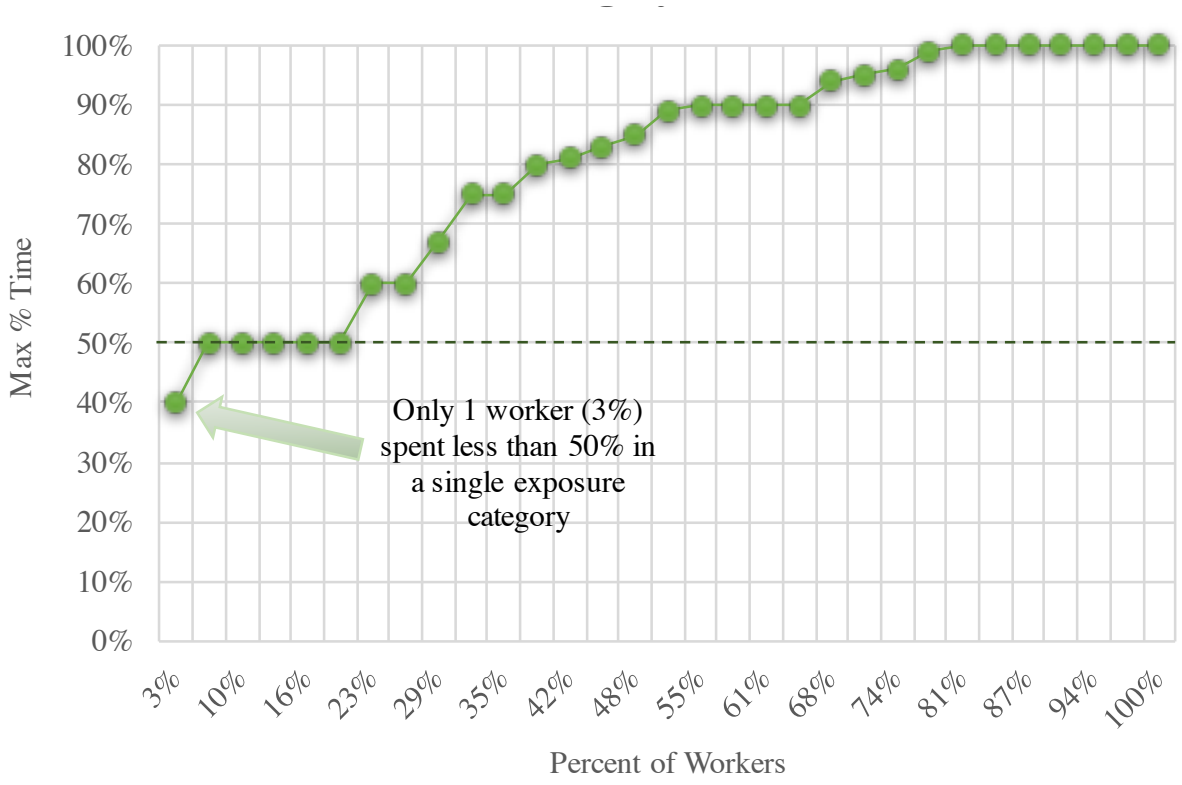

Figure 3: Maximum percent-time spent in a single exposure category. 97% of workers (30 out of 31) spent 50% or more of their time in a single exposure category.

The relationship between worker exposure (task) and dermal, ocular, nasal, and respiratory symptoms was determined using a multiple logistic regression model for each symptom:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X + \varepsilon_{n,}$$

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X + \beta_2 X + \varepsilon_{n,}$$

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 X + \beta_2 X + \beta_3 X + \beta_4 X + \varepsilon_{n,}$$

In these models, β_0 represents the estimated log odds ratio of the predicted outcome for the reference (baseline) condition, β_1 represents changes in log odds ratio of being in the medium and high exposure categories compared to being in low exposure category. The first model for each symptom is unadjusted. The second model is adjusted for age, and the third model is adjusted for age, gender, and tobacco smoke. β_2 represents changes in log odds ratio based on

age, β_3 represents changes in log odds ratio based on gender, β_4 represents changes in log odds ratio based on tobacco smoke, and $\varepsilon_{n,}$ is the residual error term for cohort subject n.

Age was treated as a continuous co-variate, while gender and tobacco smoke were treated as categorical co-variates. For tobacco smoke, employees were categorized into ever (past or present) versus never.

Age, gender, and tobacco smoke were considered to be potential confounders in our population because of their effects on both exposure categories and symptoms. However, because of a small sample size (n=31), we did not have enough statistical power to adjust for many variables. Thus, we also included unadjusted models, and models adjusted only for age because we considered age as the most important confounder of all three. Models were not adjusted for cannabis smoke because 97% of our population smoked cannabis.

Aim 2

Employees' health measurements were examined throughout two weeks to determine the variation between pre- and post-shift (cross-shift). For example, for each employee the pre- and post-shift difference in FeNO was calculated for each day (n=4). These cross-shift differences were then averaged for each employee and used in a linear regression model. The relationship between cross-shift measurement of FeNO was examined using a linear model below:

$$\text{FeNO (mean }_{\text{post-pre}}) = \beta_0 + \varepsilon_{n,}$$

The same method was used to aggregate cross-shift FVC and FEV_1 measurements and the relationship between cross-shift measurements was examined using linear regression models below:

$$\text{FVC (mean }_{\text{post-pre}}) = \beta_0 + \varepsilon_{n,}$$
$$FEV_1 \text{ (mean }_{\text{post-pre}}) = \beta_0 + \varepsilon_{n,}$$

In these models, β_0 represents the average cross-shift change in health measurements and $\varepsilon_{n,}$ represents the residual error term for cohort subject n.

In addition, the relationship between pre-shift on Monday and post-shift on Friday (cross-week) measurements of FeNO, FVC, and FEV_1 were also examined using linear regression models. For each employee, the cross-week difference was calculated (n=2), averaged, and used in a corresponding linear regression model below:

$$\text{FeNO (Mean (Fri}_{post} - \text{Mon}_{pre})) = \beta_0 + \varepsilon_{n,}$$

$$\text{FVC (Mean (Fri}_{post} - \text{Mon}_{pre})) = \beta_0 + \varepsilon_{n,}$$

$$FEV_1 \text{ (Mean (Fri}_{post} - \text{Mon}_{pre})) = \beta_0 + \varepsilon_{n,}$$

In these models, β_0 represents the average cross-week change in health measurements, and $\varepsilon_{n,}$ is the residual error term for cohort subject n.

CHAPTER THREE: RESULTS

Phase 1 Results:

The first phase of the study consisted of 31 cannabis workers in one indoor growing facility, including 19 males (61%) and 12 females (39%). The majority of workers in this facility were Caucasian, had some college experience, and worked full-time. Average age of participants was 31.8 years old with age ranging between 21 and 56 years. More demographic information can be seen in Table 4.

Table 4: Demographic Characteristics (Phase 1)

	Phase 1 (n=31)
Gender	
Male	19 (61%)
Female	12 (39%)
Age	
Male	29.8 (± 6.2)
Female	33.2 (± 8.8)
Race	
Caucasian	23 (74%)
Hispanic/Latino	4 (13%)
Alaskan Native	1 (3%)
Two or More	3 (10%)
Education Level	
No Schooling	0
Grade 1-11	2 (6%)
Completed High School	7 (23%)
Some College But no Degree	9 (29%)
Bachelor's Degree	11 (35%)
Graduate/Professional School	2 (6%)
Existing Medical Condition (Atopy)	
Asthma	8 (26%)
Eczema	8 (26%)
Hay Fever	7 (23%)
Current Smoker	
Tobacco	10 (35%)
Cannabis	30 (97%)

Table 5: Frequency of cannabis use in workers

Cannabis Type	Total	Multiple Times a Day	Once a Day	Once a week or more	About Once a Month	Every Few Months	Once or Twice a Year	Never
Edible[1]	27 (87%)	0	0	6 (19%)	6 (19%)	6 (19%)	9 (29%)	4 (13%)
Smoking	30 (97%)	25 (81%)	1 (3%)	2 (6%)	1 (3%)	0	1 (3%)	1 (3%)
Vaping[2]	25 (81%)	4 (13%)	1 (3%)	9 (29%)	3 (10%)	7 (23%)	1 (3%)	6 (19%)
Dabbing[3]	24 (77%)	9 (29%)	3 (10%)	4 (13%)	2 (6%)	3 (10%)	3 (10%)	7 (23%)
Topical[4]	22 (71%)	0	1 (3%)	5 (16%)	2 (6%)	6 (19%)	8 (26%)	9 (29%)
Any	30 (97%)	NA	NA	NA	NA	NA	NA	NA

1: Cannabis infused food
2: Inhaling and exhaling the vapor produced by an electronic device containing cannabis concentrate
3: Inhaling small quantities of vapored cannabis resin/wax
4: A lotion or ointment containing cannabis

Table 6: Frequency of smoking tobacco in workers

Tobacco Use	Total	pack-year < 5	5 <pack-year< 10	10 < pack-year < 20	pack-year > 20
Current	10 (32%)	9 (29%)	0	0	1 (3%)
Past	10 (32%)	5 (16%)	4 (13%)	1 (3%)	0
Never Smoker	10 (35%)	0	0	0	0

Workers were also asked questions about their personal cannabis and tobacco use. Frequency of different types of cannabis use is shown in Table 5. According to the table, 97% of the study population smoke cannabis, with 81% smoking multiple times a day. Frequency of tobacco smoking in this population is shown in Table 6. About one-third of workers were current smokers and about one third of workers smoked tobacco in the past.

Out of the 22 health symptom questions in the baseline questionnaire, 11 questions aimed to identify work-related health symptoms (Table 2). Examples of common work-related questions are: “does contact with certain materials, chemicals or anything else in your work makes your symptoms worse?” or “do your symptoms improve when you are away from your normal work?”

The prevalence of work-related dermal, ocular, nasal, and respiratory symptoms in 31 workers in this facility is shown in Figure 4. Overall prevalence of health symptoms is also shown for comparison (Figure 5).

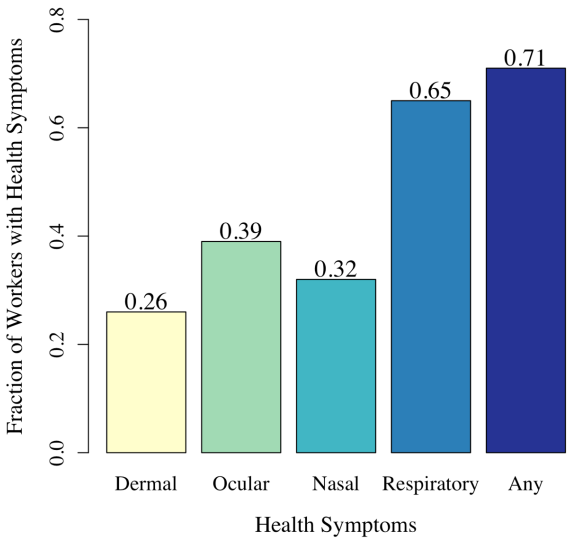

Figure 5: Prevalence of work-related health symptoms amongst cannabis worker (n=31), based on corresponding work-related questions. “Any” is an indicator of the prevalence across all symptom groups.

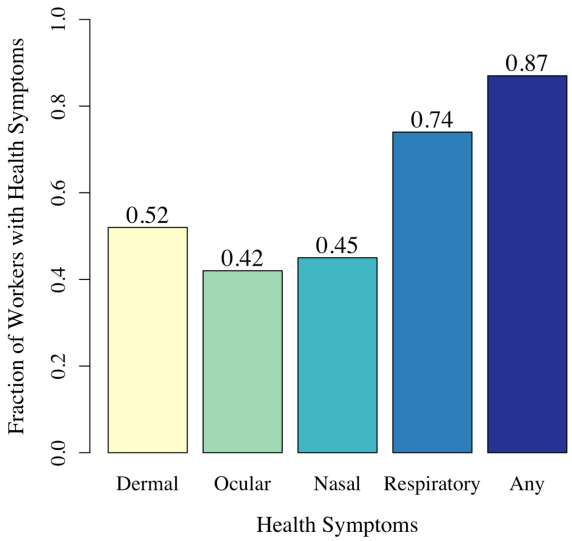

Figure 4: Prevalence of overall symptoms amongst cannabis workers (n=31), based on general symptom questions. “Any” is an indicator of the prevalence across all symptom groups.

For work-related symptoms, the highest symptom prevalence is respiratory, followed by ocular, nasal. Work-related dermal symptoms have the lowest prevalence amongst workers. For overall

symptom prevalence, the highest is respiratory, followed by dermal and nasal. Ocular symptoms have the lowest prevalence for overall symptoms amongst workers.

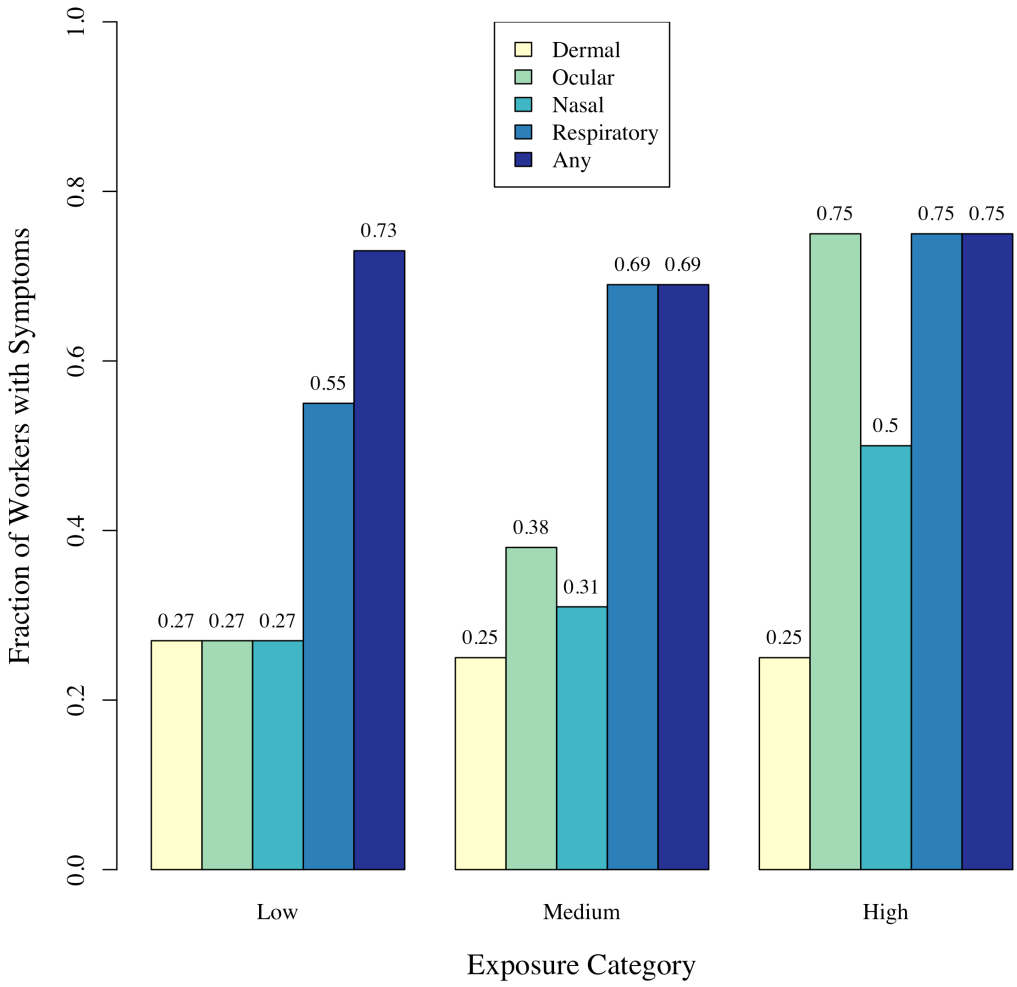

Figure 6: Prevalence of work-related health in each exposure (task) category.

As shown in Figure 6, the prevalence of respiratory, nasal and ocular symptoms are all higher in the medium and high exposure (task) categories, compared to the low exposure category. The presence of dermal symptoms is slightly lower in the medium and high exposure categories versus the low category. These results are consistent with the outcomes of the logistic regression models in Figure 7.

The odds ratios of low, medium, and high exposure categories are compared and shown in Figure 7. Odds ratios are extracted from the results of logistic regression models. More details on the results of all models can be found in Appendix I, Table 4.

The odds ratios of having work-related nasal symptoms increased with increasing exposure, as expected (Figure 7). The odds of having nasal symptoms increased, comparing low and medium exposures (1.33 [0.25 – 8.2]). The odds nearly tripled, comparing low and high exposures (2.7 [0.23-33]). Odds ratios had the same directions when adjusted for age alone, or adjusted for age, gender, and tobacco-smoke. However, confidence intervals had a wide range, so it was difficult to infer a positive association with certainty. The odds ratios of having work-related ocular and respiratory symptoms followed the same trend as the nasal symptoms.

The odds ratios of having "any" symptoms also increased with increasing exposure, as expected (Figure 7), but the increase was much smaller than the increase in odds of nasal, ocular, and respiratory symptoms. The odds of having "any" symptoms increased 3%, comparing low and medium exposures (1.03 (0.16-6.0)). The odds for any symptom increased 13%, comparing low and high exposures (1.13 (0.09-28)). Similar trends were seen when adjusting the model for age. However, when adjusting for age, gender, and tobacco smoke, odds of having symptoms increased only for the medium exposure category, and decreased for the high exposure category. As with the other symptoms, confidence intervals for "any" symptoms had a wide range, so it was difficult to infer a positive association with certainty.

Finally, odds of having dermal symptoms had an opposite direction to what was hypothesized *a priori* - the odds for dermal symptoms were lower in both the medium and high exposure categories compared to the low exposure category.

When adjusted for age, odds ratios changed only slightly from the unadjusted models for all but ocular symptoms, suggesting that the association between task and these symptoms was not greatly affected by age. The odds of ocular symptoms being in the high exposure category significantly increased when adjusted for age, suggesting that increase in age was associated with increase in work-related ocular symptoms. When adjusted for age, gender, and tobacco smoke, odds changed slightly, but the direction of association did not change except for the "any" symptom group. Odds of "any" symptom decreased comparing high to low exposure categories, when adjusted for age, gender, and tobacco smoke.

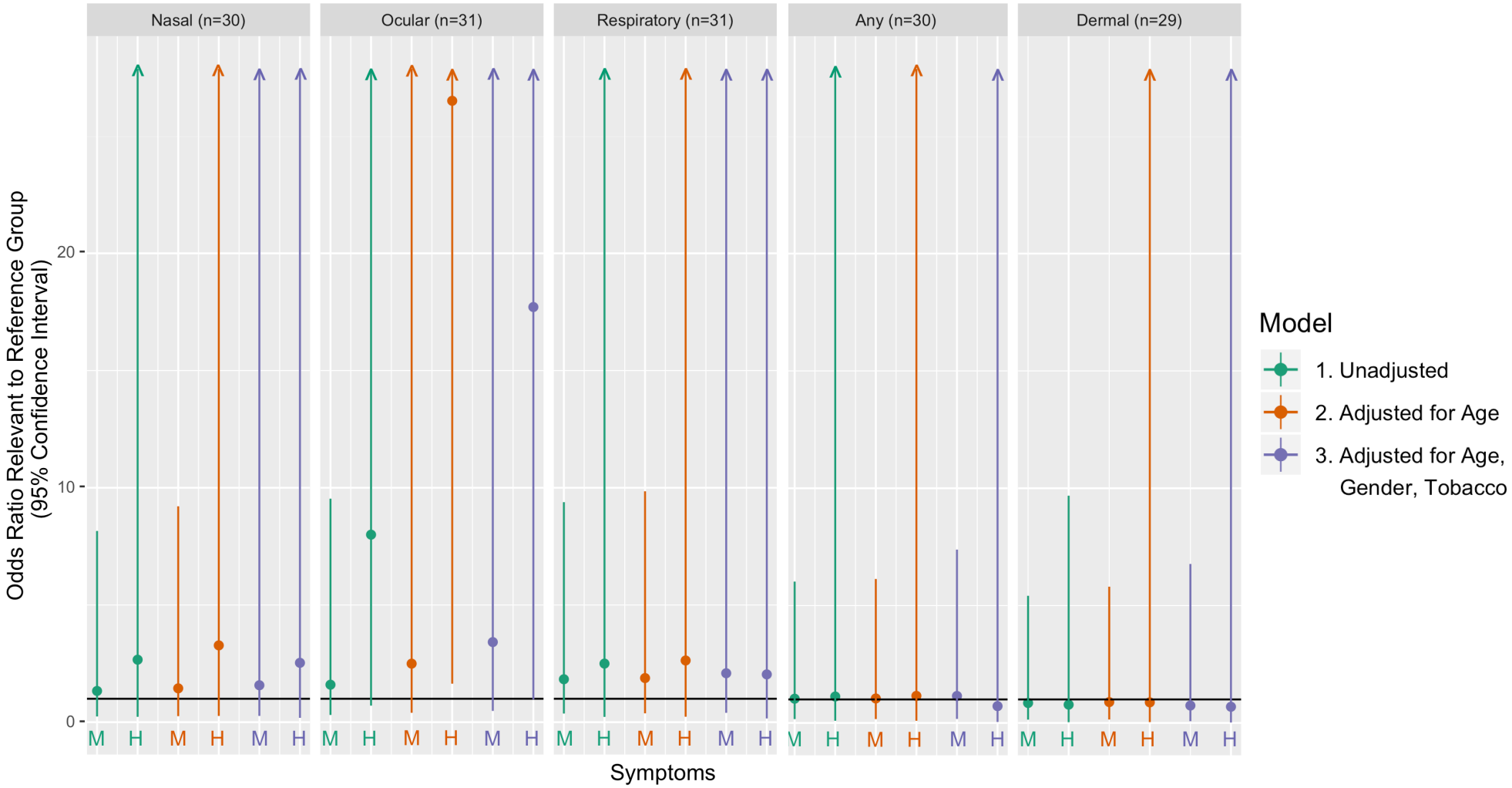

Figure 7: Odds ratios of association between exposure (task) and work-related nasal, ocular, respiratory, dermal, and any symptoms. Medium and high are odds ratios are relative of low exposure (reference).
↑: Confidence interval larger than 30

Phase 2 Results:

Ten workers with work-related symptoms were recruited (Figure 2) to participate in a sub-study cohort in which pre- and post-shift measurements of pulmonary function and airway inflammation were obtained for during two non-consecutive weeks (two Mondays and two Fridays). Demographic information of Phase 2 can be seen in Table 7. Phase 1 demographics are also shown for comparison. The majority of workers are Caucasian males. Four out of ten workers are current tobacco smokers and 10 out of 10 are cannabis smokers. Overall, the-sub cohort demographics reflect the larger study group in Phase 1.

Table 7: Demographic Characteristics (Phase 1 and 2)

	Phase 1 (n=31)	**Phase 2 (n=10)**
Gender		
Male	19 (61%)	7 (70%)
Female	12 (39%)	3 (30%)
Age		
Male	29.8 (± 6.2)	33.7 (± 13.2)
Female	33.2 (± 8.8)	30.3 (±9.2)
Race		
Caucasian	23 (74%)	8 (80%)
Hispanic/Latino	4 (13%)	2 (20%)
Alaskan Native	1 (3%)	0
Two or More	3 (10%)	0
Education Level		
No Schooling	0	0
Grade 1-11	2 (6%)	0
Completed High School	7 (23%)	2 (20%)
Some College But no Degree	9 (29%)	3 (30%)
Bachelor's Degree	11 (35%)	4 (40%)
Graduate/Professional School	2 (6%)	1 (10%)
Existing Medical Condition (Atopy)		
Asthma	8 (26%)	3 (30%)
Eczema	8 (26%)	4 (40%)
Hay Fever	7 (23%)	2 (20%)
Current Smoker		
Tobacco	10 (35%)	4 (40%)
Cannabis	30 (97%)	10 (100%)

Table 8: Summary of health measurements. Existing medical conditions or atopy (asthma, eczema, and hay fever) are extracted from specific questions in the baseline questionnaire.

Subject	Abnormal FeNO	Decreased Lung Function	Cannabis Sensitization	History of Asthma	History of Eczema	History of Hay Fever
4						
6						
9						
12						
13						
15						
19						
21						
23						
28						

Borderline FeNO High FeNO

Results of our health measurement are shown in Table 8:

- Two out of ten workers had abnormal FeNO and three had borderline FeNO.
- Seven workers demonstrated airway restriction or obstruction based on FVC and FEV_1 measurements.
- Five workers had cannabis sensitization. Out of six atopic workers, three demonstrated cannabis sensitization and three were not sensitized to cannabis.
- Four out of five workers with cannabis sensitization, demonstrated decreased lung function.
- Three workers demonstrated abnormal FeNO, decreased lung function, and cannabis sensitization. Two of these workers had a history of atopy.

Average FeNO, FVC and FEV_1 can be found in Appendix I, Table 5. Tests for common PNW molds were mostly negative with two exceptions: one subject had a mild reaction to *Helminthosporium* (weal <5mm) and another subject had a mild reaction to *Alternaria* (weal <5mm). More details on the severity of cannabis and mold sensitization can be found in Appendix I, Table 6.

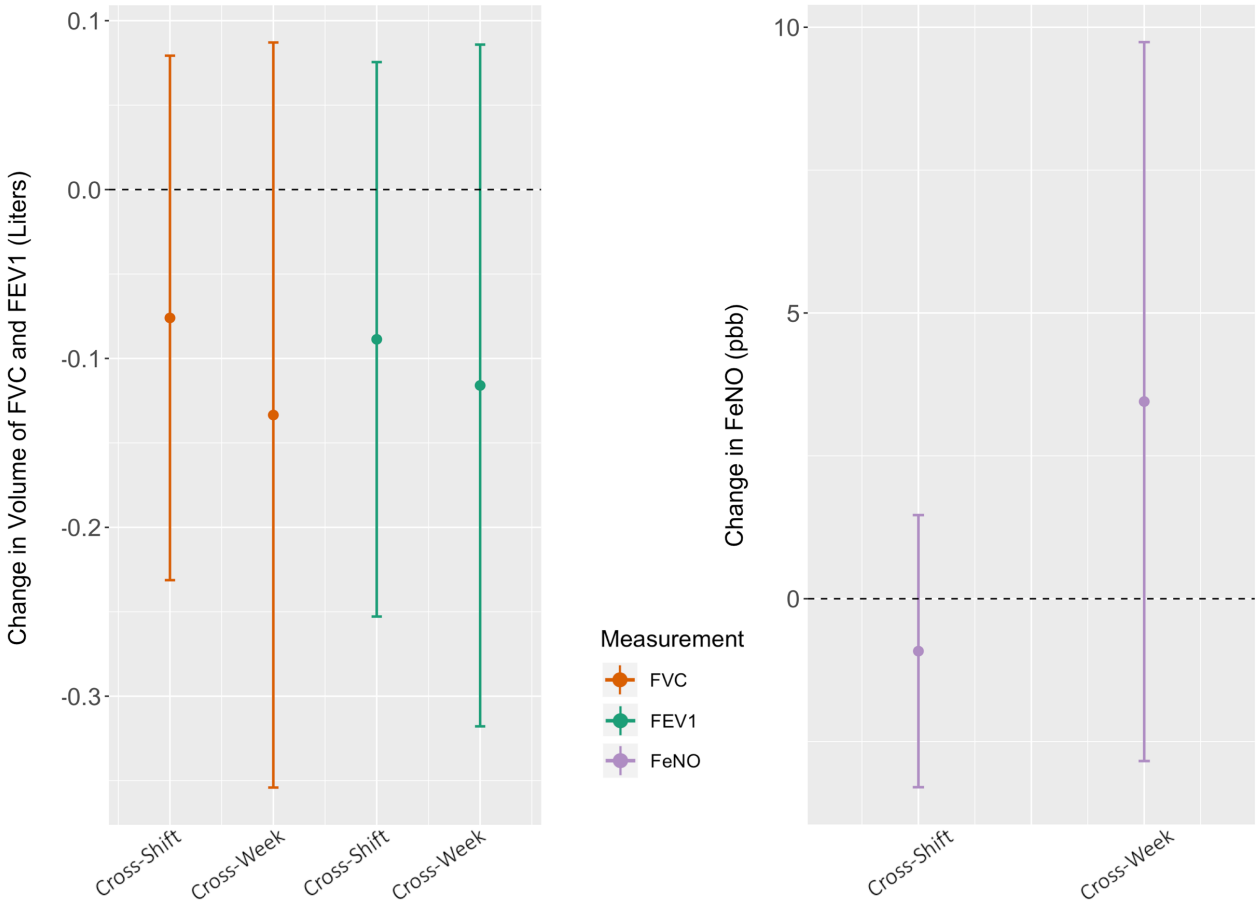

Figure 8: Cross-shift and cross-week changes in measurements of airway obstruction and inflammation in cannabis workers with work-related symptoms.

Changes in pre- and post-shift (cross-shift) as well as Monday morning and Friday evening (cross week) in measurements of FeNO, FVC, and FEV_1 were evaluated using linear regression models. The point estimates and their confidence intervals are shown in Figure 8.

Lung obstruction, which was determined based on measurements of FVC and FEV_1, was worse (decline in FEV_1 and FVC) comparing pre- and post-shift, and comparing Monday morning and

Friday evening. However, these changes were small and not statistically significant. The confidence intervals included no change in all four models.

FeNO decreased by 0.92ppb [CI: -3.3, 1.5 ppb] comparing pre- and post-shift, against what we hypothesized *a priori*. FeNO increased 3.5 ppb [CI: -2.8, 9.7 ppb], comparing Monday morning and Friday evening in the direction we hypothesized. However, both changes were small with wide confidence intervals, and not statistically significant.

In addition to cross-shift and cross-week, changes in pre-shift, post-shift, and difference of differences were also evaluated using linear regression models. Pre-shift was defined as change in health measurements comparing pre-shift on Friday minus pre-shift on Monday. Post-shift was defined as change in health measurements comparing post-shift on Friday minus post-shift on Monday. Difference of differences is defined as change in pre- and post-shift comparing Monday and Friday (i.e. (Fri-post – Fri-pre)-(Monday-post – Monday-Pre). Point estimates for these changes were not statistically significant, as with the cross-shift and cross-week changes. More details can be found in Appendix I, Figure 1 and Table 7. Models were also stratified by atopy and cannabis sensitization to evaluate point estimates in atopic and sensitized employees, respectively. In general, cross-shift and cross week changes in FeNO, FEV_1 and FVC were more pronounced in the hypothesized directions for subjects with cannabis sensitization, compared to subjects without cannabis sensitization. However, these changes were small with wide confidence intervals, and not statistically significant. (Appendix 1, Tables 8-10).

CHAPTER FOUR: DISCUSSION

Phase 1:

This pilot study is the first to evaluate health symptoms amongst cannabis workers in a legal cannabis production facility. In general, the prevalence of work-related dermal, nasal, ocular, and respiratory symptoms in cannabis workers in this facility was high (Figure 4). Respiratory symptoms had the highest prevalence among workers (71%) and dermal symptoms had the lowest (26%). Overall health symptoms had higher prevalence than work-related symptoms (Figure 4). However, these differences are less than 10% for ocular, nasal, and respiratory symptoms, indicating that most of these symptoms are indeed work-related.

Symptom prevalence was generally higher in our study population, compared to other similar studies. In a study on jute and hemp workers by Mukremin, 24% reported chest tightness, 20% reported cough, 11% reported dyspnea, and 5% reported wheezing at work [10]. In the same study, when asked about throat tickling, nasal itching, sneezing, eye burning, and skin itching, 11%-17% workers reported experiencing these symptoms. In a cross-sectional study in Colorado, cannabis workers were asked about their symptoms after handling pesticides [38]. Participants who worked in indoor, outdoor, and greenhouse grow operations, reported skin irritation (17.6%), eye irritation (13.4%), difficulty breathing (7%), and chest discomfort (5.9%). The prevalence of all health symptoms in the Colorado study is lower than the prevalence we observed in the current study.

In order to evaluate the association between exposure and work-related symptoms, task was used as a measure of exposure. Each task was allocated into one of three exposure categories, low, medium, and high. Each employee then was assigned to a single exposure category based on max percent-time spent on task(s) corresponding to that category.

Our results regarding the association between task and work-related symptom are compatible with a wide range of outcomes (Figure 7). However, the direction of association is as we predicted for ocular, nasal, and respiratory symptoms, and that is spending a majority of work-shift performing high exposure task(s) increases odds of having these symptoms. Our results were the opposite direction of what we predicted for dermal symptoms. Figure 6 shows the prevalence of each symptom by exposure category. The prevalence is higher for all symptoms in

high and medium categories except for dermal symptoms which is slightly lower. These results are compatible with the results from the dermal logistic regression models. For some work-related symptoms, we had one or two missing data points. For example, dermal symptoms had two missing data points which could potentially affect the direction of association due to small sample size.

Mukremin also compared byssinosis and local irritation symptoms in hemp and jute workers who work in sections with high versus low density of dust [10]. Significantly higher prevalence of chest tightness, dyspnea, and cough were observed in workers in sections with high density of dust ($p = 0.01$). A significant increase was also observed in all local irritation symptoms, including skin and eye irritation, difficulty breathing, and chest discomfort. However, the two exposure categories (high vs. low dust density) were determined using dust concentrations in multiple sections of the factory rather than by task [10]. Even though our results were not statistically significant, the direction of association for local irritation symptoms and respiratory symptoms are compatible with the results in the study described above.

Because we had very few task-based exposure measurements (Statistical Analysis, aim 1b), our assignment of some of the tasks into specific exposure categories is at best an educated guess. This is because the nature of working in this facility required workers to rotate among different tasks depending on demand, and these rotations could differ day by day. The question "Please indicate typical % time spent on each task" was intended to capture exposure, but because of task rotation about 75% of workers were typically responsible for more than one task. In addition, we haven't specified exposure for our analyses. A task could be high for one exposure (e.g. VOCs), but not high for particulate matter, or vice-versa.

Another reason for exposure misclassification is using max percent-time to assign workers to low, medium, or high exposure categories. Max percent-time might not truly capture worker exposure because some workers might spend 20% of time performing high exposure tasks and 80% of the time performing low exposure tasks. It is possible that the workers' symptoms occur when they are performing high exposure tasks, but they are classified in the low exposure category because of the 80% they spend performing low exposure tasks.

In addition, some of the low, medium, and high exposure tasks in this facility were performed in the same room within a large warehouse. Pre-roll was the main task performed in this large room. Usually, 6-8 workers were performing this task at one time. In the same room, 10-20 feet away from the pre-roll tables, high exposure tasks such as knockbox and grinding were also performed. In addition, about eight computer desks were located in this room, where workers performed office tasks. Figure 9 shows approximate locations of these tasks. It is possible that workers who mainly performed low exposure tasks, experienced symptoms when high exposure tasks were performed in close proximity to them.

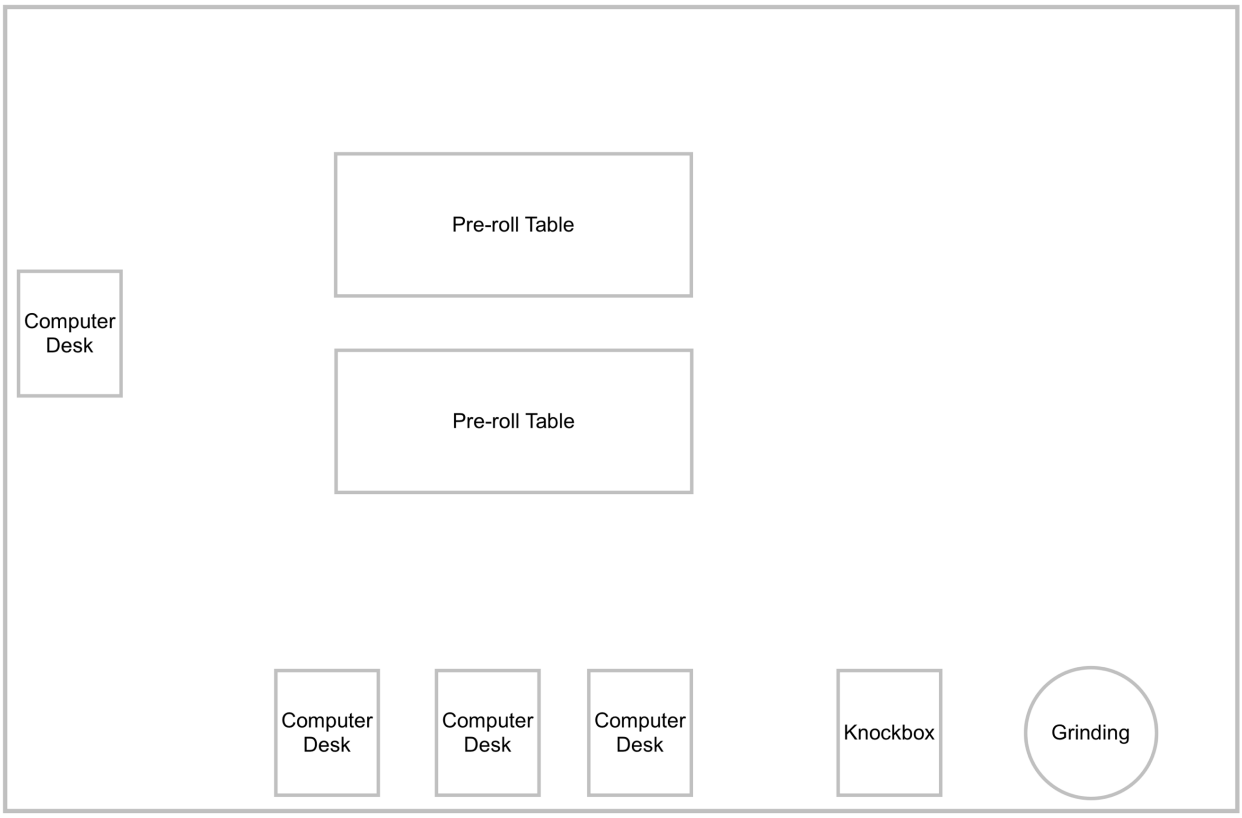

Figure 9: Approximate locations of each task performed in a large room within the facility. Computer task (low), pre-roll (medium), and knockbox and grinding (high) were all performed in the same room.

Phase 2

Overall, the demographic characteristics of participants in Phase 2 reflect the Phase 1 population. Because we selected for workers with symptoms, this subset of workers had at least one or more work-related symptom(s).

Based on health measurements conducted in a period of two weeks, two out of ten workers had abnormal fractional exhaled nitric oxide (FeNO) and an additional three had borderline FeNO (Table 8). According to ATS, high FeNO is likely to indicate significant airway eosinophilia. In symptomatic individuals, high FeNO could mean that the patient has steroid-responsive airway inflammation [41]. Borderline airway inflammation (FeNO 25-50ppb) and normal (< 25 ppb) should be interpreted cautiously, especially in this population, because of high prevalence of cannabis smoke. Multiple studies demonstrated that the peak FeNO concentration is significantly lower in smokers than that in controls [47] [48]. Although these studies investigated tobacco smokers, this could also be relevant in our population because of the high prevalence of cannabis smoking (100%). This could mean that FeNO measurements might underestimate airway inflammation in our population.

According to spirometry measurements, seven out of ten workers had decreased lung function as a result of airway restriction and/or obstruction. The high prevalence of decreased lung function amongst these workers, however, is not fully attributable to working in this facility because we did not have baseline measurements of lung function for these workers prior to their starting work at this facility. Furthermore, since all these workers smoked cannabis, it is not clear the extent to which their personal smoking behaviors contributed to their impaired lung function.

Finally, five out of ten (50%) workers had cannabis sensitization (Table 8) determined by skin prick testing of two strains of cannabis. All five workers had an allergic reaction to both strains. Of five research scientists on our study team who were also tested for cannabis sensitivity, none exhibited a positive response. In addition, 100% of participants in our study are cannabis consumers, thus cannabis sensitization observed in this group cannot be solely attributed to working in a cannabis production facility. In fact, a study on allergic hypersensitivity to cannabis in illicit drug users reported the highest levels of positive cannabis skin prick test in habitual and dependent cannabis consumers (60% combined) [49]. Non-consumers, on the other hand, had a lower percentage of positive skin prick test (29%). However, the control group participants in this study were specifically selected from asthmatic patients with atopy, thus cross-reactivity with these two risk factors is possible. Cross-reactivity of cannabis sensitivity with allergenic compounds such as non-specific lipid transfer proteins or thaumatin-like proteins present in most

plants is previously reported [24]. Cross-reactivity is a possibility in our study, too, as 60% of workers had a history of asthma or atopy.

Skin test reactivity has been associated with low FEV_1/FVC ratios, especially in current and former smokers [50]. Thus, it was not surprising to see that in five workers with cannabis sensitization, four had decreased lung function. According to our study physician, we can be confident in saying that these participants showing obstruction in lung function testing and positive cannabis sensitization had work-related asthma. To truly distinguish asthma from COPD or other lung diseases, lung function improvement with a bronchodilator (albuterol) must be observed. However, it is very significant that we saw that most people with allergic reaction to cannabis had either airflow obstruction or an abnormal FeNO.

Cross-shift and cross-week changes in FeNO, FVC, and FEV_1 were small and indicated no change in these health measurements. Results were similar for changes in pre-shift, post-shift, and difference of differences (Appendix I, Table 7). We chose to stratify our population by atopy because, as mentioned previously, atopy has been described as a risk factor for decreased lung function, especially amongst current and former tobacco smokers [50]. It was reasonable to stratify by these two risk factors as 100% of our study participants were cannabis smokers. We stratified by cannabis sensitization for the same reason. In general, cross-shift and cross week changes in FeNO, FEV_1 and FVC were more pronounced in the hypothesized directions for subjects with cannabis sensitization, compared to subjects without cannabis sensitization. However, these changes were small with wide confidence intervals, and not statistically significant. Overall, results of our analyses did not provide strong evidence for acute changes in FeNO, FVC, and FEV_1 in this small sub-study cohort, even though five of 10 workers showed evidence of chronically elevated FeNO and seven of ten showed evidence of chronically decreased lung function.

A high prevalence of acute and chronic decrease in lung function was previously reported in hemp workers of two mills [13]. Acute change in lung function was assessed by cross-shift measurements of FVC and FEV_1 on a Monday and all changes were found to be statistically significant, unlike our findings. The chronic decrease of lung function, however, was less prevalent in hemp workers (3%-11%) than that of cannabis workers of our study. One possible

explanation for incompatibility between these results could be the fact that we selected for workers with at least one work-related respiratory symptom. Smoking cannabis could be another reason for increase in prevalence of chronically decreased lung function.

Limitations and Future Studies

There are several limitations associated with this pilot study:

First, the study population was small which limited the power of the statistical analyses and the robustness of our study findings. Future studies should consider recruiting a larger number of workers for their studies.

Second, 97% of the study population were cannabis smokers, with 81% smoking multiple times a day. Because of the high prevalence of cannabis smokers in our study, we couldn't account for the role of smoking cannabis in our analyses. Future studies should consider recruiting workers who don't smoke cannabis in addition to workers who do, to be able to account for this variable.

Third, we used "task category" (high/low or high/medium/low) as a measure of exposure to cannabis. This might not truly capture workers' exposure because of variation in exposure amongst tasks within a single task category, and variation of exposure within a single task. This might have led to exposure misclassification in establishing the association between tasks and symptoms. For example, office tasks were placed into the "Low" exposure category, but based on observations, some office desks were located in the warehouse in close proximity to areas where "Medium" and "High" exposure tasks were also performed. Future studies should consider recruiting workers who are more specialized in one task if task is used as a measure of exposure. Measurement of airborne contaminant concentrations using either area or personal samplers is another, more accurate, way to measure (or estimate) individual exposures.

Fourth, this study was conducted in only one indoor growing facility which might not be representative of other indoor facilities, nor of the overall cannabis production industry which includes indoor, outdoor and shade house grows of a variety of sizes. Future studies should consider doing their measurements in multiple facilities in order to capture a wider range of

growing methods and scales of productions, such that the study conclusions would be more generalizable.

Last, our Phase 2 (repeated measures) study was designed primarily to assess acute or short term (cross-shift and cross-week) changes in lung function. However, we found that a significant proportion of workers had chronically elevated airway inflammation, or chronically impaired lung function. Our findings may have been biased by the healthy worker effect, in that workers who developed more severe respiratory illness may have self-selected out of the industry, or out of the highest exposure category tasks. Anecdotally, we were told of several workers who left the industry on account of chronic respiratory symptoms. Future studies could engage an inception cohort of workers without prior cannabis exposure, and follow these workers longitudinally over time, to evaluate whether respiratory symptoms and cannabis sensitization develop in response to occupational exposure to cannabis.

CHAPTER FIVE: CONCLUSIONS

The high prevalence of work-related symptoms, cannabis sensitization and impaired lung function observed in our study, raises the possibility that occupational exposures to cannabis are harmful to workers in this industry.

Given the nascent nature of the legality of recreational cannabis, it will likely take a long time to establish standards and regulations to protect cannabis workers. In the meantime, a few preventive measures can be implemented to reduce worker exposure to high levels of cannabis. For example, cannabis dust-generating tasks, such as the knockbox can be automated to where there's no need for workers to be close to the instrument. Another dust-generating task was sifting to separate out small plant parts from the flowers. Worker exposure can be reduced by mechanizing this process, and placing an enclosure equipped with local exhaust ventilation around the device.

In this specific facility, some of the low, medium, and high exposure tasks were performed in the same room within a large warehouse. For example, a few computer tasks (low exposure) were located near high dust-generating areas in the warehouse. Removing those workers away from the warehouse can limit exposure to a fewer number of workers. In general, all dust-generating tasks should be isolated to lessen exposures to workers in lower-risk tasks. If higher-risk tasks are isolated, local exhaust can be used more effectively to further limit exposures.

Finally, proper use of personal protective equipment (PPE) can be adopted from other industries to further reduce exposure. In some cases, workers in this facility used a bandana as a dust mask which does not prevent them from being exposed to cannabis dust. The employer should consider implementing a respiratory protection program to ensure that all workers are protected from respiratory hazards properly. Workers in this facility were provided with respirators, but there was no respiratory protection program to ensure that the respirator was correctly selected or fit-tested. A respiratory protection program includes a respirator selection process, medical evaluation, fit testing, and training for correct use of the respirator. In addition, program's effectiveness should be regularly evaluated by on-going monitoring of lung function.

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Works Cited

[1] M. Booth, Cannabis: A History, London: Transworld Publishers, 2003.

[2] A. Hazekamp, J. T. Fischedick, M. L. Diez, A. Lubbe and R. L. Ruhaak, "Chemistry of Cannabis," in *Comprehensive Natural Products II: Chemistry and Biology*, Leiden, Elsevier Ltd, 2010, pp. 1034-1077.

[3] J. Cox, "The marijuana industry looks like the fastest-growing job market in the country," CNBC, 2019.

[4] J. Hudak, Marijuana, A Short History, Washington: Brookings Institution Press, 2016.

[5] Washington State Liquor and Cannabis Board, "Annual Report Fiscal Year 2018," Washington State Liquor and Cannabis Board, Olympia, 2018.

[6] Washington State Liquor and Cannabis Board, "Marijuana Licensing," Washington State Liquor and Cannabis Board, 2018. [Online]. Available: https://lcb.wa.gov/mjlicense/marijuana-licensing. [Accessed 12 March 2019].

[7] Washington State Liquor and Cannabis Board, "Marijuana Dashboard," 2018. [Online]. Available: https://data.lcb.wa.gov/stories/s/WSLCB-Marijuana-Dashboard/hbnp-ia6v/. [Accessed 2019].

[8] A. Bouhuys, A. Barbero, S. Lindell, S. Roach and R. S. F. Schilling, "Byssinosis in Hemp Workers," *Archives of Environmental Health: An International Journal,* vol. 14, no. 4, pp. 533-543, 1976.

[9] J. M. Mcpartland, "Byssinosis in Hemp Mill Workers," *Journal of Industrial Hemp,* vol. 8, no. 1, pp. 33-44, 2003.

[10] E. Mukremin, A. E. Salih, U. D. Ahmet, S. T. Peter, K. Yalcin and B. Nazmi, "Byssinosis and COPD Rates Among Factory Workers Manufacturing Hemp and Jute," *International Journal of Occupational Medicine and Environmental Health,* vol. 29, no. 1, pp. 55-68, 2016.

[11] B. Ramazzini, De Morbis Artificum Diatriba [Diseases of Workers], Chicago: Chicago University Press, 1940.

[12] Z. E. Bouhuys A., "Chronic Respiratory Disease in Hemp Workers: A Follow-up Study," *Annals of International Medicine,* vol. 84, pp. 398-405, 1976.

[13] E. Zuskin, B. Kanceljak, D. Pokrajac, E. Schahter and T. Witek, "Respiratory Symptoms and Lung Function in Hemp Workers," *British Journal of International Medicine,* vol. 47, pp. 627-632, 1990.

[14] A. Hazekamp, J. T. Fischedick, M. L. Diez, A. Lubbe and R. L. Ruhaak, "Comprehensive Natural Products Chemistry II," in *Chemistry of Cannabis*, Second ed., The Netherlands, Oxford: Elsevier Ldt, 2010, pp. 1033-1084.

[15] J. R. Edwardson, "Hops: Their Botany, History, Production and Utilization," *Economic Botany,* vol. 6, no. 2, pp. 160-175, 1952.

[16] C. Skórska, B. Mackiewicz, A. Góra, M. Golec and J. Dutkiewicz, "Health effects of inhalation exposure to organic dust in hops farmers," *Annales Universitatis Mariae Curie-Sklodowska. Sectio D: Medicina,* vol. 58, no. 1, pp. 459-65, 2003.

[17] A. Garcia, "Occupational rhinoconjunctivitis due to hops exposure in a brewery worker," *The Journal of Allergy and Clinical Immunology,* vol. 113, no. 2, p. S62, 2004.

[18] J. D. Radoslaw Spiewak, "Occupational airborne and hand dermatitis to hop (Humulus lupulus) with non-occupational relapses," *Annals of Agricultural and Environmental Medicine,* vol. 9, no. 2, pp. 249-252, 2002.

[19] R. Spiewak, A. Gòra and J. Dutkiewicz, "Work-related Skin Symptoms and Type I Allergy Among Eastern-Polish Farmers Growing Hops and Other Crops.," *Annals of Agricultural and Environmental Medicine,* vol. 8, no. 1, pp. 51-56, 2001.

[20] C. Reeb-Whitaker and D. Bonauto, "Respiratory Disease Associated with Occupational Inhalation to Hop (Humulus lupulus) During Harvest and Processing.," *Annals of Allergy, Asthma, and Immunology,* vol. 113, no. 5, pp. 534-538, Nov 2014.

[21] M. Davidson, R. Reed, J. Oosthuizen, G. O'Donnell, P. Gaur, M. Cross and G. Dennis, "Occupational health and safety in cannabis production: an Australian perspective," *International Journal of Occupational and Environmental Health,* vol. 24, pp. 75-85, 2018.

[22] Colorado Department of Public Health and Environment, "Guide to Worker Safety and Health in the Marijuana Industry," Colorado Department of Public Health and Environment.

[23] J. W. Martyny, K. A. Serrano, J. W. Schaeffer and M. V. Van Dyke, "Potential Exposures Associated with Indoor Marijuana Growing Operations," *Journal of Occupational and Environmental Hygiene,* 2013.

[24] I. I. Decuyper, A. Van Gasse, M. Antje Faber, C. Mertens, J. Elst, H.-P. Rihs, V. Sabato, H. lapeere, M. Hagendorens, C. Bridts, L. De clerck and D. Ebo, "Occupational Cannabis Exposure and Allergy Risks," *Occupational and Environmental Medicine,* vol. 76, pp. 78-82, 2019.

[25] D. Fishwick, L. J. Allan, A. Wright and A. D. Curran, "Assessment of Exposure to Organic Dust in a Hemp Processing Plant," *Annals of Occupational Hygiene,* vol. 45, no. 5, pp. 577-583, 2001.

[26] T. P. P. N. H. D. Douwes J, "Bioaerosol Health Effects and Exposure Assessment: Progress and Prospects," *Annals of Occupational Hygiene,* vol. 47, no. 3, pp. 187-200, 2003.

[27] M. J. Nieuwenhuijsen, K. S. Noderer, M. B. Schenker, V. Vallyathan and S. Olenchock, "Personal Exposure to Dust, Endotoxin and Crystalline Silica in California Agriculture," *Annals of Occupational Hygiene,* vol. 43, no. 1, pp. 35-42, 1999.

[28] A. Adhikari, J. Gupta, J. R. Wilkins, R. L. Olds, R. Indugula, K. J. Cho, C. Li and M. Yermakov, "Airborne Microorganisms, Endotoxin, and (1 -> 3)-beta-D-Glucan Exposure in Greenhouses and Assessment of Respiratory Symptoms Among Workers," *Annals of Occupational Hygiene,* vol. 55, no. 3, pp. 272-285, 2011.

[29] M. W. Giese, M. A. Lewis, L. Giese and K. M. Smith, "Development and Validation of a Reliable and Robust Method for the Analysis of Cannabinoids and Terpenes in Cannabis," *Journal of AOAC International,* vol. 98, pp. 1503-1522, 2015.

[30] J. Couch, D. Wiegand, G. R. Grimes, B. J. Green, A. R. Lemons, E. Glassford, L. Zwack, S. R. Jackson and D. Beezhold, "Evaluation of a Medicinal Cannabis Manufacturing Facility with an Indoor and Outdoor Grow Operation," National Institute for Occupational Safety and health, 2018.

[31] Safety and Health Assessment and Research for Prevention, "Injury and Illness in the Emerging Legal Cannabis Industry," Washington State Workers' Compensation Claims, Washington State, 2017.

[32] J. Couch, K. Victory, B. Lowe, N. C. Burton, B. J. Green, A. Nayak, A. R. Lemons and D. Beezhold, "Evaluation of Potential Hazards during Harvesting and Processing Cannabis at an Outdoor Organic Farm," Health Hazard Evaluation Report , Atlanta , 2017.

[33] W. Popp, L. Ritschka, H. Zwick and H. Rauscher, "Berry sorter's lung or wine grower's lung – an exogenous allergic alveolitis caused by Botrytis cinerea spores," *Prax Klin Pneumol,* vol. 41, no. 5, pp. 165-169, 1987.

[34] T. Herzinger, F. Ruëff, P. Schöpf and B. Przybilla, "IgE-Mediated Hypersensitivity Reactions to Cannabis in Laboratory Personnel," *Journal of Allergy and Clinical Immunology,* vol. 119, no. 1 , p. S21, 2007 .

[35] M. Mayoral, H. Calderon, R. Cano and M. Lombardero, "Allergic rhinoconjunctivitis caused by Cannabis sativa pollen," *Journal Of Investigational Allergology And Clinical Immunology,* pp. 73-74, 2008 .

[36] Deloitte Access Economics, "Modelling the cost of Medicinal Cannabis," Department of Health – Office of Drug Control, 2016.

[37] L. I. Johnson and D. J. Miller, "Consequences of Large-Scale Production of Marijuana in Residential Buildings," *Indoor and Built Environment ,* vol. 21, no. 4, pp. 595-600, 2012.

[38] K. M. Walters, G. G. Fisher and L. Tenney, "An Overview of Health and Safety in the Colorado Cannabis Industry," *American Journal of Industrial Medicine,* pp. 451-461, 2018.

[39] M. Chmielinski, *Ultraviolet and Visible Light Exposure Among Indoor Agricultural Workers,* Seattle: University of Wahington, 2016.

[40] P. Burney, C. Luczynska, S. Chinn and D. Jarvis, "The European Community Respiratory Health Survey.," vol. 7, no. 5, pp. 954-60, May 1994.

[41] R. A. Dweik, P. B. Boggs, S. C. Erzurum, C. G. Irvin, M. W. Leigh, J. O. Lundberg, A.-C. Olin, A. L. Plummer and D. R. Taylor, "An Official ATS Clinical Practice Guideline:

Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications," *American Thoracic Society Documents,* vol. 184, pp. 602-615, May 2011.

[42] CIRCASSIA, *NIOXVERO® Airway Inflammation Monitor User Manual,* CIRCASSIA, 2017.

[43] M. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C. van der Grinten, P. Gustafsson, R. Jensen, D. Johnson, N. MacIntyre, R. McKay, D. Navajas, O. Pedersen, R. Pellegrino, G. Viegi and J. Wanger, "Standardisation of spirometry," *European Respiratory Journal,* vol. 26, pp. 319-338, 2005.

[44] T. Robins, N. Seixas, A. Franzblau, L. Abrams, S. Minick, H. Burge and A. Schork, "Acute Respiratory Effects on Workers Exposed to Metalworking Fluid Aerosols in an Automotive Transmission Plant," *American Journal of Industrial Medicine,* vol. 31, pp. 510-524, 1997.

[45] R. Pellegrino, G. Viegi, V. Brusasco, R. Crapo, F. Burgos, R. Casaburi, A. Coates, C. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. MacIntyre, R. McKay, M. Miller, D. Navajas, O. Pedersen and J. Wanger, "Interpretative Strategies for Lung Function Tests," *European Respiratory Journal,* vol. 26, no. 5, pp. 948-68, Nov 2005.

[46] B. Silvey, *Characterization of Occupational Exposure to Airborne Contaminants in an Indoor Cannabis Production Facility,* Seattle: University of Washington, 2019.

[47] M. Persson, O. Zetterstrom, V. Agrenius, E. Ihre and L. Gustafsson, "Single-breath Nitric Oxide Measurements in Asthmatic Patients and Smokers," *The Lancet,* vol. 343, pp. 146-147, 1994.

[48] R. Robbins, T. Millatmal, K. Lassi, S. Rennard and D. Daughton, "Smoking Cessation Is Associated with an Increase in Exhaled Nitric Oxide.," vol. 112, pp. 313-318, 1997.

[49] A. Armentiae, J. Castrodezaa, P. Ruiz-Munozb, J. Martínez-Quesadac, I. Postigoc, M. Herreroe, M. Gonzalez-Sagradod, D. de Luisd, B. Martín-Armentiad and J. Guisantes, "Allergic Hypersensitivity to Cannabis in Patients with Allergy and Illicit Drug Users," *Allergologia et Immunopathologia,* vol. 39, no. 5, pp. 271-279, 2011.

[50] B. Burrows, M. D. Lebowitz and R. A. Barbee, "Respiratory Disorders and Allergy Skin Test Reactions," *Annals of Internal Medicine,* vol. 74, no. 2, pp. 134-139, 1376.

[51] T. Ocampo and T. Rans, "Cannabis Sativa: The Unconventional “Weed” Allergen," *Annals of Allergy, Asthma, and Immunology,* vol. 114, pp. 187-192, 2015.

APPENDIX I: Supplemental Tables and Figures

Table 1: Dates health measurements were obtained for each employee. Subject 15 missed a post-shift measurement on December 14th, so a third week of measurements were obtained for that subject.

	Week 1		Week 2		Week 3		Week 4	
	Monday	Friday	Monday	Friday	Monday	Friday	Monday	Friday
Subject ID	Dec 3rd 2018	Dec 7th 2018	Dec 10th 2018	Dec 14th 2018	Jan 14th 2019	Jan 18th 2019	Jan 21st, 2019	Dec Jan 25th 2019
4			x	x			x	x
6			x	x			x	x
9	x	x			x	x		
12					x	x	x	x
13	x	x			x	x		
15	x	x	x	x	x	x		
19					x	x	x	x
21	x	x					x	x
23	x	x	x	x				
28			x	x				

Table 2: List of quality grades for spirometry tests. Quality grades help the operator to assess the quality of a completed test.

Rating	Criteria
A	At least 3 acceptable trials (for age 6 and under: 2 acceptable) AND the difference between the best two FEV_1 and FVC values is equal to or less than 100 mL (80 mL if FVC < 1.0 L) (for age 6 and under: 80 mL or 8% of FVC or FEV_1 whichever is greater)
B	At least 3 acceptable trials (for age 6 and under: 2 acceptable) AND the difference between the best two FEV_1 and FVC values is equal to or less than 150 mL (100 mL if FVC < 1.0 L) (for age 6 and under: 100 mL or 10% of FVC or FEV_1 whichever is greater)
C	At least 2 acceptable trials AND the difference between the best two FEV_1 and FVC values is equal to or less than 200 mL (150 mL if FVC < 1.0 L) (for age 6 and under: 150 mL or 15% of FVC or FEV_1 whichever is greater)
D (1)	At least 2 acceptable trials but the results are not reproducible according to 'C'. Quality message: *Result not reproducible*
D (2)	Only one acceptable trial Quality message: *Only one acceptable trial*
F	No acceptable trial available

Table 3: Task Description

Task	Description
Office	Performing administrative or sales duties
Inventory	Record keeping for materials to make sure that the inventory is well-stocked
Delivery	Delivering products to retail shops
Internal Interview	Interviewing employees for internal jobs
Picking Order	Finding products from the warehouse to fulfill customer orders
Order Fulfillment	Processing products from point of sales inquiry to delivery to the customer
Waste Disposal	Disposing of any unwanted materials
Labeling	Labeling products, such as packaged flowers, tubed pre-roll joints, and concentrates
Cleaning	General cleaning of the facility
Packaging	Packaging flowers and other products
Weighing	Weighing flowers, concentrates, and oils for packaging
Hand-trimming	Shaping and forming sellable buds from the newly bucked plants
Pre-roll	Filling and compacting pre-rolled cones by hand
Tubing	Placing two rolled joints into their packaging at a time until the lot is depleted
Spraying	Spraying plants with pesticides
Growing	General pruning
Plant Survey	Checking plants quality
Transferring Plants	Transferring plants from one grow room to another when the plants reached a certain grow stage
Consolidating	Combining materials for delivery
Spinning	Verifying the weight of pre-rolled joints and tapping down the ground leaf and spinning them in order to form a flag used for lightening them with the excess paper
Sifting	Separating out undesired plant materials, such as leaves and stems using a sift box
Grinding	Grinding dried flowers to a coarse powder to be used in pre-roll joints, concentrates, and oils.
Knock Box	Filling and compacting pre-rolled cones using the knockbox instrument
Harvesting	Removing large stems from fully mature plants and hang them to dry

Table 4: Results of Logistic Regression Models

Symptom	Type	Exposure	Odds Ratio	95% CI	P-value
Dermal	Unadjusted	M	0.85	0.14 - 5.4	0.86
		H	0.78	0.031 - 9.7	0.85
	Adjusted for age	M	0.89	0.15 - 5.8	0.90
		H	0.88	0.034 - 12	0.92
	Adjusted for age, sex, tobacco	M	0.74	0.075 - 6.8	0.78
		H	0.69	0.019 - 15	0.81
Ocular	Unadjusted	M	1.6	0.31 - 9.5	0.58
		H	8.0	0.71 - 203	0.12
	Adjusted for age	M	2.5	0.40 - 19	0.34
		H	27	1.6 - 1030	0.037 *
	Adjusted for age, sex, tobacco	M	3.4	0.49 - 35	0.25
		H	18	0.97 - 760	0.077
Nasal	Unadjusted	M	1.3	0.25 - 8.2	0.74
		H	2.7	0.23 - 33	0.42
	Adjusted for age	M	1.4	0.26 - 9.2	0.68
		H	3.3	0.27 - 45	0.34
	Adjusted for age, sex, tobacco	M	1.6	0.27 - 11	0.62
		H	2.5	0.19 - 37	0.47
Respiratory	Unadjusted	M	1.8	0.37 - 9.4	0.46
		H	2.5	0.23 - 60	0.48
	Adjusted for age	M	1.9	0.38 - 9.9	0.44
		H	2.6	0.24 - 64	0.46
	Adjusted for age, sex, tobacco	M	2.1	0.40 - 12	0.38
		H	2.0	0.16 - 52	0.60
Any	Unadjusted	M	1.0	0.16 - 6.0	0.97
		H	1.1	0.091 - 28	0.93
	Adjusted for age	M	1.0	0.16 - 6.1	0.96
		H	1.2	0.091 - 29	0.92
	Adjusted for age, sex, tobacco	M	1.1	0.17 - 7.4	0.88
		H	0.72	0.043 - 20	0.82

Table 5: Average FeNO, FVC, and FEV_1 for each subject

Subject ID	FeNO	FVC	% Predicted (FVC)	FEV_1	% Predicted (FEV_1)	FEV_1/FVC	% Predicted (Ratio)
4	27.9	4.91	100	4.35	106	0.89	107
6	18.9	5.77	107	3.99	96	0.69	89
9	34.8	5.52	98	3.83	84	0.69	85
12	17.4	6.02	104	4.92	105	0.82	100
13	10.0	5.51	98	4.53	99	0.82	101
15	16.1	4.03	108	3.17	98	0.78	91
19	25.4	3.80	73	2.76	69	0.73	95
21	18.1	3.18	76	2.22	66	0.70	85
23	64.9	3.85	101	2.62	79	0.68	78
28	90.0	5.05	96	3.83	87	0.76	91

Table 6: Prevalence and severity of cannabis and mold sensitization for each subject

	Mold				Cannabis	
Subject ID	**Helminthosporium**	**Alternaria**	**Penicillium**	**Aspergillus**	**Fruity Pebbles**	**Durban Poison**
4	0	0	0	0	2	3
6	0	0	0	0	0	0
9	0	1	0	0	4	4
12	0	0	0	0	0	0
13	0	0	0	0	4	4
15	0	0	0	0	0	0
19	0	0	0	0	0	0
21	0	0	0	0	0	0
23	1	0	0	0	4	3
28	0	0	0	0	4	4

1: wheel present
2: wheel 5-7 mm, erythema > 10 mm
3: wheel 7-10 mm, erythema > 20 mm
4: wheel > 10 mm, erythema > 30 mm

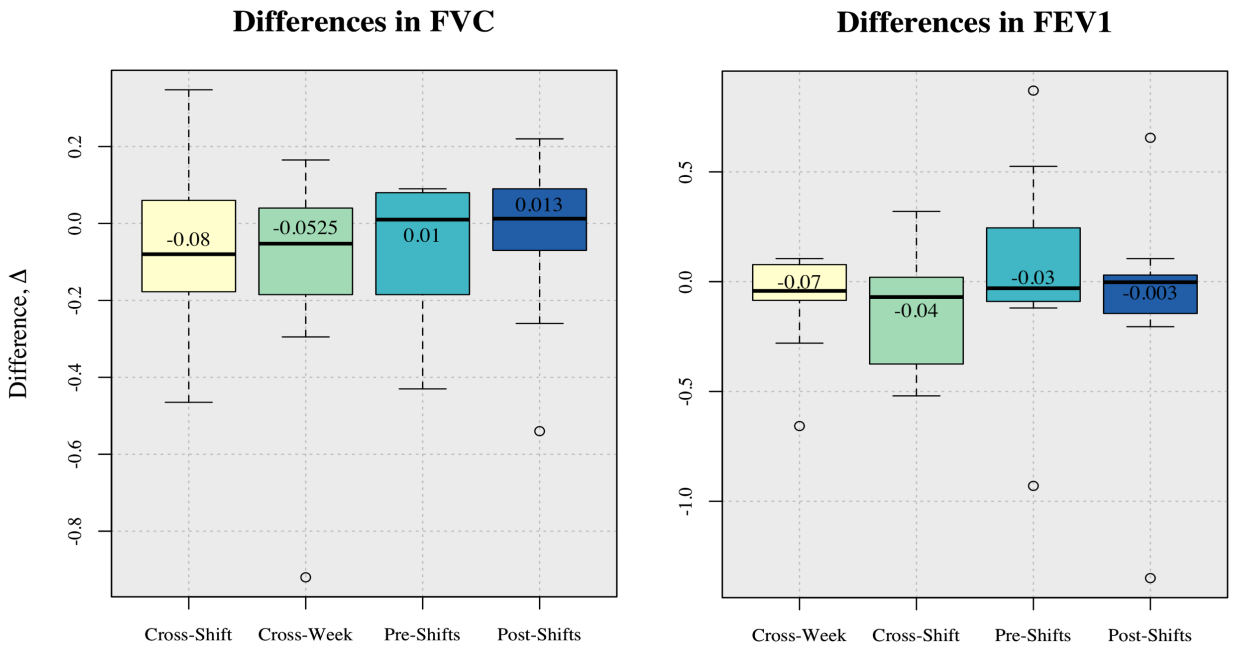

Figure 1: Cross-shift, cross-week, pre-shift, and post-shift changes in FVC and FEV1

Table 7: Change in health measurements

		Change	CI		P-value
			Lower	Upper	
FeNO	Cross-shift	-0.92	-3.30	1.46	0.41
	Cross-week	3.45	-2.84	9.74	0.25
	Pre-shift	5.70	-2.37	13.77	0.15
	Post-shift	3.50	-0.09	7.09	0.055*
	DID	-2.80	-11.37	5.77	0.48
FVC	Cross-shift	-0.08	-0.23	0.08	0.30
	Cross-week	-0.13	-0.35	0.09	0.20
	Pre-shift	-0.08	-0.22	0.05	0.20
	Post-shift	-0.03	-0.19	0.13	0.65
	DID	0.06	-0.11	0.24	0.44
FEV_1	Cross-shift	-0.09	-0.25	0.08	0.25
	Cross-week	-0.12	-0.32	0.09	0.23
	Pre-shift	0.04	-0.29	0.38	0.79
	Post-shift	-0.10	-0.45	0.26	0.56
	DID	-0.14	-0.76	0.47	0.61

Table 8: Change in FeNO stratified by atopy and cannabis sensitization

Stratified by Atopy		**Change**	**CI**		**P-value**
			Lower	**Upper**	
Atopic	Cross-shift	-2.0	-3.5	-0.5	0.018*
	Cross-week	0.6	-6.9	8.1	0.85
	Pre-shift	1.6	-7.2	10.3	0.66
	Post-shift	4.3	-2.0	10.6	0.14
	DID	1.8	-4.4	7.9	0.50
Non-Atopic	Cross-shift	0.7	-7.2	8.5	0.80
	Cross-week	7.8	-8.6	24.1	0.23
	Pre-shift	11.9	-9.5	33.3	0.18
	Post-shift	2.3	-3.3	7.8	0.29
	DID	-9.6	-35.8	16.5	0.33
Stratified by Cannabis Sensitization					
w/ Cannabis	Cross-shift	0.6	-4.7	5.9	0.77
Sensitization	Cross-week	8.5	-3.6	20.6	0.12
	Pre-shift	10.8	-6.3	27.9	0.15
	Post-shift	5.0	-2.0	12.0	0.12
	DID	-5.8	-26.4	14.8	0.48
w/o Cannabis	Cross-shift	-2.4	-3.8	-1.0	0.0085*
Sensitization	Cross-week	-1.6	-6.6	3.4	0.42
	Pre-shift	0.6	-6.5	7.7	0.83
	Post-shift	2.0	-3.5	7.5	0.37
	DID	0.2	-6.0	6.4	0.93

Table 79: Change in FVC stratified by atopy and cannabis sensitization

Stratified by Atopy		**Change**	**CI**		**P-value**
			Lower	**Upper**	
Atopic	Cross-shift	-0.02	-0.25	0.20	0.80
	Cross-week	-0.02	-0.16	0.13	0.78
	Pre-shift	-0.06	-0.27	0.15	0.49
	Post-shift	0.07	-0.05	0.19	0.19
	DID	0.15	-0.09	0.39	0.17
Non-Atopic	Cross-shift	-0.16	-0.52	0.21	0.27
	Cross-week	-0.31	-0.99	0.37	0.25
	Pre-shift	-0.12	-0.44	0.21	0.34
	Post-shift	-0.19	-0.63	0.25	0.26
	DID	-0.07	-0.43	0.28	0.55
Stratified by Cannabis Sensitization					
w/ Cannabis	Cross-shift	-0.09	-0.45	0.28	0.55
Sensitization	Cross-week	-0.18	-0.72	0.36	0.41
	Pre-shift	-0.14	-0.44	0.16	0.27
	Post-shift	-0.05	-0.41	0.32	0.74
	DID	0.09	-0.23	0.41	0.47
w/o Cannabis	Cross-shift	-0.07	-0.25	0.11	0.36
Sensitization	Cross-week	-0.09	-0.27	0.09	0.24
	Pre-shift	-0.03	-0.18	0.13	0.64
	Post-shift	-0.02	-0.22	0.18	0.81
	DID	0.03	-0.29	0.35	0.79

Table 10: Change in FEV_1 stratified by atopy and cannabis sensitization

Stratified by Atopy		**Change**	**CI**		**P-value**
			Lower	Upper	
Atopic	Cross-shift	-0.12	-0.41	0.17	0.34
	Cross-week	-0.14	-0.45	0.17	0.29
	Pre-shift	-0.12	-0.61	0.37	0.55
	Post-shift	0.08	-0.23	0.38	0.54
	DID	0.19	-0.41	0.79	0.45
Non-Atopic	Cross-shift	-0.04	-0.31	0.22	0.63
	Cross-week	-0.08	-0.57	0.41	0.64
	Pre-shift	0.29	-0.35	0.93	0.25
	Post-shift	-0.36	-1.43	0.72	0.37
	DID	-0.64	-2.32	1.04	0.31
Stratified by Cannabis Sensitization					
w/ Cannabis	Cross-shift	-0.18	-0.68	0.32	0.25
Sensitization	Cross-week	-0.18	-0.68	0.32	0.37
	Pre-shift	0.12	-0.73	0.98	0.71
	Post-shift	-0.13	-1.04	0.79	0.72
	DID	-0.25	-1.83	1.33	0.68
w/o Cannabis	Cross-shift	0.00	-0.10	0.11	0.95
Sensitization	Cross-week	-0.05	-0.13	0.03	0.17
	Pre-shift	-0.04	-0.12	0.03	0.20
	Post-shift	-0.07	-0.20	0.07	0.24
	DID	-0.03	-0.21	0.14	0.63

APPENDIX II: Baseline Questionnaire

Health Effects Baseline Questionnaire

Technician initials: _____

Subject identifier: _____

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1. What is your age? ____
2. What is your biological sex? ☐ Male ☐ Female

3. What is your self-described race/ ethnicity?
   - ☐ Caucasian
   - ☐ Hispanic/ Latino
   - ☐ Black or African American
   - ☐ Asian
   - ☐ Other (please specify) _____

4. What is the highest degree or level of education that you completed?
   - ☐ No schooling
   - ☐ Grade 1-11
   - ☐ Completed high school
   - ☐ Some college but no degree
   - ☐ Bachelor's degree
   - ☐ Graduate or Professional school

5. Do you now, or have you ever, smoked tobacco cigarettes?

☐ Never ☐ Current (past 30 days) ☐ Past (year quit)

If you answered "Never," go to question 9

6. How old were you when you first started smoking tobacco cigarettes? _____

7. On average, about how many tobacco cigarettes a day do/ did you smoke? _____

8. Do live with a current smoker? ☐ Yes ☐ No

9. Have you ever used any other tobacco products?

	Never	Current (past 30 days)	Past
Pipe			
Cigars/ cigarillos			
Snuff			
Chewing tobacco			
Electronic cigarette			
Hookah			

10. Have you ever consumed marijuana products?

☐ Never ☐ Current (past 30 days) ☐ Past (_____ year quit)

If you answered "Never," go to question 12

11. Please complete the following table that summarizes the ways in which you use/ used marijuana? If you are using currently (past 30 days), please indicate current use patterns.

	Multiple times daily	Once a day	Once a week or more	About once a month	Every few months	Once or twice a year
Edible						
Smoked						
Smokeless/vape						
Dabbing						
Topical						

12. What is your job title? _____

a) For how long have you held this position? __ years __ months ___ days

b) For how long have you worked at this facility? __ years __ months ___ days

c) For how long have you worked in the marijuana industry? __ years __months __days

d) How many hours per week do you work in this job? ____

13. Do you perform any of the following tasks at work?
(please indicate typical % time spent on each)

Task	Yes	No	% time
Nursery worker			
Sort/grade dry product			
Trimmer			
Roll joints			
Packaging			
Preparation of concentrates/distillates			
Office work			
Waste Disposal			
Other (please specify)			

14. Do you ever wear any of the following when you work? If you answer yes to any of the questions, please specify % time you use this equipment, and the specific tasks where you use this equipment

a) Gloves? ☐ Yes ☐ No
% time _____
Tasks _____

b) Safety goggles? ☐ Yes ☐ No
% time _____
Tasks _____

c) Dust mask? ☐ Yes ☐ No
% time _____
Tasks _____

d) Cartridge respirator? ☐ Yes ☐ No
% time _____
Tasks _____

15. Do you perform any other paid work regularly? ☐ Yes ☐ No
a) What kind of work? _____
b) How many hours per week? _____

16. Have you ever been involved with cannabis cultivation or processing outside of this specific facility?

☐ Never ☐ Currently ☐ Previously

17. Please list any prior jobs

18. Do you have any chronic medical conditions? ☐ Yes ☐ No
If yes, please list them:

19. Are you on any medications? ☐ Yes ☐ No
If yes, please list the names and dose:

Medication	Dose

20. Have you ever been told that you have any of the following medical conditions?

	Yes	No	Don't know	Age at diagnosis
Asthma				
Hay fever (allergies involving the nose and/ or eyes)				
Chronic bronchitis				
Chronic obstructive pulmonary disease (COPD)				
Pneumonia or bronchopneumonia				
Eczema (skin allergy)				

21. Does anyone in your family have asthma? ☐ Yes ☐ No
If yes, please specify

22. Do you have any work-related health concerns? □ Yes □ No
If yes, please describe: _____

The following questions relate to health symptoms		
23. Have you ever had eczema or any kind of skin allergy?	☐ Yes	☐ No
24. Have you ever had an itchy rash that has been coming and going for at least 6 months? If "No", go to question 27 below.	☐ Yes	☐ No
a) Have you had this itchy rash in the past 12 months?	☐ Yes	☐ No
b) Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttock or around the neck, ears or eyes?	☐ Yes	☐ No
c) Has this itchy rash at any time affected any of the following places: the hands, wrists, or forearms?	☐ Yes	☐ No
25. If you answered yes to one of the statements in questions 23 and 24 above, does contact with certain materials, chemicals or anything else in your work makes this rash worse?	☐ Yes	☐ No
What? _____		
26. Does the rash improve when you are away from your normal work?	☐ Yes	☐ No
27. In the past 12 months, have you had a problem with itchy, red or watery eyes? If "No," go to question 31 below.	☐ Yes	☐ No
a) Are you currently taking any medications (including eye drops, pills, capsules or tablets) for the treatment of your eye symptoms?	☐ Yes	☐ No
28. When you are at work, do you develop symptoms of itchy, red, or watery eyes?	☐ Yes	☐ No
29. If you answered yes to one of the statements in questions 27 or 28, does contact with certain materials, chemicals or anything else in your work make your symptoms worse?	☐ Yes	☐ No
What? _____		
30. If you answered yes to one of the statements in questions 28 or 29 above, do these problems related to your work lessen or disappear during the weekend or during holidays?	☐ Yes	☐ No
31. Do you have nasal allergies, including hay fever?	☐ Yes	☐ No

32. In the past 12 months, have you ever had problems with nasal irritation, nose bleeds, sneezing, or a runny or a blocked nose when you did not have a cold or the flu? If "No", go to question 36 below.	☐ Yes	☐ No
a) Has this nose problem been accompanied by itchy, red or watery eyes?	☐ Yes	☐ No
b) Are you currently taking any medications (including nasal sprays, pills, capsules or tablets) for the treatment of your nasal symptoms?	☐ Yes	☐ No
33. When you are at work, do you develop symptoms of nasal irritation, sneezing, a runny or a blocked nose?	☐ Yes	☐ No
34. If you answered yes to one of the statements in questions 31 to 33 above, does contact with certain materials, chemicals or anything else in your work make your symptoms worse?	☐ Yes	☐ No
What? _____		
35. If you answered yes to one of the statements in questions 33 or 34 above, do these problems related to your work lessen or disappear during the weekend or during holidays?	☐ Yes	☐ No
36. Have you ever had wheezing or whistling in your chest, anytime in the last 12 months?	☐ Yes	☐ No
a) Have you been at all breathless when the wheezing noise was present	☐ Yes	☐ No
b) Have you had this wheezing or whistling when you did not have a cold?	☐ Yes	☐ No
37. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	☐ Yes	☐ No
38. Have you been awoken by an attack of shortness of breath at any time in the last 12 months?	☐ Yes	☐ No
39. Have you been awoken by an attack of coughing at any time in the last 12 months?	☐ Yes	☐ No
40. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?	☐ Yes	☐ No
41. Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?	☐ Yes	☐ No
42. Have you ever had asthma?	☐ Yes	☐ No
a. Have you ever been diagnosed with asthma by a doctor?	☐ Yes	☐ No
b. Have you had an attack of asthma any time in the last 12 months?	☐ Yes	☐ No
c. Are you currently taking any medications (including inhalers, aerosols or tablets) for asthma?	☐ Yes	☐ No
43. Do you experience any of the following while you are at work?		
a. Start to cough?	☐ Yes	☐ No
b. Start to produce sputum?	☐ Yes	☐ No

c. Start to wheeze?	☐ Yes	☐ No
d. Start to feel short of breath or get chest tightness?	☐ Yes	☐ No
e. Start to have a sore throat, hoarseness or loss of voice?	☐ Yes	☐ No
44. If you answered "yes" to any of the respiratory symptoms described in questions 36- 43, does contact with certain materials, chemicals or anything else in your work make your symptoms worse?	☐ Yes	☐ No
What? _____		
45. If you answered yes to one of the statements in questions 36 to 45, do these respiratory symptoms lessen or disappear when you are away from work, including evenings, weekends or during holidays?	☐ Yes	☐ No

APPENDIX III: Daily Symptoms Questionnaire

Daily Health Symptom Questionnaire
Participant ID: _____ Technician Initials: _____
Date: ____/____/_____
Time: _____

Have you used tobacco products in the last 24 hours?

	No	Yes	Time Frame	Total # hours
Cigarettes				
Pipe				
Cigars/ cigarillos				
Snuff				
Chewing tobacco				
Electronic cigarette				
Hookah				

Have you used marijuana products in the last 24 hours?

	No	Yes	Time Frame	Total # hours
Edible				
Smoked				
Smokeless/vape				
Dabbing				
Topical				

If taking medication, please list names and dose:

_____

1. During the past shift, did you have any problems with skin rashes, irritated or red skin? If "No," go to question 2)	☐ Yes	☐ No
a. Please rate the severity of your skin rashes/ irritation over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your skin symptoms worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the symptoms first began?		
d. Did you have any skin rashes, irritation or redness upon arrival to work today	☐ Yes	☐ No
2. During the past shift, did you experience any symptoms of nasal irritation, sneezing, a runny or a blocked nose? If "No," go to question 3)	☐ Yes	☐ No
a. Please rate the severity of your nasal symptoms over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your nasal symptoms worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the symptoms first began?		
d. Did you have these nasal symptoms upon arrival to work today	☐ Yes	☐ No
3. During the past shift, did you experience any throat irritation or voice hoarseness? If "No," go to question 4)		
a. Please rate the severity of your throat symptoms over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your throat symptoms worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the throat symptoms first began?		
d. Did you have these throat symptoms upon arrival to work today	☐ Yes	☐ No
4. During the past shift, did you experience any symptoms of watery, red or irritated eyes? If "No," go to question 5)	☐ Yes	☐ No
a. Please rate the severity of your eye symptoms over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your eye symptoms worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the symptoms first began?		
d. Did you have these eye symptoms upon arrival to work today	☐ Yes	☐ No
5. During the past shift, did you experience any symptoms of chest tightness? If "No," go to question 6)	☐ Yes	☐ No
a. Please rate the severity of chest tightness over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your chest tightness worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the symptoms first began?		
d. Did you have chest tightness upon arrival to work today	☐ Yes	☐ No

6. During the past shift, did you experience any wheezing? If "No," go to question 7)	☐ Yes	☐ No
a. Please rate the severity of your wheezing over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your wheezing worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the symptoms first began?		
d. Did you have wheezing upon arrival to work today?	☐ Yes	☐ No
7. During the past shift, did you experience any symptoms of shortness of breath? If "No," go to question 8)	☐ Yes	☐ No
a. Please rate the severity of your shortness of breath over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your shortness of breath worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the shortness of breath first began?		
d. Did you have shortness of breath upon arrival to work today?	☐ Yes	☐ No
8. During the past shift, did you experience any symptoms of cough? If "No," go to question 9)	☐ Yes	☐ No
a. Please rate the severity of your cough over the past shift: □ None □ Very mild □ Mild □ Moderate □ Severe		
b. Did your cough worsen during your shift?	☐ Yes	☐ No
c. What were you doing when the symptoms first began?		
d. Did you have cough upon arrival to work today	☐ Yes	☐ No

Participant ID: _____ Technician Initials: _____
Date: ____/____/_____;
Time that form is completed: _____

Please fill in the following task-activity record. Complete a separate line for each unique task you worked on during the day. The first row has been completed as an example to help you complete the table. Continue on back of page if needed.

Task description	**Location in building**	**Time period during which task was performed**	**Personal protection used**	**Strains worked with**	**Other relevant comments?**
Moving small plants	*Nursery & pre-flower room*	*9am-noon and 1pm-4pm*	*e.g. Gloves, sunglasses, ballcap, dustmask, respirator*	*Gorilla glue, Dutch treat*	-

Continuation of task-activity record:

Task description	**Location in building**	**Time period during which task was performed**	**Personal protection used**	**Strains worked with**	**Other relevant comments?**

Appendix IV: Data Flagging and Traceability

Table 1: Summary table of flags meanings and associated actions

Flag	Meaning	Action
Blank	Question was answered correctly by the subject in the field	No change to value
1	Question was answered by the subject but not correctly	Field was left blank
2	Question was answered by the subject but not by the desired format *	Value was determined/corrected
3	Question was left blank by the subject	No value was substituted

* Certain specific fields were filled in by subjects in ways that were either erroneous or vague (for example, the % of time spent on each activity, summed together, does not add up to 100%), In these cases, Niloufar made alterations to the survey field contents during entry into the excel spreadsheet. She gave each corresponding flag variable a value of "2" for a corrected erroneous or vague entry. Specific details are outlined in the survey data dictionary.

Raw Data Location

Folder containing raw data tables and data dictionaries associated with them are stored in

NG Computer: /Desktop/Thesis/Data

Data Storage

Original paper surveys and health measurement documents are currently stored in the Cannabis Respiratory Health binder in Room HSB F-225 B (Simpson Office).

Electronic version of surveys and health measurement documents are stored in Cannabis Respiratory Health folder shared with the study team on Online Google Docs

- **File Contents (Phase 1):** Baseline questionnaires
- **File Content (Phase 2):** FeNO and spirometry measurement documents + post-shift questionnaires + skin prick test documents