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**Review**

# The onset of occupational diseases in mushroom cultivation and handling operators: a review

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## Abstract

The paper presents a review on health hazards involving operators that cultivate and handle mushrooms. Intensive production of edible and medicinal fungi is a common agricultural management all over the world and involves a number of operators whose health must be safeguarded due the number of risks. Growth techniques and environmental conditions for producing and handling mushrooms expose workers to several types of allergens that possibly cause occupational diseases. Namely, mushroom workers suffer from allergic pulmonary diseases and, more rarely, from forms of contact dermatitis. The cause of these clinical manifestations may be found in the exposure to several factors, such as the peculiar production conditions leading to the presence of many allergens (bacteria, moulds, mycotoxins, endotoxins) and the direct contact of workers with some fungal species, which are themselves allergens.

**Key words:** Antigens; bacteria; mycotoxins; hypersensitivity pneumonitis; contact dermatitis.

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## Introduction

Fungi are microorganisms that sometimes form reproductive structures (sporomata) big enough to be handpicked. These structures are commonly called “mushrooms” or improperly “fruiting bodies” and produce meiotic spores. Only edible fungi are picked up and sold for food use. For several centuries many saprotrophic fungi have been cultivated in Europe and Asia (Chang and Miles, 2004), since they can grow indoor on properly treated organic material (compost).

Besides saprotrophic fungi, like champignon [*Agaricus bisporus* (J.E. Lange) Imbach], pleurotus [*Pleurotus* (Fr.) P. Kumm.], velvet pioppini [*Cyclocybe aegerita* (V. Brig) Vizzini], the market offers highly prized fungi that can only grow in nature, being symbionts of tree root systems, like porcini (*Boletus edulis* Bull.), Caesar's mushrooms [*Amanita caesarea* (Scop.) Persoon], chanterelle (*Cantharellus cibarius* Fr.) and various species of truffles (*Tuber* spp.), which are processed and transformed. World production of edible and medicinal mushrooms reaches a total of approximately 10 million tons per year. Italy is among the top-ranking countries with a percentage slightly below 7%, equal to approximately 680,000 tons (Food and Agriculture Organization of the United Nations, 2016).

The intensive production involves a number of workers and great attention must be paid to their health. The process of fungal growth and environmental conditions needed for sporoma development expose operators to various types of allergens, possibly leading to diseases classifiable as ‘occupational diseases’. Compost, which represents the food source for some mushrooms, is the first source of exposure risk. Compost consists of variable percentages of various decaying organic

materials (wheat straw and hay, oat, rice bran, virgin olive pomace, bird or horse manure, etc.), sometimes mixed with inorganic matter (chalk, limestone gravel, agriperlite, etc.). Other cultivated fungal species only require grinded plant materials, usually sterilised, or logs.

The quantity of allergens dispersed in the working environment may vary according to cultivation methods. Some species of edible mushrooms, such as Shiitake [*Lentinula edodes* (Berk.) Pegler], are cultivated on a substratum of a mixture of wet wood sawdust, wheat straw, and protein flour promoting the development of specific moulds (*Penicillium* spp. and *Trichoderma* spp.) that are considered powerful immunogens (Gaitán-Hernández et al., 2014). All the stages of the process are a source of environmental contamination due to several microbes (bacteria, moulds) and their metabolites (toxins) that may be dangerous for the health of susceptible individuals. In some cases, workers are exposed to allergens through the manipulation of fruiting bodies, hyphae and spores (Koivikko and Savolainen, 1988). Moreover, mushrooms are kept in peculiar climate conditions (high temperature and relative humidity) favouring microbial bioaerosol contamination, which is considered the main cause of the inflammatory reactions of workers (O’Gorman and Fuller, 2008).

Bioaerosols found in greenhouses or indoors where edible fungi are grown include particular microbial species (Table 1). This demonstrates the widely diversified presence of allergens in the air, with a concentration that can be higher than 109 colony-forming units (CFU)/m<sup>3</sup> of air (Chun et al., 2012).

**Table 1** - Microorganisms and toxins found in bioaerosols of fungal cultivations in indoor environments

Gram-negative bacteria	<i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Pedobacter</i> , <i>Herbaspirillum</i> , <i>Flavobacterium</i> , <i>Chryseobacterium</i> , Enterobacteriaceae
Gram-positive bacteria	<i>Bacillus</i> spp., <i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., <i>Arthrobacter</i> , <i>Microbacterium</i> , <i>Rhodococcus</i> , <i>Actinomyces</i> spp., <i>Streptomyces</i> spp.
Fungi	<i>Penicillium</i> spp., <i>Cladosporium</i> spp., <i>Aspergillus</i> spp., <i>Trichoderma</i> spp., <i>Alternaria</i> spp., <i>Rhizopus</i> spp., <i>Epicoccum</i> spp., <i>Fusarium</i> spp., <i>Geotricum</i> spp., <i>Botrytis</i> spp., <i>Mucor</i> spp.
Endotoxins	Molecules originated from gram-negative bacteria
Mycotoxins	Aflatoxins, fumonisins, ochratoxins

The most common clinical manifestations are lung-related diseases, like more or less serious forms of sensitisation, fibrosis or chronic obstructive pulmonary diseases and interstitial pulmonary diseases (Dudley et al., 2014). Workers have been found to suffer from a form of hypersensitivity pneumonitis caused by an immune reaction of the organism to the inhalation of fungal antigens. (Cano-Jiménez et al., 2016). Some antigens can induce hypersensitivity reactions of type I (immediate: allergies, asthma, eczema), type III (immunocomplex-mediated: serum sicknesses such as vasculitis, nephritis and arthritis), and type IV (delayed: contact hypersensitivity and dermatitis) (Torricelli et al., 1997; Curnow and Tam, 2003).

### **Pneumonitis and hypersensitivity in mushroom workers**

Over 300 antigens have been found that may induce severe or chronic forms of pulmonary diseases (bronchial asthma, alveolitis, fibrosis) deriving from farming-related agents (exposure to ticks, mites, arthropods, antigens of animal origin, above all birds, flours, moulds, fungi, plants, pollens) (European Respiratory Society, 2018). Some of these affections have a short latent period between exposure and clinical manifestation. Others have a longer latent period and a correlation between cumulative exposure and symptomatology (European Respiratory Society, 2018).

Not only exposure time but also exposure dose plays a role in the onset of the diseases. In fact, high levels of organic dusts for a long exposure time may cause pneumoconiosis or chronic obstructive pulmonary diseases (Barreiro et al., 2016). However, low exposure levels that comply

with law limits may also cause some allergic forms in workers (Basketter et al., 2015). It has been observed that agricultural workers may suffer from allergic alveolitis, with possible evolution to hypersensitivity pneumonitis, due to continuous exposure to specific organic antigens (thermophilic actinomycetes and fungal spores) (Table 2) (Lacey and Dutkiewicz, 1994; Hayes and Rooney, 2014; Liu et al., 2015).

**Table 2** - Correlation between diseases and exposure to specific organic antigens in agri-food workers (updated from Mahmoudi, 2016)

Antigen	Source	Disease
Thermophilic actinomycetes <sup>†</sup> <i>Fusarium</i> spp. <i>Penicillium brevicompactum</i> <i>Saccharomonospora viridis</i> <i>Absidia cerymbifera</i> <i>Wallemia sebi</i>	Vegetable compounds (mouldy hay, ensiled wheat) Dry leaves and grass Manure Mouldy fodder	Farmer's lung
Thermophilic actinomycetes <sup>†</sup> <i>Monocillium</i> spp. <i>Pleurotus ostreatus</i> * <i>Hypsizygus marmoreus</i> * <i>Lycoperdon perlatum</i> *	Fungal compost Indoor mushroom cultivation Peat Mushrooms	Mushroom farmer's lung
<i>Botrytis cinerea</i>	Mouldy grapes	Winemaker's lung
<i>Penicillium expansum</i> <i>Penicillium cyclopium</i> <i>Penicillium chrysogenum</i> <i>Cephalosporium acremonium</i> <i>Alternaria</i> spp. <i>Bacillus subtilis</i>	Mouldy wood Wood dust	Woodworker's lung
<i>Aspergillus</i> spp. <i>Aspergillus clavatus</i>	Mouldy barley	Maltworker's lung
<i>Candida</i> spp. <i>Ulocladium botrytis</i> <i>Thermoactinomyces vulgaris</i>	Mouldy sugarcanes	Sugarcane worker's lung
<i>Aspergillus</i> spp. <i>Penicillium</i> spp.	Greenhouse soil	Greenhouse worker's lung
<i>Penicillium casei</i> <i>Penicillium roqueforti</i> <i>Penicillium cyclopium</i> <i>Penicillium chrysogenum</i> <i>Penicillium camemberti</i> <i>Acarus siro</i>	Cheese moulds Salami moulds	Cheese worker's lung Sausage worker's lung

<sup>†</sup>*Saccharopolyspora rectivirgula*/*Microspolyspora faeni*, *Thermoactinomyces vulgaris*, *Thermoactinomyces viridis*, *Thermoactinomyces candidus*, *Thermoactinomyces sacchari*

\*Basidiospores

Van den Bogart et al. (1993) compared the species of microorganisms identified in the bioaerosol of compost fermentation tunnels with the antibodies found in the serum of workers suffering from hypersensitivity pneumonitis. The identified immunocomplexes were exclusively directed towards actinomycetes (*Excellorspora flexuosa*, *Thermomonospora alba*, *T. curvata*, *T. fusca*) and not towards fungal species [*Aspergillus fumigatus* Fresen., *Penicillium brevicompactum* Dierckx, *P. chrysogenum* Thom, *Scytalidium hyalinum* C.K. Campb. & J.L. Mulder, *S. thermophilum* (Cooney & R. Emers.) Austwick and *Trichoderma viride* Pers.]. Also, the study demonstrated a positive correlation between the antibody titer, and the occupational seniority, particularly towards

actinomycetes, confirming the hypothesis that these microorganisms are the main causal agents of hypersensitivity pneumonitis (Pereira et al., 2016). It is an inflammatory syndrome of the lower respiratory tract resulting from inhalation of organic dusts containing antigens (bacteria spores, fungi, animal proteins or bacterial products) and represents the most common disorder suffered by workers employed in mushroom cultivation (Sakula, 1967). It was first identified in the United States in 1959, in some workers exposed to compost used for mushroom cultivation, but the agent or substance that induced it was still unknown (Bringhurst et al., 1959).

Studies conducted on other agricultural workers suffering from lung disorders similar to hypersensitivity pneumonitis showed that etiologic agents were antigens derived from bacteria of the genus *Actinomyces* (particularly *Micropolyspora faeni* and more rarely *Thermoactinomyces vulgaris*), that had developed in decomposing hay (Pepys et al., 1963; Pepys and Jenkins, 1965). Sakula (1967) was the first to coin the specific term “mushroom worker’s lung” to identify hypersensitivity pneumonitis. The author classified it as occupational disease after finding immunocomplexes directed towards actinomycete antigens in the serum of mushroom workers.

Hypersensitivity pneumonitis is a disorder resulting from an immunopathogenic IgG-mediated inflammatory reaction cell-mediated by T-lymphocytes. It is characterized by a high antibody titer towards the antigens causing alveolitis in the presence of normal IgE and eosinophil values. The process is induced by a repeated exposure to antigens, present in the breathable fraction of organic dust (particles with a diameter below 5 µm, PM5) that reach bronchioles and alveoli, where they combine with antibodies to form immunocomplexes. The antigens more frequently responsible for the formation of immunocomplexes derive from fungi of the genus *Aspergillus* (e.g. *A. fumigatus*), from thermophilic actinomycetes (e.g. *T. vulgaris*, *Saccharopolyspora rectivirgula*, *M. faeni*, etc.) and from the basidiospores of some species of edible mushrooms (Kleyn et al., 1981; Shen et al., 1991; Van den Bogart et al., 1993; Xu et al., 2002). On the other hand, immunocomplexes activate macrophages to produce molecules mediating an acute inflammatory reaction (Suga et al., 1997; Nance et al., 2005).

Severe hypersensitivity pneumonitis is the most common form of this disease. It appears after hours or days from the exposure to the antigen with fever, cough, dyspnoea, asthenia and discomfort and is characterized by fibrosis and angiogenesis (Bertorelli et al., 2000). The symptoms may persist for about a week after removing the causal agent.

Repeated exposure in time to antigens causes a positive feedback cycle for T-lymphocytes, constantly activated to produce pro-inflammatory molecules, creating a chronic inflammation condition that, in the sub-severe form, leads to the formation of a granuloma. The clinical evolution is devious, with productive cough, exertional dyspnoea and asthenia (Yamane and Paul, 2012). A severe or sub-severe form or, more rarely, a chronic form of the disease may occur according to intensity and frequency of exposure and to the different immunological response determined by individual susceptibility (Riario Sforza and Marinou, 2017). The chronic form is less than 5% of cases, in which a persistent inflammatory condition is caused by repeated acute or subacute episodes, due to prolonged inhalation of low doses of antigens, and causes an irreversible lung damage. This form is more devious than the sub-severe one and may stay silent for long, with recurring episodes of dyspnoea and low-grade fever until the appearance of serious dyspnoea and full-blown respiratory failure (Bourke et al., 2001; Patel et al., 2001).

## **Hypersensitivity pneumonitis: a multifactorial disease?**

### *Histamine*

The connection between the presence of specific antibodies to actinomycetes and moulds and hypersensitivity pneumonitis is now widely ascertained. It has also been supposed that the inflammatory state at the origin of the disorder may be multifactorial, including the production of histamine or endotoxins of fungal or bacterial origin (Smuda and Bryce, 2011). For example, *T. viride* conidia, even in very low concentrations (0.1 ng ml<sup>-1</sup>), increases the release of IgE-mediated

histamine by mastocytes in the mucosae of the respiratory tract, suggesting a role of this mediator as co-factor of the pathological implications of pneumonitis (Larsen et al., 1996; Enríquez-Matas et al., 2009). These results were also found on workers involved in activities not related to the production of edible mushrooms (cork, cheese, salami processing) (Campbell et al., 1983; Cormier et al., 1998; Guglielminetti et al., 2001; Winck et al., 2004; Merget et al., 2008; Marvisi et al., 2012). This shows that exposure to some allergens (*A. fumigatus*, *M. faeni* and *T. vulgaris*), in different contexts, induces hypersensitivity pneumonitis according to the same mechanisms (Che et al., 1989; Hinojosa et al., 1996).

*Aspergillus fumigatus*, like other mold species, through a high content of beta-glucans found in cell walls, acts directly on macrophages and neutrophils inducing the production of pro-inflammatory molecules and an IgE-mediated type I reaction (immediate hypersensitivity) (Hohl et al., 2005; Geoffrey et al., 2006; Yoshikawa et al., 2007; Wang et al., 2016).

### *Gram-negative bacteria*

Hypersensitivity pneumonitis may also be due to gram-negative bacteria, which abound in fermented plant products and animal faeces (materials present in compost) and produce a lipopolysaccharide endotoxin (Lange et al., 2003; Henrik and Wolff, 2011). In vitro experiments have demonstrated that a high concentration of this lipopolysaccharide can induce the production of the same pro-inflammatory molecules (IL1, IL6, IL8 and TNF- $\alpha$ ) found in severe hypersensitivity pneumonitis in the macrophages of alveoli and lung epithelium cells (Dutkiewicz, 1978; Olenchock et al., 1983; Jagielo et al., 1996a,b; Allermann and Poulsen, 2000, 2002; Thorn, 2001; Smit et al., 2006).

Recently, a lipopolysaccharide endotoxin from *Pantoea agglomerans* has been identified as a possible emerging occupational pathogen agent. *Pantoea agglomerans*, known above all for opportunistic infections in immunocompromised individuals, is also considered responsible for occupational diseases associated with exposure to wheat dust and other organic dusts of agricultural origin (Al-Amluji et al., 1982; Naha et al., 2012; Dutkiewicz et al., 2015). The bacterium can reach a relatively high concentration in bioaerosol where plant materials and their by-products are processed. The immunogenic component of *P. agglomerans* lipopolysaccharide (10-50 nm globular nanoparticles) allows the molecule to be inhaled and transferred to the lower respiratory tract. Experiments conducted in vivo with various strains of *P. agglomerans* isolated from cereal dust and their endotoxin have shown that these extracts can cause inflammatory processes and pulmonary fibrosis (Dutkiewicz et al., 2015; Dutkiewicz et al., 2016). The in vivo results in agreement with clinical studies show that agricultural workers exhibit a high immunological reactivity to wheat and *Pantoea* allergenic extracts and a higher incidence of allergic alveolitis and asthma (Lantz et al., 1985; Milanowski, 1994).

The lipopolysaccharide endotoxin of *P. agglomerans* is not the only one to induce hypersensitivity pneumonitis. Other gram-negative bacteria, like *Escherichia coli*, may be involved too, confirming the hypothesis that the cause of clinical manifestations (cough, chest pain, dyspnoea, decreased respiratory function) identified in exposed individuals is the concentration of endotoxin in the air and not of dust particulate (Ryan et al., 1994; Jagielo et al., 1996a; Von Essen, 1997; Burch et al., 2010). A study performed in mushroom greenhouses (Simpson et al., 1999) measured a concentration of endotoxins units (EU) in bioaerosol ranging from a minimum of 10 EU/m<sup>3</sup> to a maximum of 1300 EU/m<sup>3</sup>. Concentrations above 100 EU/m<sup>3</sup> may lead to respiratory tract inflammations and those above 1,000 EU/m<sup>3</sup> cause acute effects with respiratory symptoms defined as organic dust toxic syndrome (Simpson et al., 1999).

### *Spores*

Spores of edible mushrooms may be allergens too; spores of some cultivated fungi [*Hypsizygus marmoreus* (Peck) H.E. Bigelow, *L. edodes*, *Pholiota nameko* (T. Itô) S. Ito & S. Ima, *Lyophyllum aggregatum* (Schaeff.) Kühner and *Pleurotus eryngii* (DC.) Quél.] consumed in Japan have caused hypersensitivity pneumonitis in production workers (Nakazawa and Tochigi, 1989; Tsushima et al.,

2001; Saikai et al., 2002). The causes can be found in the exposure to small spores (4-6  $\mu\text{m}$  in diameter) of these Basidiomycetes, which reach alveoli easily, and in the high concentration of spores in greenhouses during harvesting and packaging.

*Lentinula edodes* can cause hypersensitivity pneumonitis because the IgG produced against the antigens present in its spores have been found in cultivator serum (Sastre et al., 1990; Matsui et al., 1992; Murakami et al., 1997; Senti et al., 2000; Suzuki et al., 2001; Ampere et al., 2012). *Lentinula edodes* can produce a great quantity of spores: their indoor concentration can reach 40 million/ $\text{m}^3$  of air (van Loon et al., 1992). Investigations have also highlighted a diversification in the quantity of airborne spores among fungal species (Madsen et al., 2009). Shiitake and *Pleurotus* mushrooms release large quantities of spores in the atmosphere determining high concentrations in indoor cultivations (Sastre et al., 1990; Matsui et al., 1992; Senti et al., 2000).

After champignon (*A. bisporus*), Shiitake is the second most cultivated and eaten fungus in the world. It is important to stress that in recent years this mushroom has become quite common in western markets as well. If large-scale cultivation of these fungi will spread in Europe, specific measures of health protection will have to be adopted in order to safeguard the mushroom workers against hypersensitivity pneumonitis. Likewise, *Pleurotus ostreatus* (Jacq.) P. Kumm. spores are considered allergens involved in the etiogenesis of hypersensitivity pneumonitis. Since the gills of this fungus, are not veiled like in *Agaricus* spp. or *Lentinula* spp., a great number of spores is spread. A study conducted by Sonnenberg et al. (1996) demonstrated that, according to the development stage of the fruiting body, the species *Pleurotus* can release up to a billion spores per day per gram of fungus (Olsen, 1987).

## Allergic dermatitis

Another health risk that has been investigated over the years regards dermatologic affections induced by edible mushrooms. Such manifestations are rarer than hypersensitivity pneumonitis. However, case studies have been reported for individuals exposed to mushrooms for professional reasons (picking up, packaging, selling, processing). The fungal species most responsible for this disease are champignons (*A. bisporus*) and porcini (*B. edulis*). To date, the origin of contact dermatitis has not been ascertained, but this disorder has been put in connection with hypersensitivity reactions of type I, III and IV or with forms of hypereosinophilia (Korstanje et al., 1990; Kanerva et al., 1998; Simeoni et al., 2004; Baruffini et al., 2005).

Shiitake may cause an IgE-mediated allergic form that may manifest as contact urticaria, protein contact dermatitis (PCD) or both. Cutaneous symptoms are different from those of 'Shiitake dermatitis' (toxicodermia), which is a non-allergic dermatitis caused by the consumption of raw Shiitake. In fact, the patch test (allergy test to determine if a substance causes allergic inflammation of the skin with cell-mediated mechanism) against Shiitake allergens is positive in patients with allergic contact dermatitis (Tarvainen et al., 1991; Nakamura, 1992; Ueda et al., 1992; Hanada, 1998; Aalto-Korte et al., 2005). Shiitake hyphae are moderately allergenic, as demonstrated by the Guinea pig maximization test for hypersensitivity type IV (Ueda et al., 1992). Aalto-Korte et al. (2005) have been the first to associate Shiitake as aetiological agent of an eczematous eruption on the hands of two growers. The prick test (skin allergy test for the diagnosis of respiratory and food allergies) showed that both patients had reactions to shiitake and that there were specific IgEs against this fungus in their serums. The patients had an IgE-mediated allergy to shiitake with consequent diagnosis of occupational protein contact dermatitis. Some cases of allergic contact dermatitis caused by this fungus, also correlated to symptoms of asthma (Curnow and Tam, 2003), hypersensitivity pneumonitis and contact urticaria have been reported in literature (Tarvainen et al., 1991; Ueda et al., 1992). Some mushroom workers develop eczematous contact eruption and immediate allergy.

White Pom Pom mushroom [*Hericiium erinaceum* (Bull.) Pers.], also known as 'monkey head mushroom' or 'lion's mane mushroom', is a very valuable edible fungus used in medicine. This fungus may cause allergic contact dermatitis too (Maes et al., 1999).

## Mycotoxins and pulmonary pathology

Another possible cause of diseases in those who work in this sector is exposure to mycotoxins produced by moulds present in their working environment. It is necessary to stress that they are a risk factor that is not completely known and, maybe, underestimated. Although mycotoxins are not much volatile and human exposure to them is linked to the ingestion of contaminated food, there might be a potential route of exposure to mycotoxin by inhalation, conveyed in alveoli by spores or contaminated substrata (Emanuel et al., 1975; Sorenson, 1981; Dvorackova and Pichova, 1986). Cases of pulmonary mycotoxicosis have been described in agricultural and textile workers. Although the symptoms are similar to those of a disease induced by an allergic reaction, it was not possible to determine the cause for the lack of granulomas in the lungs and circulating antibodies against fungal antigens. Loughheed et al. (1995) have maybe been the first to associate pulmonary disease cases to the presence of aflatoxin B1 by exposure to a working environment contaminated by *Fusarium* spp.

## Conclusions

Although there is an evident correlation between occupational exposure to biological agents (microorganisms, mycotoxins, allergens, mites, endotoxins) and effects on workers' health, an occupational exposure limit for biological risk has not been established yet. Even though values have been suggested by several institutes, like the DECOS (Dutch Expert Committee on Occupational Health Standard), which recommended for endotoxins an exposure limit of 90 units (EU)/m<sup>3</sup> of air sampled in 8 working hours.

Two standards have been drawn up for evaluating occupational exposure to biological agents: the EN 13098 (European Committee for Standardisation: UNI EN 13098, 2002), defining the rules for measuring airborne microorganisms, and the EN 14031 (European Committee for Standardisation: UNI EN 14031, 2003), totally dedicated to measuring airborne endotoxins. If limit values for microorganisms, endotoxins or mycotoxins are established, it is not possible to separate an evaluation of biological risk from the microorganism/host relationship. This does not mean that complying with law limits may guarantee a complete safeguard of workers, because it is important to take into account individual susceptibility determined by biological characteristics (lifestyle, genetics, age, sex) of the individual exposed. Mushroom cultivation is a peculiar example of exposure to bioaerosol, because workers risk contracting diseases at all stages of production chain. Therefore, it is important and necessary to train and inform workers as regards the biological risk they are exposed to and the correct implementation of prevention and protection measures to avoid adverse health effects. So, the main goal is to adopt collective prevention measures through an adequate air filtration system in order to have an indoor bioaerosol with a very low allergen concentration. Gloves and dust masks may offer a valid personal protective equipment, particularly for susceptible persons or in contexts where it is not possible to install an air filtering system. In the case of individuals suffering from clinical manifestations, the competent doctor must ensure that they remain away from the allergen source (Pozzi et al., 1998).

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