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# Health Effects of Fungi, Bacteria, and Other Bioparticles

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## Introduction

Most health effects associated with biological particles are various respiratory conditions and skin reactions. Their mechanisms vary from infections, irritation symptoms, and allergic diseases to toxic or immunotoxic reactions and other conditions with less evident pathophysiology. It is often the case that epidemiological and clinical evidence of the association between biological agents and the adverse health effect is strong, but the causal link between the exposing agents and the disease are poorly known. Furthermore, the mechanistic pathways leading to a certain condition are often not well known.

The health outcomes where the causal connection to certain microorganisms is evident and better understood are infections and allergies. For example, *Legionella* bacteria cause an infection known as legionellosis, and the allergen *Der p*I is the main causal agent for house dust mite allergy. For other health effects of biological particles, the links between the agent and the health condition have been shown as time- and space-specific associations but usually the causal connection and the pathophysiological mechanisms by which the health effects develop are not well understood.

Furthermore, in the cases of non-infectious and non-allergic reactions, the exposures usually are complex mixtures of various micro-organisms, their components and metabolic products, and the roles of individual molecules, microbial species, or other agents in development of adverse health effects are yet to be identified.

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## Infections and allergies

Pathogenic bacteria and viruses are the main infectious agents that cause disease in humans. Less common are the infections that are caused by certain fungi or amoebae. The fight against infectious diseases caused by bacteria and viruses is based on vaccinations, general hygiene, and use of antibiotics.

Examples of common infectious agents are rhinoviruses that cause 'common colds', noroviruses that cause gastric infections, and pathogenic bacteria, such as certain streptococci, staphylococci, pneumococci, and clostridia. In case of infectious diseases, the causal agent is usually detectable and the route of infection is most often human to human contact, either directly or indirectly through surfaces or via an airborne route. In hospitals and institutions, specific bacterial strains that are resistant to the known antibiotics, form an increasing challenge to the health care systems worldwide.

While infections are usually spread via human to human route, there is one well known infectious agent, i.e., the bacterium *Legionella*, the source of which is the indoor environment and water system within it (Tobin et al. 1980). Legionellae proliferate typically in man-made water systems, i.e., cooling systems and humidifiers (Arnow et al. 1982; Kusnetsov 1997). Humans may get infected by inhaling aerosolized legionella bacteria, and the infection may be lethal if proper antibiotic treatment is not available.

Allergies are conditions where the contact to the allergen causes an immunological reaction via IgE-mediated pathway in the exposed individual, leading to symptoms of varying severity. A prerequisite to allergy is atopy, a genetic tendency towards such reaction to allergens. Allergies are usually very specific and they can be treated with medication and avoidance policies. While allergies to food items are common, the most important environmental allergens are pollen and fungi in outdoor air; and indoors, cat, dog, house dust mites, cockroaches, and some plants. In occupational settings, some bacterial proteins and glycoproteins, such as proteolytic enzymes produced by, e.g., *Bacillus subtilis* may act as allergens and have importance as causative agents of an occupational disease (Göthe et al. 1972).

## Indoor dampness and mold

Environmental exposure to microbes and biological material is often characterized by the complexity of the exposure, that may consist of a myriad of various microbial species, particles, cell components, microbial products, and other biological material, be it hay, straw, wood dust, dirt, or other matrix depending on the exposure situation. One situation that has gained a lot of attention during the last decades has been the problem of moisture, dampness, and mold in buildings and associated health effects.

Population studies in the late 1980s and later revealed that residential moisture, dampness, and mold growth are a risk factor for many respiratory diseases and other symptoms (IOM 2004; WHO 2009). The issue has been thoroughly studied since then, and is today recognized as one of the most common building-related health risks.

Dampness and moisture problems of the building may be caused by several factors. Inadequate ventilation, leaks, condensation, and capillary raise of moisture from the ground are among the major reasons of moisture accumulation in the building

structures. Then, whenever a surface or material of the building is moist for prolonged time, microbial growth will start, which includes bacteria, fungi, and other organisms. When this growth becomes visible, it is recognized as 'mold' or 'mildew' that often has a characteristic odor of 'cellar' or 'earth'. It is not exactly known why such mold growth is harmful for health, but its emissions into indoor air include spores, fragments, and other particles from the mycelium, volatile compounds known as MVOC (microbial volatile organic compounds), and non-volatile microbial products, i.e., mycotoxins and bacterial toxins. In addition, chemical substances with non-biological origin may be emitted into indoor air as a result of moisture-induced disruption of materials.

Exposure in a moisture- or mold-affected indoor environment is verified by studying the building. Any signs of dampness or moisture, i.e., damp spots, discolored wood, loosening tiles, or peeling paint may be visible to the naked eye and tell about the risk of mold growth behind the surface if the growth is not visible. While visual observation of the telltale signs of moisture is the first step of the building investigation, it usually takes many kinds of professional skills to detect, locate, and assess such problems. Microbial sampling of indoor air is one of those methods. Sampling strategy and choice of methods need to be planned carefully as the fungal levels are affected by not only mold growth in the building but by many other factors as well.

## Human health effects associated with dampness and mold

The health outcomes associated with moisture, dampness, and mold of buildings have been evaluated by working groups of WHO (WHO 2009) and Institute of Medicine (IOM 2004) and later on, reviewed by Mendell et al. (2011) and Kanchongkittiphon et al. (2015). The health effects that have been best documented include irritant effects of the respiratory system and mucous membranes, increased and prolonged respiratory infections, and exacerbation of previous asthma and onset of new asthma. Other, less strongly documented effects include ODTS (organic dust toxic syndrome), allergic alveolitis, sarcoidosis, and autoimmune diseases including rheumatic conditions. A systematic review by Tischer et al. (2011) concluded that visible mold in the home increases the risk of wheezing (adjusted odds ratio (aOR) 1.68, 95% confidence interval (95%CI) 1.48–1.90) and asthma (aOR 1.49, 95%CI 1.28–1.72).

Health effects are reported among both children and adults, among atopic and non-atopic individuals, and in all kinds of buildings, i.e., residences, schools, offices, hospitals, and other public buildings. Not all individuals react in the same way, and recognition and identification of a situation where dampness and mold are behind a health condition may be challenging. There are no good diagnostic tools to verify if someone's symptoms or disease is related to exposure to indoor mold but a timely occurrence of exposure and recovery of symptoms during absence from the building are important diagnostic criteria. Individual factors also affect the recovery of the symptoms which may take place slowly, even for years (Rudblad et al. 2002).

The health outcomes that WHO (2009) recognized as relatively well documented are listed in Table 7-1.

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**Table 7-1.** Health effects observed in damp buildings. The respiratory health effects for which WHO (2009) found (a) sufficient evidence or (b) limited or suggestive evidence of an association with indoor dampness-related factors.

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| (a) Asthma exacerbation, upper respiratory tract symptoms, cough, wheeze, asthma development, dyspnea, current asthma, respiratory infections |
| (b) bronchitis, allergic rhinitis |

## Agents that may potentially have causal role in dampness-related health effects

The pathophysiological pathways that lead to the symptoms and diseases in moldy buildings are still poorly known. Although many symptoms mimic allergic reactions, IgE-mediated allergies are only seldom observed and therefore this mechanism does not explain all the symptom findings (Taskinen et al. 2001). Fungi do contain and produce allergens and antigens, but most well-characterized human allergens come from fungi that occur mainly outdoors (Miller 2011). Other possible mechanistic aspects are, e.g., irritation, inflammation, and toxic mechanisms.

Inflammation is a local response of tissues to injury or irritation, serving as a mechanism initiating the elimination of noxious agents and of damaged tissue (Huttunen et al. 2003). There are indications that inflammation would play a role in the development of symptoms in damp and mold-problem buildings. Many microbial agents are capable of inducing a number of inflammatory responses both *in vitro* and *in vivo* (Miller et al. 2010); probably the best known example is bacterial endotoxin (Heine et al. 2001). Fungi also contain a cellular component in their cell walls with observed inflammatory potential, i.e., glucans. Glucans of various types of fungi have been shown to induce an inflammatory response as summarized by Miller (2011).

Microbial strains, especially bacteria, isolated from mold-damaged indoor environments have shown remarkable proinflammatory activity. For example, Gram positive bacteria *Bacillus cereus* and *Streptomyces californicus* and the Gram negative bacterium *Pseudomonas fluorescens* were compared in an experimental set-up to the fungi *Stachybotrys chartarum*, *Aspergillus versicolor*, and *Penicillium spinulosum*, all isolated from indoor environments (Huttunen et al. 2003). The inflammatory potency was observed especially in the various bacteria, and the potency decreased in the order *Ps. fluorescens* > *Str. californicus* > *B. cereus* > *S. chartarum* > *A. versicolor* > *P. spinulosum*. It is noteworthy that while the Gram negative *Pseudomonas fluorescens* showed the highest potency for inflammation—probably due to its endotoxin—the Gram positive *Streptomyces* also had remarkable potency. Cytotoxicity is measured in *in vitro*-studies for assessment of a toxic mechanism. When potency-to-cause cytotoxicity was measured in the experimental set-up described, the rank order was *Ps. fluorescens* > *S. chartarum* > *Str. californicus* > *A. versicolor* > *B. cereus* > *P. spinulosum* (Huttunen et al. 2003). Inflammatory potential of airborne particles was shown to be associated with the amount of microbial material in air samples in a study focusing on personal exposures (Roponen et al. 2003).

Increase of proinflammatory markers in nasal lavage fluid of individuals exposed to a moisture-problem school environment have been reported (Hirvonen et al. 1999). This increase was observed during the exposure period, a decrease to control levels of the same markers during a break in the exposure (summer vacation), and an increase again at the end of the following exposure period. Interestingly, this phenomenon could not, however, be shown in a similar time-series study in sawmill workers although their microbial exposure levels are much higher (Roponen et al. 2002). Inflammation was also the main pathway observed in a murine model studying effects of mycotoxins such as atranone C, brevianamide, cladosporin, mycophenolic acid, neoechinulin A and B, sterigmatocystin, and TMC-120A. The doses used in the study were within the estimated range of possible indoor-related human exposure (Miller et al. 2010).

In addition to inflammation, toxic mechanisms also appear to be involved in the development of symptoms in mold-infested indoor environments. This is not, however, a well known aspect of indoor-related exposures where the main route of exposure is assumed to be inhalation, as most documentation concerning acutely toxic secondary metabolites comes from studies focusing on dietary dosing.

## Protective effects of microbial exposures

Consistent observations in population studies in different countries have revealed that children of farmers have less allergies than urban children (Adler et al. 2005; Braun-Fahrländer et al. 1999; von Mutius and Vercelli 2010; Ege et al. 2011). It has been postulated that the more intense and diverse microbial exposure in the farming environment could serve as a protective quality by challenging the developing immune system of infants with a natural microbial material. So far, no individual microbial species or factor has been shown to have a critical role in this phenomenon.

The agricultural environment does not, however, protect from the occupational health risks that have been identified with many work situations. As mentioned before, in these cases, exposure levels are usually very high, i.e., several orders of magnitude higher than in the indoor air of the home, be it a farming home or an urban home.

As the adverse health effects of damp and moldy indoor environments and the beneficial protective effect in a farming environment are compared in parallel, an interesting paradox can be suggested. In both these domestic environments, microbial levels are elevated compared to "normal" urban homes with no moisture or mold problem (Hyvärinen et al. 2001; Green et al. 2003; van Strien et al. 2004). In homes that have observed dampness, moisture, or mold, there is a risk for adverse health effects such as irritative, allergic, or other respiratory health effects including an increased risk for asthma (e.g., Norbäck et al. 2013). In farming homes, a protective effect from allergies is seen (Genuneit 2012) while they have higher microbial concentrations due to many natural sources in their immediate surroundings (Ege et al. 2011). However, the farming environment does not necessarily protect from adverse effects of moisture damage exposure (Karvonen et al. 2009).

It is evident that microbial concentrations as such do not explain either the beneficial or the adverse health effects observed in domestic environments. However, when this phenomenon that appears as a paradox at a first glance is analyzed in more

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detail, it is clear that it is a question of different environments with different sources of microbial exposures. Microbial exposures are not a uniform concept but a highly variable range of microbial species, their cellular components, and metabolic products, with a wide array of potential biological effects. Not only do microorganisms have health-relevant potential but also other agents, such as pollen, protozoa, and animal allergens may contribute to the health effects of biological particles. The knowledge on the complex interactions with these agents and other air pollutants will increase in the future, facilitated with the significant methodological progress in the assessment of biological exposures.

## Occupational diseases linked with biological particles

In occupational environments where organic material is being handled and processed, exposure levels to organic dusts and biological particles may be very high. Such occupational environments are found in, e.g., agriculture, food processing, animal care, tobacco processing, and waste handling and processing. Measurements have shown that the concentrations of viable fungi and bacteria in such environment may be $10^5$–$10^7$ CFU $m^{-3}$, orders of magnitude higher than the concentrations in any other indoor environment (Table 7-1). The organic dusts in such occupational environments are usually mixtures of fungi, bacteria, and other microorganisms, combined with plant, animal, and waste material depending on the industry in question. Several types of occupational diseases are known to occur in such environments.

Hypersensitivity pneumonitis or allergic alveolitis is an occupational disease that may lead to irreversible impairment of lung function. It has been linked with exposures to very large concentrations of microbes and organic dust in, e.g., agricultural work, sawmills, and composting facilities (Kotimaa et al. 1984; Lacey and Crook 1988; Malmberg et al. 1993). The disease is named according to the occupation, e.g., farmer's lung, wood trimmer's disease, cheese washer's disease, or bird breeder's lung. The disease has even been observed in situations with much lower levels of exposure, such as office environments with dampness, moisture, and mold problems (Jarvis and Morey 2001).

The onset of hypersensitivity pneumonitis has traditionally been connected with fungi of the genera *Acremonium*, *Aspergillus*, *Aureobasidium*, *Cladosporium*, *Mucor*, *Penicillium*, *Rhizopus*, *Sporobolomyces*, and *Trichoderma* (doPico 1986; Lacey and Crook 1988; Richerson 1994; Levetin et al. 1995). Among bacteria, actinomycetes, especially species of *Streptomyces* and thermophilic species growing at temperatures 40–60°C, such as *Saccharopolyspora rectivirgula* and species of *Thermoactinomyces* have been associated with the disease in dairy farms and other occupational settings with high levels of organic dust (Kotimaa et al. 1984).

In agricultural environments, a disease called organic dust toxic syndrome (ODTS) has been described (doPico 1986). It is a non-infectious febrile illness resembling influenza with major symptoms being fever and malaise (Emanuel et al. 1975). It typically occurs after a heavy inhalation exposure to organic dust.

The risk of asthma has been shown in many occupational settings with exposure to biological dusts. Asthma has also been connected with exposure to moisture- and mold-affected indoor environments. Visible mold or mold odor was shown to be a risk factor for asthma in work places (Jaakkola et al. 2002). Clusters of asthma cases have also been reported in moisture damaged schools (Patovirta et al. 2004), hospitals (Seuri et al. 2000), offices (Yossifova et al. 2011), and other buildings (Bornehag et al. 2001).

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# Synergic Influence of Gaseous, Particulate, and Biological Pollutants on Human Health

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