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Invited Review

Indoor fungi: companions and contaminants

Abstract This review discusses the role of fungi and fungal products in indoor environments, especially as agents of human exposure. Fungi are present everywhere, and knowledge for indoor environments is extensive on their occurrence and ecology, concentrations, and determinants. Problems of dampness and mold have dominated the discussion on indoor fungi. However, the role of fungi in human health is still not well understood. In this review, we take a look back to integrate what cultivation-based research has taught us alongside more recent work with cultivation-independent techniques. We attempt to summarize what is known today and to point out where more data is needed for risk assessment associated with indoor fungal exposures. New data have demonstrated qualitative and quantitative richness of fungal material inside and outside buildings. Research on mycotoxins shows that just as microbes are everywhere in our indoor environments, so too are their metabolic products. Assessment of fungal exposures is notoriously challenging due to the numerous factors that contribute to the variation of fungal concentrations in indoor environments. We also may have to acknowledge and incorporate into our understanding the complexity of interactions between multiple biological agents in assessing their effects on human health and well-being.

A. Nevalainen, M. Täubel, A. Hyvärinen

Institute for Health and Welfare, Kuopio, Finland

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A. Nevalainen
Institute for Health and Welfare
POB 95, 70701 Kuopio
Finland
Tel.: +358 50 3261013
e-mail: Aino.Nevalainen@thl.fi

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Practical implications

Present knowledge on indoor fungi, human exposures, and their associations with health is discussed, and research needs are identified. Fungal growth due to dampness is linked with adverse health effects and, as a major public health issue, should be eliminated and prevented. Consistent guidance to manage the problem is available. A less known aspect of fungal exposures is their possible role in a protective effect from allergies, evidence of which derives from studies of farming environments.

Introduction

Background

Fungi are an important group of microorganisms present in all buildings. They are sometimes thought to be the most important type of microbes in indoor environments, but this view may be partly because fungi sometimes can be apparent to building occupants as visible mycelial growth and via their characteristic musty smell. When conducting a building investigation, fungi are relatively easy to sample, to view in the microscope, and to culture into visible colonies with simple techniques. However, this approach fails to reveal the true diversity of the indoor fungi and overlooks the complexity of their role not only as indoor contaminants but also as our companions, always present in any given indoor environment.

This review summarizes the state of knowledge on fungi as indoor environmental agents. There are many points of view from which fungi can be discussed; our focus will be on their role as agents of human exposure present in the indoor environment and thus closely related to human well-being and health. Their sources and removal as well as the factors determining their occurrence and behavior will be discussed. We do not touch here on basic fungal biology, as there are many excellent texts on that topic (Adan and Samson, 2011; Dix and Webster, 1995).

Generally, the role of indoor fungi has drawn attention in many disciplines, for example, in botany, biology, ecology, mycology, aerobiology, health sciences, and aerosol science. Over the past decades, many useful reviews on various aspects of indoor fungi have been published. Some have focused on

exposure-related aspects (Chapman et al., 2003; Després et al., 2012; Fischer and Dott, 2003; Górny, 2004; Horner, 2003; Horner et al., 1995; Madelin, 1994; Matte and Jacobs, 2000; McGinnis, 2007; Méheust et al., 2014; Miller and McMullin, 2014; Fog Nielsen, 2003; Qian et al., 2014; Rayner, 1996; Rintala et al., 2012; Robbins et al., 2000; Rogers, 2003; Srikanth et al., 2008; Thorne et al., 2004; Tischer and Heinrich, 2013; van Loo et al., 2004; Wu et al., 2007). Others have emphasized on health effects associated with indoor fungi (Bornehag et al., 2001; Bornehag et al., 2004; Douwes and Pierce, 2003; Fung and Hughson, 2008; Hope, 2013; Hope and Simon, 2007; Johanning, 2004; Johanning et al., 2014; Kanchongkittiphon et al., 2014; Kolstad et al., 2002; Kuhn and Ghannoum, 2003; Meggs, 2009; Mendell et al., 2011; Mihinova and Pieckova, 2012; Sauni et al., 2013; Seltzer and Fedoruk, 2007; Tischer et al., 2011). A short description of the fungal components and metabolites, which are relevant from the perspective of fungal exposure and indoor air sciences, is presented in Table 1.

While we focus on fungi and exposure, we want to make the point that fungi are members of a complex community of biological indoor agents. Houses are not homes only to humans and their pets, but they are also inhabited by many microorganisms, such as bacteria, viruses, and protists, such as amoebae; pollen and other plant material; and even arthropods, such as house dust-mites and ants. There are also other types of biological material, such as excreta, traces, and debris from all organisms large and small, and their metabolic products. Fungi rarely occur in isolation but almost invariably they exist in conjunction with other biological material. This is a crucial point from the exposure point of view: One could argue that indoor exposure to fungi and their possible effects should not be differentiated from simultaneous exposure to multiple agents, especially outcomes of their interactions. As yet, the nature, significance, and consequences of such interactions are poorly explored topics.

Bioaerosols and biological material in the indoor environments have been mostly studied in relation to their well-recognized allergenic potential; many fungal allergens have indeed been identified (Simon-Nobbe et al., 2008). However, also their irritant, toxic, immunotoxic, and other biological properties are important from the health point of view, as will be discussed in Indoor fungi and health.

Fungal occurrence indoors is first determined by the complexity and vast variations in indoor habitats. Factors contributing to this complexity include 'major' phenomena, such as climate, geography, season, and

Table 1 Fungal components and products relevant for indoor air sciences

Fungal agent	Short description	Applications in indoor air research	References
Fragments	Particles of fungal origin that are smaller than whole spores (typically $<1\ \mu m$)	May have relevance as exposure agents related to health effects	Górny et al. (2002)
Ergosterol	Sterol specific to fungal cells Present in most fungal cells, underrepresented in yeasts No specific role as health-relevant agent	Ergosterol content used as a proxy for fungal biomass	Axelsson et al. (1995), Miller et al. (1988), Miller and Young (1997), Pasanen et al. (1999)
Glucans	Major structural components of fungal cells (1-3) and (1-6) linked polymers of D-glucose Non-allergenic but possess proinflammatory properties	Glucan content is used as a proxy of bioactive portion of fungal biomass	Douwes (2005), Iossifova et al. (2008)
Extracellular polysaccharides (EPS)	Stable, high molecular weight sugar polymers on the surface of fungal cells, produced during growth	Marker of fungal biomass (mainly *Penicillium* and *Aspergillus*) No longer widely used	Douwes et al. (1999), Noterman and Soentoro (1986)
Fungal allergens	Antigenic substances of fungi capable of stimulating an IgE-mediated response	Indoor exposure and role in health effects insufficiently known	Green et al. (2003), Green et al. (2005), Horner et al. (1995), Salo et al. (2009)
MVOC	Highly volatile low molecular weight chemicals, produced by growing fungi (and bacteria) as primary and secondary metabolites Include alcohols, aldehydes, amines, ketones, terpenes and aromatic hydrocarbons Relatively low toxicity	Recognized as odor of mold Measurement of MVOCs is not a good indicator of fungal growth as there are very few VOCs specific to microbial sources only	Korpi et al. (2009), Schleibinger et al. (2008)
Mycotoxins	Nonvolatile fungal secondary metabolites with a variety of chemical structures Chemically stable, and some of them are thermally stable Many are bioactive, and some are acutely toxic by ingestion May be present airborne attached to other particles	Occurrence in indoor air has been shown Role as causative agents of symptoms possibly due to their toxicity and inflammatory potential Specific studies on their connection to health still lacking	Bloom et al. (2009b), Brasel et al. (2005a), Täubel et al. (2011)
Fungal nucleic acids DNA and RNA	Polymeric macromolecules composed of nucleotides Contains the genetic information of a fungal cell (DNA) or acts in converting of the genetic information (RNA) Located in the different cellular organelles and the mycoplasm	No relevance as a potential causative agent of health outcomes Widely used as a target in DNA-based methods that are increasingly applied in indoor air research (including quantitative PCR, DNA fingerprinting, and sequencing applications)	Adams et al. (2013b, 2013c), Amend et al. (2010b), Haugland and Vesper (2002), Pitkäranta et al. (2008, 2011)

location, and 'minor' factors which refer to individual buildings and their occupants, such as building construction and maintenance, current and historical use of the building, ventilation, moisture control, surface materials, occupants themselves, and their activities and lifestyles. All these major and minor factors contribute to the stage on which the indoor microbiome performs. The actual performance of individual species is affected both by these factors and by the species in question.

We will summarize the history of research on indoor fungi and the literature on fungi from perspective of the indoor air sciences. Much of the knowledge we have today on indoor fungi has been acquired using methods that are based either on culturing or on microscopic, chemical, and immunochemical techniques. However, today DNA-based methods are providing tools not only to complement this knowledge but also to open new frontiers. We will also discuss future topics, that is, what still needs to be learned about the relationships between various biological exposures and human health, especially the role played by fungi in these interactions.

Fungi are universal

Nature is a rich source of all kinds of fungi; these microorganisms play essential roles in biodegradation processes and in nutrient cycles, and they are associated with many other organisms (Blackwell, 2011). Along with bacteria and other microorganisms, fungi inhabit most plant, soil, and rock surfaces, contributing number densities of 10^4–10^8 cells/cm^2 on surfaces in different natural environments (Després et al., 2012). Fungal material is emitted into the atmosphere at an estimated rate of 28–50 Tg per year (Yamamoto et al., 2012). In a background station in the Austrian Alps, fungi accounted for approximately 1.5% of the organic carbon (OC) in cloud water, 0.9% of OC in total aerosol samples, and 9.9% of OC in the coarse size fraction (2.1–10 μm) (Bauer et al., 2002). Fungal diversity is extensive; the newest estimates based on molecular methods suggest that there may exist as many as 5.1 million species (Bass and Richards, 2011; Blackwell, 2011).

Much of the fungal material released from natural sources is likely to be distributed into nearby areas (Adams et al., 2013b). Fungal material is also effectively transported over long distances via air by wind and air currents (Meier and Lindbergh, 1935) and by other processes, such as in clouds of desert dust (Shinn et al., 2003). At all locations where outdoor air fungi have been monitored, extensive variations due to seasonal and climatic factors have been observed (Pepeljnjak and Segvic, 2003; Raisi et al., 2013). In recent studies using DNA-based pyrosequencing techniques, it has been claimed that the fungal diversity in the atmosphere is close to that in the terrestrial environment (Fröhlich-Nowoisky et al., 2009; Yamamoto et al., 2012).

Fungi also are exploited in many human activities, both in industrial and at smaller scales (Knuf and Nielsen, 2012; Posch et al., 2012). The pharmaceutical industry uses so-called cell factories during its production of antibiotics, the best-known example being penicillin, which is produced by fungus *Penicillium rubens* (Houbraken et al., 2011). Enzymes used in detergents and foodstuffs are produced by either fungi or bacteria. Fungi are utilized in a variety of fermentation processes, such as making of beer and wine, as well as (in association with bacteria) in production of cheese and various sour milk products such as kefir. Bread baking utilizes yeasts and other fungi. Fungi and fungal products are also used in various biocontrol applications. On the other hand, the decomposing characteristics of fungi are everyday phenomena causing the spoilage of foodstuff. Furthermore, many fungal species are pathogens of humans, animals, and plants.

Thus, fungi in indoor environments represent only one aspect of the global occurrence and importance of fungi. In essence, fungi are ubiquitous, having adapted to live in all kinds of habitats, and this includes the indoor environment. When viewed from the human perspective, fungi are associated with both beneficial and detrimental processes. This is also the case regarding their presence in indoor environments: They can be considered as both contaminants and companions as we will discuss in this review.

A short history of research on indoor fungi

Airborne fungi have been registered and monitored since the 19th century. A few examples of the early research are presented here. Maddox (1870) described one of the first instruments for collecting airborne biological particles. A decade later, some results of air monitoring were published, for example, by Miquel as mentioned by Comtois (1997). During the early years of fungal monitoring, the focus was mainly on basic botanical research of outdoor air, and, somewhat later, the scope expanded to plant pathogens and the allergological aspects of fungal occurrence (Gregory, 1977). The hypothesis that mold spores could cause not only hay fever but also asthma was postulated at that time, as was the connection between asthma development and living in damp housing (Nilsby, 1949).

The work by Feinberg and Little (1936), based on yearlong monitoring of daily fungal concentrations outside a building in Chicago, revealed the extensive variation in outdoor spore counts. Several hundred fungal species were recorded; among the most prevalent were those of the genera *Alternaria*, *Cladosporium*, *Penicillium*, *Aspergillus*, *Rhizopus,* and *Mucor*. Remarkable variations in the occurrence were recorded

for most fungal genera. It was found that *Alternaria* (followed by *Cladosporium*, *Aspergillus,* and *Penicillium*) was the most common genus in a 2-year aerobiological survey conducted in nine states across the USA (Morrow et al., 1941). In the UK, aerobiological research was also active in the early decades of the 20th century, and regular outdoor fungal monitoring was established by the 1950s when the automatic spore trap was developed (Hirst, 1952). Fungal spores in outdoor air were monitored in two urban and one rural site in UK; one of the two urban sites had clearly lower concentrations of molds than the rural and the other urban location (Hamilton, 1959). These early observations of the major variations in the fungal concentrations were subsequently confirmed with various determination methods, as will be presented later (Factors that cause variation in indoor air concentrations of fungi – Sampling aspects and concentrations of airborne fungi in various regions and buildings).

Several researchers worked within the paradigm of microbiological Indoor Air Quality during the first half of the 20th century. The first researchers of airborne fungi were already aware that outdoor fungal spores could enter the indoor environment, that exposure to fungal allergens could take place via both outdoor and indoor air, and that damp and mold in the home posed a health risk (Richards, 1954). The contribution of mold growth to the indoor air counts of fungi was also recognized early: A Swedish study showed that while the average count of settling plates indoors was five colonies per plate, an average of 55 colonies per plate could be recorded in homes with mold problems (Nilsby, 1949). House dust and furniture stuffing were shown to be potential sources of indoor fungi, and the resuspension of settled spores was demonstrated in the 1950s (Maunsell, 1952; Swaebly and Christensen, 1952). Vacuumed house dust samples were used, and the fungal content of dust was found to be related to that of volumetric air samples (Schaffer et al., 1953). The role of the mechanical ventilation system in decreasing the fungal contamination of hospital air was demonstrated in the scientific literature by the 1970s (Lidwell and Noble, 1975). The fact that the ventilation and air conditioning system itself may also act as a source of fungal contamination was also realized (Ager and Tickner, 1983). At that time, the main concern was about allergic diseases, such as humidifier fever and infections, but the essence of the problem, still valid today, was stated, 'whenever water is stored and circulated in a building services system, the potential exists for causal organisms to grow and be transferred to the building atmosphere' (Ager and Tickner, 1983).

The researchers working in the first half of the 20th century were already well aware of the limitations of culture-based sampling and analysis, such as nonviability of some spores, as well as of the effects of air direction and velocity on particle collection efficiency, such as in impaction and sedimentation sampling (Feinberg and Little, 1936; Maunsell, 1952). Richards (1954) also pointed out that there were different aspects that may partly explain the variations of measured concentrations: particle size and characteristics of spores, and the duration of sampling. The possibility of health-related interactions between different agents such as fungi, bacteria, viruses, chemicals, and outdoor smog was also discussed (Schaffer et al., 1953).

These pioneer scientists identified many essential research questions that are still being investigated today, and important scientific findings were made with the simple methods available. Many of those discoveries have later been confirmed with more sophisticated methods and with larger data sets from different countries.

Particle sizes of airborne fungal material

In an indoor environment, fungal material may be present in the air, on different surfaces, and within various matrices such as house dust, mattresses, carpets, textiles, and porous surface materials. When airborne, particle size is the main variable that determines the behavior of the fungal particles, as is the case with other airborne particles (Kulkarni et al., 2011). Important behavioral aspects include settling and deposition, short- and long-range transport, retention in the filtration devices and other sinks, the release of spores and other fungal material (Kildesø et al., 2003), penetration into the buildings (Liu and Nazaroff, 2003), and resuspension into the air (Qian et al., 2014). Particle size is also one of the main variables that control human exposure, that is, via deposition in the respiratory system. Regional deposition efficiency and associated clearance mechanism are strongly influenced by particle size (Yamamoto et al., 2012). In general, fungal spores exist across a wide size range: approximately from 2 to 100 μm, and even larger for spores with elongated shape, such as *Helminthosporium* (Ellis, 1971). Not all spores are spherical, and their aerodynamic behavior varies accordingly. Fungal materials may also occur in air as fragments, aggregates, or chains (Green et al., 2011).

The size distributions of culturable airborne fungi indoors are close to those found in outdoor air (Reponen et al., 1994). Particle size studies of indoor fungi have indicated that *Penicillium* exists mainly as naturally dispersed spores or hyphae, but *Aspergillus* also can be present as aggregates of biological cells (Górny et al., 1999). The winter concentrations of fungi in mold problem homes were as much as double those found in the reference homes, and the maximum difference in concentrations between moldy and nonmoldy homes was observed for particles in the size range 2.1–3.3 μm (Hyvärinen et al., 2001; Reponen

et al., 1994). The size distribution in moldy houses was skewed toward larger particles when compared to reference buildings, but even small differences in particle size may lead to major differences in settling velocities (Reponen, 1995). Fungal particles originating from mold growth may settle faster than particles from other sources, and this might explain why airborne fungal concentrations do not differ so much between moldy and reference buildings in cross-sectional studies (see Factors that cause variation in indoor air concentrations of fungi).

Particle size is the main variable driving the airborne behavior of fungal particles. It is particularly important for understanding exposure phenomena. Reponen (1995) used previously published measurement data on fungi in moldy and non-moldy residences (Reponen et al., 1992; Reponen et al., 1994) and calculated the respiratory deposition of fungal particles with either nasal or oral breathing patterns (Martonen et al., 1992). It was estimated that, for example, more *Aspergillus* spores would deposit in the alveoli of occupants of moldy homes than in the reference homes (Reponen, 1995). Nonetheless, the importance of the particle size aspect for the actual inhaled dose of fungi has attracted too little attention in efforts to understand their health aspects.

Fungal submicron-sized fragments

While non-culturable methods have demonstrated the previously unknown communities of unculturable microbes, the aerosol measurement approaches have also revealed the existence of submicron-sized fungal fragments that could not be observed with traditional bioaerosol sampling. This is such an important topic that it deserves some discussion of its own.

Experiments investigating the dispersal of fungal particles from moldy surfaces showed that there were also remarkable numbers of particles smaller than spores (Górny et al., 2002; Green et al., 2006; Kildesø et al., 2003; Seo et al., 2009). These smaller particles are termed 'fungal fragments,' the fungal origin of which was confirmed by immunological analyses. By count, the fragments were released in amounts of up to 500 times more than spores, for example $>5 \times 10^5$ particles per cm^2 during a 30-min experiment (Górny et al., 2002). It is possible that fragments may not only be pieces of spores or hypha, but they may be derived from some intracellular or extracellular fungal structures (Green et al., 2006), or they may be due to the nucleation of semi-volatile secondary metabolites released by growing mold (Brasel et al., 2005a; Górny et al., 2002). Such fragments have also been observed in field studies in moldy houses (Adhikari et al., 2013; Reponen et al., 2007), where the ratio of fragment number/spore number was 10^3 for fragment size 0.3 μm and 10^6 for fragment size 0.03 μm. The formation mechanisms and occurrence of fungal fragments in indoor environments have been thoroughly discussed elsewhere (Green et al., 2011).

The health effects of submicron-sized particles, including the fungal fragments, are potentially more dramatic than those of larger particles. This is due not only to their more efficient penetration into the alveolar region of lungs but also to the much larger surface area per mass, enhancing exposure to any agents on the surfaces of the particles (Green et al., 2006). At present, little is known about the health relevance of fungal fragments, but in a recently published study, submicron-sized fungal materials, measured as (1-3)-β-D-glucan, were significantly higher in the homes of asthmatic children than those in non-asthmatic children (Seo et al., 2014). The small size of these fragments imposes special demands on sample collection techniques (Cho et al., 2005). Recently, a specific fragment sampling system has been developed (NIOSH two-stage cyclone) and applied in field studies (Seo et al., 2014).

Sampling of fungi and fungal components

Any measurement of the concentration of an agent or exposure assessment consists of two equally important phases: sample collection and analysis of the agents in question (Reponen et al., 2011). Many methods can be exploited in the determination of fungal concentrations in indoor environments. Fungi and fungal material can be sampled from air, from surfaces, from house dust, and from samples of building materials, and the latter usually chosen in cases when the suspicion of mold growth on that material needs to be confirmed (Scott et al., 2011). Airborne fungi are collected with instruments that are applications of particle measurement techniques, especially developed for collection of biological particles. The principles commonly used in these methods are inertial impaction, impingement into liquid, centrifugal collection, collection onto a filter, and electrostatic collection (Reponen et al., 2011). In the approaches that use culturing methods for analysis, collection may take place directly onto an agar surface (impactors) or into a liquid medium (impingers). Samples collected on filters are then suspended into a liquid and used for many types of analysis. The samples that are collected with these methods are quantitative in the sense that the volume of air that has gone through the instrument is precisely known, and the result can be expressed as the concentration per cubic meter of air. There are several extensive presentations and reviews available on the collection methods (Pasanen, 2001; Reponen et al., 2011; Scott et al., 2011; Thorne et al., 2004).

In large population studies, where fungal exposure in hundreds of homes or other indoor settings needs to be assessed, air sampling is typically too costly and

labor intensive. The aspects of costs and feasibility may also apply to building investigations in Indoor Air Quality practices (Prezant et al., 2008). Therefore, sampling approaches where settled house dust samples are collected have been developed, assuming that house dust samples are indicative of long-time integrated conditions for human exposure indoors (Gehring et al., 2007). House dust, which consists mainly of textile fibers, hair, and skin scales, also contains many microbes, both fungi and bacteria (Rintala et al., 2012), and insects, pollen, and other debris from animal and plant sources. Samples from carpets, floors, and mattresses are usually collected by vacuuming a defined area and for a predetermined time to standardize the sampling (Giovannangelo et al., 2007; Karvonen et al., 2012). The collected amount of dust is weighed, and fungal material is extracted from the sample matrix before the analysis. The results are usually expressed per gram of dust, or as surface load of fungi, that is, per meter squared. In allergy-related studies, samples of mattress dust are often used due to their proximity to the breathing zone during sleep, and due to their good reproducibility as compared to floor or air samples (Hyvärinen et al., 2006a).

Samples vacuumed from carpets and other surfaces provide information about fungi that are present in that indoor environment, but these kinds of samples do not describe what part of the collected fungal material has actually been airborne. Therefore, passive collectors have been developed for collecting settled dust from elevated surfaces such as shelves and cupboards (Noss et al., 2010; Wörtz et al., 2005). In this sampling approach, the effect of foot traffic and the greater contribution of larger particles are avoided. A more precise estimation of respiratory exposure can be achieved than with samples vacuumed from the floor. Passive collectors also enable longer sampling times than labor-intensive active sampling, and they are considered to reflect long-term airborne exposure conditions (Noss et al., 2010).

Methods to analyze fungi

After a sample has been collected, there are several ways by which its fungal content can be analyzed. No method alone can describe and quantify the richness of fungal characteristics, but each method tends to reveal one or more particular aspect. The main methods are briefly mentioned here. Microscopical methods have been extensively used to count and identify fungal particles especially for allergen monitoring and in plant pathology (Flannigan et al., 2001). Some spore types can be identified and quantified directly from samples, but in general, microscopic counting does not provide taxonomic discrimination. For indoor environments, direct microscopy is one of the methods that can be used in Indoor Air Quality-related building investigations. The second method is culturing which exploits the viability or culturability of the fungal spores or propagules present in the sample. Incubation takes place under standardized conditions followed by counting and microscopical identification of visible fungal colonies. This method can provide—with sufficient mycological expertise—low-level taxonomical discrimination, but only for a small fraction of the community (Prezant et al., 2008). Culturing is a selective method, as the given nutrient medium, and incubation temperature and light conditions regulate which microorganisms will form detectable colonies on the medium. Even the availability of space on the agar plate may limit growth, especially of slower growing organisms. While it is selective, culturing however provides both a qualitative and quantitative estimate about those fungi that are present in the sample and are able to grow under the given conditions. By applying various media and incubation conditions, the analysis can be targeted to certain fungal types. After culturing, the fungal colonies may be isolated for further studies. Culturing methods have been extensively used in the characterization of fungal concentrations and mycobiota in indoor air and for investigations of factors affecting concentrations. These studies will be further discussed in Sampling aspects and concentrations of airborne fungi in various regions and buildings.

For analysis methods other than culturing, the analyte is usually extracted from the sample and then subjected to chemical, immunochemical, enzymatic, or DNA-based analyses to quantify fungal biomass or other attributes of the mycobiota of the sample. Using chemical markers, the amount of fungal biomass can be estimated as ergosterol (Saraf et al., 1997) or as (1-3)-β-D-glucan (Larsson, 1994). The biological activity of glucans can be determined with the *Limulus* bioassay (Foto et al., 2004). The activity of the enzyme N-acetylhexosaminidase (NAHA) is used in a commercially available application (Mycometer^{R}) to assess the amount of growing mold in a surface, material, or air sample (Reeslev et al., 2003). Immunochemical methods are utilized in quantifying fungal allergens (Horner et al., 1995). Fungal products, such as microbial volatile organic compounds (MVOC) and mycotoxins, are analyzed usually with mass-spectrometry-based techniques that are coupled with pre-separation in a gas or liquid chromatograph (Bloom et al., 2007; Järnström et al., 2006; Vishwanath et al., 2011). As the DNA-based methods are becoming more popular when investigating indoor fungi, they will be further discussed in the following section.

DNA-based methods to analyze indoor fungi

It has long been known that the majority of microorganisms are uncultivable under laboratory conditions.

For samples from indoor air, the ratio of total fungi to viable fungi has been estimated to be as low as 100:1 (Toivola et al., 2002). One way to overcome this limitation is to exploit the possibilities offered by DNA-based approaches, especially sequencing, that have already revolutionized our view on microbial assemblages in other environments, including the human body. The initial step in all DNA-based methods is the extraction of DNA directly from a given environmental sample. Microbial cells are suspended from the sample matrix, and the cell envelopes are disrupted mechanically, enzymatically, and/or chemically to free the intracellular DNA, which is then further purified for subsequent analysis steps. Most of the currently used DNA-based approaches that aim at characterizing microbial communities have the amplification of a target marker in common, a DNA sequence that occurs in all microbes of interest. For fungi, the regions commonly used for this purpose are the nuclear internal transcribed spacer regions (ITS or nucITS), which are located between the fungal ribosomal RNA genes, or sequences within the rRNA genes themselves (Schoch et al., 2012). In brief, the differences in variability/conservation within these 'barcode' gene sequences, as they are often referred to, permit targeting of microbial groups at various taxonomic levels from strains and species to genera, families, or even higher taxonomic levels. Since the initial applications of quantitative polymerase chain reaction (qPCR) as a tool to assess exposure to the toxigenic fungus *Stachybotrys chartarum* in indoor environments (Haugland et al., 1999), many qPCR assays have been designed to target different indoor fungal species, genera, or groups (Haugland and Vesper, 2002). Generally, microbial levels detected with qPCR are several orders of magnitude higher than those detected with cultivation-based approaches. This outcome confirms that cultivation-based approaches underestimate both the diversity and quantities of fungi indoors. Quantitative PCR is being increasingly used, not only in studies focusing on indoor fungal exposures and human health, but also in building investigation practices. One challenge with qPCR is to decide which of the relevant assays should be applied, as this method is selective in the sense that only those microbes that are targeted by the assays will be detected.

Sequencing methods utilize a pool of fungal PCR amplicons from an environmental sample by obtaining the DNA sequences of each single PCR fragment. Highly similar sequences are then commonly organized —based on defined cutoffs for sequence similarity— into operational taxonomic units (OTUs), to study the microbial community composition and characteristics. The so-called next-generation sequencing approaches, utilizing different methods and platforms, have improved sample throughput and resolution and greatly reduced costs (Metzker, 2010). These DNA approaches, however, also encounter technical limitations, are far from being flawless, and have introduced a new dimension of uncertainties that need to be carefully considered when interpreting the results obtained. While, in theory, sequencing results should reflect the original microbial composition in a sample, this is not the case in reality, as any DNA extraction method will be selective to some extent, copy numbers vary in a target DNA marker, and PCR amplification introduces additional bias into the data. For more details of these issues, the reader is referred to a series of excellent studies discussing some of these aspects (Amend et al., 2010a; Huber et al., 2009; Rastogi et al., 2009; von Wintzingerode et al., 1997).

Fungi in the indoor environment

Sources of indoor fungi

This section deals with sources, that is, origins of fungal material found in indoor environments. In fact, the most important source of indoor fungi is outdoor air. This has been extensively shown using culturable methods, and recent sequencing data appear to confirm this basic feature (Pitkäranta et al., 2008). Concentrations of culturable fungi in outdoor and indoor measurements correlate strongly, and the seasonal patterns observed in outdoor air counts are also reflected in indoor concentrations (Burge and Rogers, 2000; DeKoster and Thorne, 1995; Dharmage et al., 1999; Fradkin et al., 1987; Kuo and Li, 1994; Lee and Jo, 2006; Su et al., 2001). Farming environments have more rich and diverse content of airborne fungi than non-farming environments, and this is usually reflected in the indoor fungal content of farming homes (Ege et al., 2011; Kotimaa et al., 1984; Olonitola et al., 1994).

The contribution of outdoor air is also seen in species composition of indoor air (Burge, 1990; Gravesen, 1979; Hyvärinen et al., 1993; Miller et al., 1988). However, the rank order of the most common indoor fungi is not necessarily identical with that outdoors; for example, the genus *Penicillium* is usually more common in the indoor air than in outdoor air (Hyvärinen et al., 1993; Li and Kendrick, 1995). The common occurrence of *Penicillium* points to potential indoor sources and spore release characteristics of this genus.

There are also intramural sources that may modify concentrations, mycobiota, and indoor/outdoor (I/O) ratios of airborne fungi. Many kinds of 'normal' everyday activities may act as occasional or regular intramural sources of fungi (Lehtonen et al., 1993). In domestic indoor environments, examples of potential fungal sources include the handling of organic or biological material (e.g., root vegetables, fruit, and blue cheese) and spoilage (e.g., moldy bread or vegetables)

(Lehtonen et al., 1993). The presence of potted house plants is also associated with higher fungal levels in indoor air and in the house dust than in indoor spaces without plants (Gehring et al., 2001; Pessi et al., 2002). Storage of household biowaste is a source of biological particles (Wouters et al., 2000), as is handling of firewood (Lehtonen et al., 1993; Leppänen et al., 2014). Experiments have also shown that fungi may grow to microcolonies on temporarily wetted surfaces within days or weeks and act as sources of spores (Pasanen et al., 1992). This is especially true for *Penicillium*, many species of which are rapid colonizers and efficient in producing and releasing spores. Any wetting or moistening of building surfaces and materials in a larger scale leads to mold growth, which may act as a major source of indoor fungal material.

The occupants of buildings—humans and pets—are first of all sources of indoor bacteria due to continuous release of the skin bacteria (Täubel et al., 2009). The impact of human occupancy on indoor bacteria has been extensively shown with a variety of methods (Hospodsky et al., 2012; Kembel et al., 2014; Meadow et al., 2014; Qian et al., 2012). This is different from fungi, the main sources of which are outdoor air and other sources described above. However, human skin, hair, and nails are also sources of indoor fungi, especially dermatophytes such as the yeast *Malassezia* (Pitkäranta et al., 2008). Even if not major sources of fungi, the mere presence of human occupants has an impact on indoor airborne fungal concentrations. The effect of occupancy is mainly due to the resuspension of settled particles (Qian et al., 2014).

Fungi, carpets, and house dust

Wall-to-wall carpeting appears to support a complex matrix of indoor fungi. Studies have shown that the relationship between carpets and fungal levels in carpet dust is driven by the amount of house dust (Gehring et al., 2001). This will be particularly true if 'fungal levels' are expressed as fungal mass per surface area (typically referred to as 'fungal load'), but the results may appear very different when the fungal levels are expressed as fungal mass per gram of dust (concentration).

Carpet was demonstrated to be a significant sink of fungi in 1 year long study, in which schools with carpeted and tile flooring were compared (Foarde and Berry, 2004). Airborne concentrations of culturable fungi were significantly lower in the carpeted school than in the school with tile flooring, but the (1-3)-β-D-glucan load per area of carpet was much higher than that of tile floor. In residences, there are also indications that carpeting may act as a sink for fungi. The presence of carpeting did not correlate with higher levels of fungi in indoor air (Chew et al., 2003; Ren et al., 2001). In a study focusing on fungal species, only half of the species found in the house dust were also detected in the indoor air (Miller et al., 1988). The effect of carpet may depend on the actual carpet type: Loop-pile-type carpet was found to retain more dust within its structure than the cut pile counterpart (Shorter, 2012).

It must be assumed that the role of a carpet is not only that of a sink. Although the carpet material may retain a significant amount of dust and fungal material, at some point, it may become overloaded and start to increasingly act as a source of resuspended dust and fungal particles, as suggested by results from experimental studies (Shorter, 2012). In fact, in many studies, higher fungal levels have been associated with carpets than with smooth flooring, irrespective of whether the values are expressed as concentrations or loads (Chew et al., 2001; Chew et al., 2003; Douwes et al., 2000; Gehring et al., 2001; Li and Kendrick, 1995; Wouters et al., 2000).

Fungal growth due to building dampness and moisture

One common characteristic of the intramural sources of fungi is that they are related to housing characteristics and occupant behavior. Although they contribute to the fungal concentrations in the indoor environment, it is not known that fungi from such sources would have any relevance from the health point of view and it is tempting to claim that these are 'normal' sources with no need to initiate any specific control measures. A very different view dominates for the fungal source type presented in the following paragraphs.

Wherever excess moisture is available, fungi and other microorganisms start to grow, developing gradually into mold that is often visible to the naked eye. Mold growth in a building acts as a source of indoor pollutants, such as spores, cells, fragments of hyphae and spores, and microbial metabolites such as volatile MVOCs and non-volatile toxins (Dales et al., 1997; Hyvärinen et al., 1993; Hyvärinen et al., 2006a, 2006b; Klanova, 2000; Sordillo et al., 2011). Mold growth due to dampness cannot be considered a 'normal' source of fungi. Due to its common occurrence (Haverinen-Shaughnessy, 2012) and its association with significant health effects, dampness-associated mold growth is a public health concern (Mudarri and Fisk, 2007). Dampness- and mold-related Indoor Air Quality problems occur in many types of buildings in different parts of the world (Haverinen-Shaughnessy, 2012; Howden-Chapman et al., 2005; Mudarri and Fisk, 2007). Why building mold is so especially harmful to health is not yet fully understood (see Fungi in the indoor environment).

Mold growth is caused by excess water in the location in question. The minimum requirements for temperature, pH, light, and availability of nutrients are usually present in buildings, and therefore, moisture is

the key factor regulating microbial growth (Adan et al., 2011). More specifically, condensed water is not necessarily needed, but it is the water activity (a_w) of the substrate that regulates growth (Adan et al., 2011; Grant et al., 1989; Sautour et al., 2001). Indoor air humidity normally fluctuates due to variations in the outdoor humidity and also due to indoor activities such as showering, cooking, heating, and cooling, and due to the emissions from people (Adan et al., 2011). While the building construction is generally aimed to keep the interior space dry, unwanted and excess moisture may occur in the indoor environment as a consequence of a failure in moisture control (Lstiburek and Carmody, 1996). Water may gain access through cracks or leakages, it may be a result of condensation of water vapor on a cool surface, or it may enter the building as rising water from the soil by capillary force (Prezant et al., 2008). At the other extreme, the total wetting of the building due to floods, storms, hurricanes and typhoons, or heavy rain can lead to massive mold growth and serious difficulties in cleaning and removing the contamination (Barbeau et al., 2010; Bloom et al., 2009a; Chew et al., 2006; Schwab et al., 2007).

Most indoor fungi have their optimum conditions for growth in a RH range 90–100%, but for example, incubation of house dust at 84–86% RH for 25 days initiated significant proliferation of fungi, such as *Aspergillus* (Korpi et al., 1997). For practical applications, it is generally agreed that surfaces can be kept free of mold growth if the relative humidity of adjacent air remains <80% (Adan et al., 2011). Fungi are also able to grow in fluctuating moisture conditions where the substrate is occasionally dry and wetted again (Pasanen et al., 2000). Examples of fungi that may grow on moist building materials are shown in Table 2, which presents data based on the analyses of samples of moldy building materials (Andersen et al., 2011; Andersson et al., 1997; Hyvärinen et al., 2002; McGregor et al., 2008; Pietarinen et al., 2008; Polizzi et al., 2009). It is notable that many bacteria—as well as protozoa and other organisms (Yli-Pirilä et al., 2004)—also grow in parallel with fungi on moldy materials (Andersson et al., 1997; Hyvärinen et al., 2002; Pietarinen et al., 2008).

The fungi that grow on moist building materials may be similar to those regularly found in the air inside buildings without moisture problems, but often they are species of different genera, for example, *Stachybotrys,* that only infrequently occur in normal indoor air (Miller et al., 2000; Tiffany and Bader, 2000). The occurrence of such organisms in air or on surface wipes can be considered as potential indication of mold growth that is not otherwise visible, and this information can be exploited in Indoor Air Quality problem-associated building investigations (Prezant et al., 2008).

Table 2 Examples of fungal genera that may grow on moist building materials

Acremonium
Aspergillus
Aureobasidium
Chaetomium
Chrysosporium
Cladosporium
Eurotium
Exophiala
Fusarium
Geomyces
Geotrichum
Monocillium
Mucor
Oidiodendron
Paecilomyces
Penicillium
Phialophora
Phoma
Rhizopus
Scopulariopsis
Sphaeropsidales group
Stachybotrys
Trichoderma
Tritirachium
Ulocladium
Wallemia
Yeasts

Dispersal, resuspension, and removal of fungal material

Fungal spores and other fungal particles are dispersed from surfaces on which they grow or get deposited into surrounding air through air movements caused mainly by ventilation, and through mechanical disturbance of contaminated structures and surfaces (Górny et al., 2001; Pasanen et al., 1991; Zoberi, 1961). Spore release is affected by relative humidity of surrounding air (Górny et al., 2001; Kildesø et al., 2003; Pasanen et al., 1991) and by the texture of the substrate surface (Frankel et al., 2014). Massive mechanical disturbance of mold growth, such as dismantling of the mold-damaged structures, enhances the release of spores efficiently, increasing the indoor air concentrations by orders of magnitude (Hunter et al., 1988; Rautiala et al., 1996).

Different fungal genera and species have different capacities to release spores and other particles into the surrounding air. Spores vary in their size, geometry, and surface characteristics, which partly explains the varying fungal composition of indoor air and its differences in relation to outdoor air. For example, dry spores of the genera *Penicillium* and *Aspergillus* are more easily released than *Cladosporium* spores under the same indoor air conditions (Pasanen et al., 1991). *Penicillium commune* released spores more easily than *Aspergillus versicolor* or *Paecilomyces variotii* (Näsman et al., 1999). This may explain at least to some extent the common occurrence of culturable *Penicillium* in indoor air (Burge et al., 2000; Górny et al., 1999; Hunter et al., 1988; Kuo and Li, 1994; Miller et al.,

1988; Pasanen et al., 1992; Ren et al., 1999b). Fungi producing spores in slime, such as *Stachybotrys, Trichoderma*, *Aureobasidium,* and *Acremonium,* or those producing spores in closed fruiting bodies, such as some species of *Chaetomium*, are not able to release spores easily (Samson, 2011); thus, their occurrence in air is less probable. On the other hand, some fungi are able to actively 'shoot' their spores and other cells into the surroundings, *Sporobolomyces* yeast as an example (Crous et al., 1995).

Humans may transport fungal particles on their clothes, skin, hair, and shoes when they come inside from outdoors, as can pets on their feet and fur. These particles are probably dispersed from the carrier into the indoor air, as observed with increased concentrations in air or in house dust (Fujimura et al., 2010; Korthals et al., 2008; Normand et al., 2011; Pasanen et al., 1989; Waser et al., 2004). It is known that entering the indoor space after a visit to a cowshed or a horse stable can elevate the levels of fungal particles in indoor air (Lehtonen et al., 1993; Pasanen et al., 1989).

Particles that have settled on surfaces can also be resuspended into the indoor air by mechanical disturbance and by occupant activities. Thus, walking, vacuuming, and other human activity cause resuspension of settled fungal particles (Qian et al., 2014) and significantly increase spore counts in the indoor air, although only temporarily (Buttner and Stetzenbach, 1993; Hyvärinen et al., 2001; Veillette et al., 2013). Similarly to the factors affecting dispersal, the extent of resuspension is dependent on the flooring type, on the fungal genus, and on environmental conditions such as relative humidity (Qian et al., 2014; Ren et al., 1999b). Even though the dust within a carpet typically supports higher fungal concentrations than the dust on a smooth floor, resuspension from carpeted surface is not necessarily efficient enough to result in higher airborne concentrations of fungi (Chew et al., 2001; Foarde and Berry, 2004). The removal of fungal particles from indoor environments takes place similarly to other particles: by exhaust ventilation and by gravitational settling of particles on surfaces from which they are then removed by cleaning (Kildesø et al., 1998).

Role of ventilation

Ventilation has two major roles regarding indoor fungi. In conjunction with the fresh intake air, outdoor fungal particles are transported indoors in amounts depending on the system. At the same time, exhaust air removes contaminants, be it particles, gaseous chemicals, or moisture from the indoor air. Mechanical intake ventilation systems equipped with a good filter can remove most of the coarse particles from the air coming indoors. This is seen as lower indoor air concentrations of fungi than those outdoors (DeKoster and Thorne, 1995; Reponen et al., 1989; Reponen et al., 1998) or than those in buildings with natural ventilation (Burge et al., 2000; Parat et al., 1997). When ventilation is based on gravity only or the system consists of mechanical exhaust alone, fresh air comes in through windows, doors, vents, or leakages in building structures and no active filtration of outdoor fungal particles takes place. However, the building envelope may act as a filter for outdoor fungal particles resulting in lower fungal concentrations indoors than outdoors and a possible accumulation of outdoor fungi in building structures (Pessi et al., 2002; Thatcher and Layton, 1995). In a building without a controlled air intake through ducts, penetration of air may take place through undesired routes such as cracks in contaminated structures (Pessi et al., 2002) and through crawl spaces (Airaksinen et al., 2004a), which may provide conditions favorable for fungal growth (Airaksinen et al., 2004b; Kurnitski and Matilainen, 2000). Penetration of *Penicillium* spores via electrical outlets into indoor spaces has also been demonstrated (Muise et al., 2010). Most effective penetration through cracks, however, takes place by particles within a size range 0.1–1.0 μm, that is, the size range of fungal fragments (Liu and Nazaroff, 2003). From the point of view of Indoor Air Quality, prevention of any outdoor particles from entering indoors is considered desirable and most effective by combining an optimized airflow together with filtration of outdoor air (Hänninen and Asikainen, 2013).

In fact, the ventilation system may act as a source of contaminating fungal particles if it is not maintained properly (Ahearn et al., 2004; Bernstein et al., 1983; Garrison et al., 1993). High relative humidity or water condensing on the inner surfaces of ducts, filters, and drip pans may encourage mold growth, as the accumulated dust and dirt can act as a nutrient substrate. In addition, uncovered insulation material within ducts may support microbial growth (Foarde et al., 1996). Air filters, which are made of fibrous or porous materials, may be good habitats for microbial growth if enough moisture is present, and then, they can represent sources of indoor fungal propagules (Buttner et al., 1999; Kemp et al., 2001) or microbial volatile compounds (Schleibinger and Ruden, 1999). Such growth may pose a risk to the Indoor Air Quality and the health of occupants, as the ventilation system is an efficient way to distribute the dispersed particles or volatile compounds into the indoor air. For example, hypersensitivity pneumonitis associated with *Penicillium* growth on duct surfaces has been reported (Bernstein et al., 1983), and aging of the ventilation system was shown to be associated with symptoms experienced by office workers (Graudenz et al., 2002).

Infectious agents may be spread via ventilation systems. One review (Li et al., 2007) concluded that there was sufficient evidence to demonstrate the association between ventilation, air movements, and the

transmission of infectious agents within buildings. Although the review concentrated on bacterial and viral infections, the risk may be similar for fungal infections, especially in hospitals where airborne fungi are a major concern (Falvey and Streifel, 2007). Fungal contamination may pose a risk in operating rooms and other facilities (Araujo et al., 2008). Recommendations for maintenance and service of the ventilation systems have been issued (Brief and Bernath, 1988) although the impact of regular cleaning of ventilation systems in maintaining good Indoor Air Quality has not been conclusively demonstrated (Zuraimi, 2010).

Cleaning and removal of fungal material

Together with ventilation, cleaning is the other major means to remove and reduce the levels of microbial material from the indoor environment. Cleaning effectiveness is related to the fungal load in house dust (Gehring et al., 2001; Schneider et al., 1996; Sordillo et al., 2011). Specifically, frequent vacuuming decreases concentrations of fungal agents in floor dust (Gehring et al., 2001; Giovannangelo et al., 2007; Leppänen et al., 2014; Salares et al., 2009; Sordillo et al., 2011). On the other hand, vacuuming and sweeping the floor increase the airborne concentrations of fungi temporarily due to their resuspension (Hunter et al., 1988; Lehtonen et al., 1993). Whether the lower fungal concentrations in house dust also are reflected in lower concentrations in indoor air is a less explored issue. Apart from routine household cleaning, there are specific cleaning operations such as professional cleaning of ventilation ducts (Zuraimi, 2010) or cleaning after mold remediation. Thorough cleaning of surfaces, furniture, and ventilation ducts after mold remediation is considered essential to ensure that occupants can safely return (Wilson et al., 2004). Situations requiring even more intensive efforts are the cleanup operations after flooding and hurricanes (Bloom et al., 2009a; Golofit-Szymczak et al., 2012; Rao et al., 2007).

Other determinants of fungal loads in indoor environments

Microbial exposures including fungi, their determinants, and links to health have been a focus of many recent epidemiological population studies that explore whether the farming environment is protective from allergy (Alfven et al., 2006; Braun-Fahrländer et al., 2002; Genuneit et al., 2011; Heinrich et al., 2002). Most of the results have been obtained from house dust samples (floor dust, mattress dust) (Giovannangelo et al., 2007; Hyvärinen et al., 2006a, 2006b), and fungal concentrations have been determined with both culturing methods and non-culture-dependent analyses (Rintala et al., 2012). Published concentrations have been reported either as load (per square meter) or as concentration (per gram), which complicates interpretation of the results. As we concluded in Fungi, carpets, and house dust, fungal loads are largely driven by the amount of dust due to their strong correlations (Gehring et al., 2001; Giovannangelo et al., 2007).

Season affects fungal concentrations in house dust (Ren et al., 1999b). Most European studies have detected the highest fungal concentrations in house dust during summer or fall (Casas et al., 2013b; Heinrich et al., 2003; Kaarakainen et al., 2009; Koch et al., 2000; Valkonen et al., 2011), but in a study conducted in Australia, the highest concentration of ergosterol in floor dust was observed in the winter season (Dharmage et al., 2002). Comparisons between continents are somewhat complicated because the weather conditions in different seasons differ.

The importance of geographic location on indoor fungi has also been analyzed. In a European multicentre study (14 cities), fungal concentrations measured for different fungal species and groups with qPCR from mattress dust varied extensively between geographical regions and cities (Valkonen et al., 2011), similarly to what was observed for bacterial endotoxin in the same multicentre study (Chen et al., 2012). However, no clear common trend was found as to whether lower or higher indoor fungal exposure levels occurred in a certain geographic region. A small qPCR-based survey comparing populations of mold species in house dust from UK and (Ohio) USA pointed to rather similar profiles in these two regions; significant differences in concentrations were found in only 13 of 81 species screened (Vesper et al., 2005).

Higher numbers of occupants have been associated with higher concentrations of fungal material in house dust (Casas et al., 2013a; Gehring et al., 2001; Giovannangelo et al., 2007), probably due to an increased tracking in of outdoor fungal material via shoes and clothes. There are several other factors that may affect indoor fungal levels, such as living close to or on a farm, storing firewood indoors, and using a fireplace (Hyvärinen et al., 2006b; Leppänen et al., 2014).

Overall, indoor and outdoor environmental characteristics considered in different studies seem to explain only a part of the variation of fungal concentrations in house dust, that is, 7–44% depending on which agent is measured and on the sample type (Casas et al., 2013b; Gehring et al., 2001; Hyvärinen et al., 2006b; Leppänen et al., 2014; Sordillo et al., 2011). Differences in the levels of explanation are possibly due to the variable time lengths to which the settled dust has been allowed to accumulate before sampling and in variations among analysis methods. It appears that a longer sample accumulation period allows more diverse factors to influence the fungal content of the sample, while shorter sample accumulation times allow for a better explanation of the variance in fungal content via a restricted set of determinants (Leppänen et al., 2014).

Number concentrations of culturable fungi in indoor air

This section specifically refers to *culturable* fungal data available from the measurements of indoor air. An extensive literature on concentrations and mycobiota of airborne fungi exists as a result of attempts to characterize the microbiological quality of indoor air in various buildings from all around the world. Examples of the results of those studies are presented in Table 3. The aims of these measurements have varied from study to study—there are descriptive studies on fungal occurrence and its variation, studies aiming to assess human exposure, and studies that collect reference data to be applied in routine Indoor Air Quality investigations. The most striking feature in the data on concentrations is their remarkable variation. As we mentioned before, each building is its own environment, and the concentrations of fungi indoors are affected not only by the outdoor concentrations but also by building- and occupant-related factors. Measurement results from one building cannot easily be extrapolated to the next one, unless it is a similar building with similar functions, and unless the measurements have been made in a similar manner. These may be some of the reasons why some of the data on indoor concentrations appear to be both scattered and contradictory.

Culturable fungi only comprise a fraction of all the fungal material in any given environment or sample matrix, a fact that also applies to indoor air (Toivola et al., 2002). Nonetheless, it can be postulated that culturable fungal propagules may act as a surrogate for how airborne fungal particles behave between outdoor and indoor environments, in different types of buildings and within each indoor environment. So far, much less data on these phenomena are available that apply to all fungal particles, whether culturable or non-culturable. In the following section, we will first summarize the factors that have been observed to contribute to the variation in concentrations of airborne fungi and then give examples of the concentrations and mycobiota that have been reported from various types of buildings from different regions.

Factors that cause variation in indoor air concentrations of fungi. Outdoor air is the main source for indoor air fungi (Burge et al., 2000; DeKoster and Thorne, 1995). Therefore, geographical, diurnal (Abdel Hameed et al., 2009; Mentese et al., 2012), seasonal (Frankel et al., 2012; Herbarth et al., 2003; Madsen et al., 2011; Ren et al., 1999a, 1999b; Reponen et al., 1992), and meteorological factors (Li and Kendrick, 1995) that alter fungi in outdoor air also influence the fungal concentrations and mycobiota of indoor air (Fradkin et al., 1987).

Seasonal variation causes a regular pattern of variation in airborne concentrations: Usually, the winter concentrations are lowest and summer concentrations are the highest. This pattern has been reported from many different climatic regions. Garrett et al. (1998) measured fungal concentrations in 80 homes in Victoria, Australia, and observed that summer concentrations of both viable and total airborne fungi were approximately three times higher than those present in the winter and, furthermore, that indoor and outdoor concentrations correlated significantly (Garrett et al., 1998). In Denmark, the correlations between indoor air and outdoor air fungal concentrations were also significant, especially in spring and summer (Frankel et al., 2012). In cold climates, where there is wintertime snow cover, the outdoor fungal concentrations in winter are negligible. Indoor air concentrations are then low unless there are strong intramural sources such as mold growth (Reponen et al., 1992). Seasonal variation has also been detected in subtropical climates (Su et al., 2001). Dependencies of indoor fungal concentrations and content on outdoor air are particularly evident in naturally ventilated buildings, whereas in buildings with a mechanical intake air, the concentrations are more stable due to the filtration of outdoor fungal material (Parat et al., 1997). In mechanically ventilated buildings, the effect of seasonal variation on the fungi of indoor air is diminished. For example, no seasonal effect was seen in Georgia, USA, either in concentrations of air or dust samples (Horner et al., 2004). It is possible that this finding was due to the ventilation system in the measured buildings that filtered most outdoor fungi from incoming air throughout the year.

It is evident that seasonal variation links to factors such as local climate, humidity, ventilation, sample type, and microbial agent measured. Therefore, the 'season' may have different effects on fungal concentrations under different local conditions. The absolute humidity (g water/m^3 of air) of indoor air usually follows that of outdoor air; the resulting relative humidity of indoor air may be very different from the relative humidity of outdoor air, depending on the temperature difference between indoors and outdoors. The higher relative humidity of indoor air seems to predict higher concentrations of culturable fungi in air (Chao et al., 2002) as also observed with non-culturable methods (Chew et al., 2003; Gehring et al., 2001; Singh et al., 2011). The seasonal effect may also be specifically linked with the fungal type in question. A clearer seasonal effect is observed with culturable fungi originating mainly from outdoors such as *Cladosporium,* which occurs in higher levels during summer months, while fungi with more indoor-related sources such as *Penicillium* and *Aspergillus* are at their highest during the winter season (Ren et al., 1999b). Indoor fungal concentrations and mycobiota are also affected by the characteristics and use of the building, which cannot be totally separated from the

Table 3 Examples of concentrations of airborne culturable fungi in various buildings reported from various countries[a]

Country	# and type of buildings	Concentration cfu/m^3	Rank order of genera	Reference
Finland	71 non-complaint dwellings	Winter GM (GM*GSD) 40 (150 Summer GM (GM*GSD) 410 (1000)		Reponen et al. (1992)
Norway	38 dwellings	Range <20–200	*Penicillium*, yeasts, *Aspergillus, Cladosporium, Mucor*	Dotterud et al. (1995)
	7 schools	Range 0–30		
Czech Republic	120 flats	Heating season 0–64 Non-heating season 10–510		Drahonovska and Gajdos (1997)
England and Scotland	62 dwellings	Median (range) 236 (12–23 070) [mold absent] Median (range) 2673 (424–21 790) [mold present]	37 fungal genera; *Penicillium, Cladosporium, Aspergillus, Ulocladium, Geomyces*	Hunter et al. (1988)
France	2 office buildings	Mean (s.d.), range 113 (271), 2–1212	*Penicillium, Cladosporium, Botrytis, Beauveria*	Parat et al. (1997)
Paris, France	28 day care centers	GM (GSD) winter 121 (1.8) summer 354 (2.4)	*Penicillium, Cladosporium, Aspergillus*	Roda et al. (2011)
Germany	1 laboratory building	Mean 20–300	*Aspergillus, Penicillium, Wallemia, Cladosporium*	Engelhart and Exner (2002)
Poland	>100 flats	Median (range) 78 (0–2000) [mold absent] 504 (49–17 000) [mold present]	*Penicillium, Aspergillus*, yeasts	Górny and Dutkiewicz (2002)
Barcelona, Spain	22 homes including houses and flats	Range 0–1666	36 genera; *Cladosporium, Penicillium, Aspergillus, Alternaria*	Gomez de Ana et al. (2006)
British Columbia, Canada	39 schools	GM (GSD) 323 (2.8)	*Penicillium, Cladosporium, Aspergillus*, yeasts, non-sporulating fungi	Bartlett et al. (2004)
USA across the country	44 office buildings	Median (range) 55 (<24–1000) Outlier: 9000 in a naturally ventilated bldg.		MacIntosh et al. (2006)
USA across the country	1717 buildings	Median (range) 82 (<DL – >10 000)	*Cladosporium, Penicillium*, non-sporulating fungi, *Aspergillus*	Shelton et al. (2002)
Boston, USA	496 homes	Mean (s.d.) 580 (1278)	*Penicillium, Cladosporium*, non-sporulating fungi, yeasts	Chew et al. (2003)
Connecticut, USA	11 dwellings	Mean (s.d.) Winter 431 (327) Summer 1036 (693)	Winter: *Aspergillus, Penicillium, Cladosporium* Summer*: Cladosporium, Aspergillus, Penicillium*	Ren et al. (1999a, 1999b)
Georgia, USA	50 dwellings	Median Winter 71–92 Summer 166–189	*Cladosporium, Penicillium, Epicoccum*, yeasts	Horner et al. (2004)
Texas, USA	50 houses	Mean (s.d.) Coarse fungi[b] winter 11 (28) Fine fungi[b] winter 78 (103) Coarse fungi summer 11 (15) Fine fungi summer 105 (101)		Mota et al. (2008)
Southern Taiwan	35 homes	Avg winter 20 550 Avg summer 6800	*Cladosporium, Aspergillus, Penicillium, Alternaria*	Su et al. (2001)
Taiwan, Taipei	6 homes	GM (GSD), range 1288 (1.95), 951–1760	*Aspergillus, Penicillium, Cladosporium*, yeasts	Li and Kuo (1994)
Taiwan, Tai-Chi	12 homes	GM (GSD), range 1950 (1.55), 1508–2502		Li and Kuo (1994)
Korea	20 homes 11 schools	GM (GSD) 3802 (1.1), summer GM (GSD) 371 (1.3), winter	*Cladosporium, Penicillium,*	Jo and Seo (2005)
Singapore	Daycare centers NV, $N = 78$ AC, $N = 19$	GM (s.d.) 820 (1312), NV 677 (1151), AC		Zuraimi et al. (2007)
Melbourne, Australia	485 houses	Median (range) 549 (37–7619)	*Cladosporium, Penicillium, Aspergillus*	Dharmage et al. (1999)

NV, natural ventilation; AC, air conditioned; DL, detection limit; avg, average.

[a]Sampling strategies, sampling methods, and culture conditions vary from study to study, and therefore, the concentrations are not fully comparable with each other.

[b]coarse fraction >8 μm, fine fraction <8 μm, based on two-stage impactor.

activities of the occupants. While the ventilation system of the building has an evident influence on levels of indoor fungi, other building characteristics may also play a role. In schools, the wooden-framed buildings were associated with higher levels of airborne fungi than the concrete-framed buildings, and older buildings had the same effect (Meklin et al., 2003). Single-family houses are associated with higher fungal concentrations than apartments (Chew et al., 2003; Hyvärinen et al., 2006b). This observation may be explained by the more direct connection between the indoor and outdoor environments, where dirt and soil trafficking occurs directly into the house rather than in an apartment buildings with external entrance halls and stairways. Non-residential buildings are different from homes in terms of their architecture, construction, and use, and they lack many of the regular fungal sources typically linked to dwellings and household activities. The differences can be reflected as lower concentrations of airborne fungi in offices (Tsai et al., 2007), schools (Meklin et al., 2002) and other non-residential buildings. Lower concentrations

are observed especially in non-residential buildings that have a mechanical ventilation system with filtering that maintains a relatively stable fungal content throughout the year. Instead, in an office building in Paris, France, which had natural ventilation, the fungal content of indoor air resembled that of outdoor air (Parat et al., 1997).

The presence of dampness- and moisture-related fungal growth is a source of fungal particles, and higher indoor air fungal concentrations have been reported in buildings with dampness and mold than in buildings with no such problems. The presence of mold increased the concentrations of culturable fungi in domestic dwellings (DeKoster and Thorne, 1995; Garrett et al., 1998; Hunter et al., 1988; Hyvärinen et al., 2001; O'Connor et al., 2004) and in schools (Lignell et al., 2005; Meklin et al., 2002).

Sampling aspects and concentrations of airborne fungi in various regions and buildings. Similarly to studies investigating the fungal content of house dust, a variety of sampling and analytical methods have been used in studies of airborne culturable fungi. Different approaches restrict the possibilities to compare the specific findings of different studies. Some of the sampling aspects concerning the published data on culturable fungi are presented in the following paragraphs.

First, sampling strategies can be designed in many different ways. Some researchers have chosen to take samples from many residences in a cross-sectional setting, while some others have used a longitudinal design of repeated sampling in one house. Second, the methods used for the sampling and analysis vary from study to study. As is well known from comparative studies, each modification to either sampling or analytical procedures may lead to somewhat different results. For example, sources of variation can be caused by collection efficiency of the sampling device and the sampling time used (Reponen et al., 2011). Third, in culturing methods, each culture medium is selective in its own way, and therefore, it is rare that two different media will yield the same results. However, the use of two different sampling media, for example, malt extract agar (MEA) and dichloran glycerol agar (DG18), can provide a broader picture of the genera and species present, although because many fungi can grow on both of these media, some overlapping of species may be observed. Even the incubation temperature is important, for example, incubation at 25°C will result in a different spectrum of colonies than would be found in a parallel sample incubated at 37°C or at 45°C. Fourth, different identification approaches of the fungal genera and species add to the poor comparability of the data. Some studies provide binary data on the occurrence of a certain genus or species, that is, the presence or absence of the fungus in question. Another way to express the findings is to report the number concentrations of each analyzed fungus or group of fungi.

Due to all these variations in the different measurement approaches, it is not feasible to compare exact number concentrations of viable (culturable) fungi between studies. Nonetheless, the results are rather comparable from the perspective of orders of magnitude. As a general conclusion, concentrations of culturable fungi in indoor air of dwellings around the world are mostly within the range 10^0–10^3 cfu/m^3, as shown in Table 3. The levels appear to be somewhat higher in the temperate and warm climates. Although they are strongly correlated with the concentrations in outdoor air, they are usually lower than those outdoors, the I/O ratio being <1. Higher concentrations, of the order of magnitude of 10^4 cfu/m^3, are reported in some studies from subtropical regions, and such high counts may even occasionally occur in other regions as well, for example, due to mold growth-related contamination. In office buildings, levels of fungi are typically lower, commonly within the range 10^0–10^2 cfu/m^3. In schools and day care centers, the range is somewhere between offices and domestic environments. Examples of studies in these settings are also shown in Table 3.

In most studies, the mycobiota has been analyzed to the genus level for the most commonly occurring fungi. The genera *Penicillium*, *Cladosporium,* and *Aspergillus* and the yeasts are the fungal genera and groups most commonly reported in studies around the world, although their rank order of frequency tends to vary from study to study (Dotterud et al., 1995; Gomez de Ana et al., 2006; Ren et al., 1999a, 1999b; Sen and Asan, 2009; Verhoeff et al., 1990). Other genera frequently found are *Alternaria, Botrytis,* and *Eurotium* (Gomez de Ana et al., 2006).

ERMI as a tool for evaluating indoor fungi

As an alternative to undertaking a comprehensive, culture-based description of fungi in residences, the metric ERMI (environmental relative moldiness index) was developed in the USA for use in evaluations of the fungal load in homes using floor dust samples and determinations of fungi with quantitative PCR (qPCR) (Vesper et al., 2007a, 2007b). It is based on the concept that the fungi present in the domestic environment can be divided into those that indicate dampness and moisture (group 1) and those that are found in 'normal' homes (group 2). Concentrations of 36 fungal species are determined, and the sum of the logs of concentrations of group 2 fungi is subtracted from those of group 1, yielding the ERMI value. The ERMI values have been found to be higher in homes of asthmatic children than in homes of non-asthmatic children (Vesper et al., 2008), and a statistically significant increase in asthma risk at age 7 years was associated with high ERMI values in child's home in infancy (Reponen

et al., 2012). The index has been claimed to have a predictive value for respiratory illness in children (Vesper et al., 2007b).

While the idea of an index that simplifies the complex assessment of the fungal load of the indoor environment is attractive, the application of the ERMI in its present form does require some caution. The original data that form the microbiological basis of ERMI were published in 2004 (Vesper et al., 2004). House dust samples were taken by vacuuming 1-m^2 carpeted floor from six homes with extensive mold damage and serious health outcomes. All of these homes were situated within close geographical proximity to each other, and, one may presume, moisture problems and building types were similar. This sampling was performed twice with one exception, so the number of samples was 11. Reference samples were taken from 26 homes with no visible moisture or mold damage, each sampled once. After qPCR analyses of 82 fungal species, the 36 most common fungi were divided into two groups as presented above. Taking into account the fact that cases of mold growth in buildings are highly variable with different species occurring in different cases (Hyvärinen et al., 2002; McGregor et al., 2008), the sampled material that formed the basis for ERMI was very limited (comprising only six moldy homes and 26 reference homes in the same region). The fungal data may also be partly clustered as the same moldy homes were sampled twice, while the reference homes were sampled only once. The 'moldiness' scale of the ERMI values was developed with an extensive sample of US homes ($N = 1144$) (Vesper et al., 2011). US EPA recommends that the index should only be used for research purposes and not for evaluating the fungal load of individual buildings (US EPA, 2013b). Microbial exposures are complex and highly variable with respect to both time and location, and they are also affected by many other determinants. Therefore, they are particularly difficult to express in a simple and meaningful way. The development of indices and other tools to simplify the expression of critical exposures would be advantageous both in epidemiological studies and in investigations of individual buildings in public health practice. The relevance and reliability of such indices would need to be confirmed with sufficient data from different regions and climates.

Indoor fungal occurrence observed with sequencing studies

Until recently, much of the work being conducted in indoor microbial ecology, indoor fungal exposures, and their links to health has relied on cultivation-based methods. In recent years, however, a shift toward DNA-sequence-based methods has taken place. Quantitative PCR (qPCR) is mostly used to quantify specific fungal groups, and amplicon sequencing techniques have been utilized in indoor fungal community analyses. By offering an increasing level of resolution, it is anticipated that next-generation sequencing approaches will widen our understanding of indoor microbial communities and their ecology and enable further studies on their functional qualities and their impact on humans. The results from the first studies on fungal assemblages utilizing these techniques will be briefly presented in this section.

Initial studies utilizing clone library sequencing of the fungal internal transcribed spacer regions (ITS) from indoor dust samples have provided preliminary information on characteristics of the indoor fungal flora determined with the sequencing approach as compared with other methods. In a small set of buildings, sequencing revealed a markedly wider diversity of indoor fungal flora than by cultivation, that is, it detected close to 400 non-redundant fungal operational taxonomic units (OTUs) at a sequence similarity level of ≥99% (Pitkäranta et al., 2008). In addition to the ascomycetes typically found by cultivation, a considerable proportion of the diversity was attributable to the basidiomycetous species, including many yeasts, uncultivable fungi, and taxa that would normally be hard to identify. On the other hand, sequencing failed to detect some of the taxa detected in cultivation, some taxa of *Penicillium* as an example. Seasonal variation of indoor fungal assemblages in house dust was observed, with the number of different OTUs peaking in fall (Pitkäranta et al., 2008). In a follow-up study, there were indications that increased fungal diversity was associated with moisture damage (Pitkäranta et al., 2011), and fungi potentially attributable to building-related growth were present. A strong variation was also observed in indoor mycobiota within and between buildings. Using pyrosequencing, Nonnenmann et al. (2012) reported detecting more than 450 fungal species in floor dust samples from 50 rural US homes in close geographic proximity, with the likely sources of these fungi being plants, soils, or human skin.

A global survey of fungi from indoor environments was conducted by sequencing 72 settled dust samples from 61 buildings on six continents (Amend et al., 2010b). Confirming the observation of the high diversity of indoor fungi, this survey indicated that global factors rather than building design and materials, or building use and function, might drive fungal composition in indoor spaces. As this conclusion differs from previous studies using culture-based approaches, it raises one unavoidable question: Could it be that global or regional factors indeed drive the total fungal assemblage in indoor environments, while building-related factors determine the culturable material? Future studies may provide more basic data with which to answer this question. Another surprising observation was that fungal diversity was higher in temperate regions than in tropics, which is unlike most other ecological patterns. The diversity and distribu-

tion of fungi on residential surfaces were studied by applying pyrosequencing to surface swabs of water drains in kitchens and bathrooms, the sills underneath windows, and from the skin of inhabitants living in non-moisture-damaged buildings (Adams et al., 2013c). The tested surfaces reflected the mycological profiles from outdoor air samples collected close by, however, being clustered by surface type. While the fungal richness across surfaces was high, the authors considered it unlikely that the majority of observed species would be able to grow on these surfaces; instead, these surfaces represented a kind of passive collector of airborne fungi. This role could even be the case for the residents' skin surfaces: Not only did they harbor known commensal genera, such as *Malassezia*, but also non-resident fungi, such as plant-associated species. In a study that examined the processes influencing the dispersal of microbes in indoor spaces, the main conclusion was that indoor fungal assemblages were structured in the first place by dispersal of outdoor fungi into the built environment and that the building occupants had less effect (Adams et al., 2013b). The conclusion was based on the observation that indoor fungal communities differed by season in a similar fashion as those in outdoor samples. Geographic distance—even though the buildings were in close vicinity to one another—was the single significant determinant of the indoor community structure remaining in a multifactor model. No specific fungal group could be identified as an overall 'indicator' of indoor air. The study also confirmed the findings of earlier studies (Amend et al., 2010b; Oliveira et al., 2009; Pitkäranta et al., 2008) that many of the fungal taxa frequently detected using pyrosequencing match to the taxa frequently detected with cultivation techniques, which in turn mostly reflect fungi that can grow on indoor surfaces, on foodstuff, etc. However, many specific fungal communities, such as plant-associated fungi, are underrepresented in analyses based on cultivation, but become visible in sequencing studies.

A study comparing the fungal content of dust from houses with asthma cases and controls (total 41 homes) by pyrosequencing (Dannemiller et al., 2014) found a significant association between reduced fungal diversity and an increased risk of asthma development, reminiscent of the findings where higher microbial diversity in farm environments appears to be protective from asthma (Ege et al., 2011). Interestingly, the presence of excess moisture in the walls was associated with an increase in fungal diversity, a rather logical finding from a microbiological perspective, and also confirming earlier reports (Pitkäranta et al., 2011). The findings of this recent sequencing study are somewhat difficult to interpret, as high fungal diversity was linked to moisture damage, but low fungal diversity to asthma development. From other studies, it is known that moisture damage is a risk factor for asthma (Mendell et al., 2011). It is relevant to refer to the work of Adams et al. (2013a) who found that the presence of one or a few fungal taxa that are highly represented in a sample may affect the calculated species richness and perceived microbial community composition if one uses the standard application of next-generation sequencing approaches. High abundance of a few taxa, for example, from actively growing species, may artificially point to an underestimation of species richness and diversity on the study sample, requiring caution when using diversity measures to explain environmental or health outcomes.

MVOCs and mycotoxins in the indoor environment

Microbial volatile organic compounds (MVOCs) and mycotoxins of fungi are chemical compounds produced by growing microbes, and these agents have been investigated in the context of dampness, moisture damage, and mold growth in indoor environments. Here, we briefly describe the main aspects of the Indoor Air Quality relevance of MVOCs and mycotoxins. As there are very few population studies that have specifically focused on health effects of MVOCs or mycotoxins in indoor air, the health aspects of these compounds will also be briefly discussed here. While most indoor air VOCs originate from outdoors or are emitted from paints and finishing materials as well as from household cleaning chemicals (Chin et al., 2014; Shin and Jo, 2013; Su et al., 2013), VOCs are also produced by growing fungi and bacteria. Such compounds are designated as MVOCs. More than 200 compounds have so far been identified as MVOCs in laboratory experiments, but none can be regarded as being exclusively of microbial origin (Korpi et al., 2009). MVOC compounds occur typically in concentrations in the range ng/m^3 to μg/m^3 of air in indoor environments (Korpi et al., 2009; Ryan and Beaucham, 2013; Sahlberg et al., 2013). Many MVOCs have a low odor threshold and are easily recognizable as contributing, for example, to the musty, cellarlike smell present in mold-affected buildings. Odorous MVOCs are often attributable to alcohols such as 1-octen-3-ol and 2-octen-1-ol. There have been proposals that MVOCs could be used as indicators of mold infestation that may be hidden inside building structures, but this concept has been criticized due to the non-specific nature of the target compounds. For example, in a Canadian study, the total variability of MVOC concentrations was not explained by mold status of buildings (Schleibinger et al., 2008). Efforts have been made to overcome this issue using combinations of MVOCs that are thought to be specific for fungal growth (Hulin et al., 2013). MVOCs can exert different health effects, with the most obvious being symptoms of irritation. However, in human exposure studies, symptoms of irritation appeared only at MVOC concentrations several

orders of magnitude higher than typical indoor concentrations (Korpi et al., 2009), and therefore, the human effects of low concentrations of airborne chemicals need to be clarified before the evidence about causality would be conclusive. There are some studies suggesting that certain MVOCs could be risk factors for the 'Sick Building Syndrome' (Kim et al., 2007; Sahlberg et al., 2013), and the involvement of 1-octen-3-ol in neurodegeneration and parkinsonism has been speculated based on work with animal models (Inamdar and Bennett, 2013).

Mycotoxins are another class of substances that are produced by growing fungi (see Table 1). These compounds are often chemically and thermally stable and very bioactive. Several hundreds of different mycotoxins have been identified and characterized so far (Bennet and Klich, 2003), but it is estimated that even more, perhaps hundreds of thousands of unique mycotoxins may be present in the environment (CAST, 2003). By definition, mycotoxins are fungal secondary metabolites that pose a potential health risk to humans and/or animals when introduced by a natural route (Smith and Solomons, 1994). Secondary metabolites of microbes are different from primary metabolites—such as amino acids or sugars—in that these compounds do not act directly in the process of growth and development of the microbial cell. Secondary metabolites either have an intrinsic function within the producing species, as for example, initiation of growth and differentiation, or act on targets external to the producing species. As such, they have considerable ecological importance as mediators in competitive interaction between microorganisms and in improving survival fitness of the producing species (Williams et al., 1989).

The occurrence of mycotoxins in indoor environments is well established (Bloom et al., 2009b; Peitzsch et al., 2012; Polizzi et al., 2009; Täubel et al., 2011). The potential role of mycotoxins in building dampness-related illness was first postulated in the 1980s and 1990s and related to cases of *Stachybotrys chartarum* contamination and the proposed intoxication of occupants with some of its highly toxic secondary metabolites. These included the macrocyclic trichothecene mycotoxins such as satratoxins, roridins, and verrucarins, as well as other compounds such as spirocyclic drimanes (Croft et al., 1986; Dearborn et al., 1999; Flappan et al., 1999; Jarvis and Miller, 2005; Jarvis et al., 1998; Johanning, 1998; Johanning et al., 1996). These cases received extensive media attention, and *S. chartarum* and its mycotoxins remained the main target of indoor mycotoxin studies for almost two decades. Only more recently have analytical methods been developed that permit the detection of many distinct mycotoxins in the same sample (Polizzi et al., 2009; Vishwanath et al., 2009).

Mycotoxins are produced by toxigenic fungi, which occur in indoor environments and can proliferate on various building materials, provided there is moisture present (Fog Nielsen, 2003; Jarvis and Miller, 2005; Nielsen, 2002; Ren et al., 1999a, 1999b). Studies on indoor mycotoxins have also demonstrated that one individual mycotoxin may be produced by different fungal strains, and one fungal strain may produce different mycotoxins. Some 30 studies published between 1986 and 2013 have described mycotoxin findings in indoor environments. A few of the studies reporting the occurrence of mycotoxins in indoor air (Brasel et al., 2005b; Charpin-Kadouch et al., 2006; Gottschalk et al., 2008; Polizzi et al., 2009) have been complemented by more mechanistic work that has shown that mycotoxins become airborne not only in association with intact conidia but also on highly respirable particles smaller than conidia (<1 μm) (Brasel et al., 2005a). The concentrations of mycotoxins in indoor samples are generally low; studies with active air sampling in moisture-damaged buildings typically report that mycotoxin concentrations are in the range of pg/m^3 up to low ng/m^3 of air. Concentrations reported in house dust have varied by several orders of magnitude, but the typical range is pg/g to ng/g dust, sometimes reaching μg/g dust. Similar, somewhat higher values have been reported from the analysis of building materials.

It is obvious that the higher availability of water on surfaces of damp buildings supports microbial growth, and growth may also be reflected in secondary metabolite production. However, the occurrence of mycotoxins in buildings is not exclusively a phenomenon found in damp indoor environments. Indeed, the few studies that have assessed a large variety of mycotoxins in damp and reference buildings have shown that mycotoxins are common in both locations, and also, outdoor sources are evident. Just as microbes are ubiquitous in the built environment, so are also their metabolic products (Peitzsch et al., 2012). In the studies conducted so far, no individual mycotoxins have been identified that could be used as indicators of dampness and mold.

The evaluation of the health relevance of indoor mycotoxins is at present based on studies conducted for other reasons than the indoor air sciences, especially from the field of food safety (Marin et al., 2013; Wu et al., 2014). Mycotoxins comprise a wide variety of chemical structures and biological activities, and their toxicological properties involve inflammatory, immunosuppressive, cytotoxic, and carcinogenic effects (CAST, 2003). However, much less is known about mechanisms and effects upon inhalation exposure of indoor-relevant mycotoxins, although there are some studies indicating that inhalation exposure to mycotoxins may be more toxic than oral ingestion (Creasia et al., 1987; Creasia et al., 1990). Only some studies have so far investigated the associations between the presence of indoor mycotoxins and

health effects in epidemiological study settings. Inverse associations have been described between the levels of verrucarol, the hydrolysis product of some macrocyclic trichothecenes, with daytime breathlessness in pupils in Malaysian schools, but the study did not specifically target moisture-damaged schools and verrucarol was only detected in 4 of the 32 classrooms (Cai et al., 2011). Multiple mycotoxins were analyzed from floor dust collected in the homes of 95 children of a Finnish birth cohort. Neither sum load nor number of toxins in the floor dust could be linked with the risk of developing asthma in this population (Kirjavainen, P.V., Täubel, M., Karvonen, A.M., Sulyok, M., Krska, R., Hyvärinen, A. and Pekkanen, J., unpublished data). Respiratory health of 645 school teachers was studied in Spain, the Netherlands, and Finland in relation to dampness and levels of mycotoxins in settled dust collected in their schools (Zock et al., 2014). Teachers from damp schools experienced more nasal symptoms and had a higher asthma symptom score than teachers from schools without dampness. Specifically, the Finnish teachers from schools with higher mycotoxin levels had a higher asthma symptom score and more nasal symptoms, and this finding was not confounded by the dampness status of the school, indicating that the microbial toxins themselves may have been mediating these effects. There are also case reports in the literature on indoor occurrence of mold and mycotoxins linked with health complaints or clinical data of the building occupants (Brewer et al., 2013; Thrasher et al., 2012). However, the information from such case studies is limited due to the small number of exposed individuals and insufficient verification of mycotoxin exposure. While mycotoxins are present in indoor environments and inhalation exposure may well take place, the typically very low exposure levels have been used as a basis to argue that mycotoxins indoors do not pose a risk to the health of building occupants. The studies by Miller et al. (2010) and Rand et al. (2011) indicated that 'real-life' exposure levels of different mycotoxins could alter the gene expression of inflammation-related genes in mouse lungs (Miller et al., 2010; Rand et al., 2011). It has also been suggested that mycotoxin concentration, for example, at the site of deposition in the nasal mucous membrane of a mycotoxin-containing fungal spore, would be high enough to elicit local effects (Carey et al., 2012). Other studies have indicated that the synergistic effects in cellular responses upon exposure to multiple mycotoxins or mycotoxins and other microbial compounds may be relevant (Islam et al., 2007; Kankkunen et al., 2009; Mueller et al., 2013). There are many reasons to suspect that mycotoxins might contribute to adverse health outcomes, and these compounds definitely deserve future attention.

Indoor fungi and health

The most common adverse health effects associated with fungi and other biological particles in indoor environments are various respiratory conditions (Institute of Medicine (IOM), 2004; WHO, 2009). For fungal infections and fungal allergies, the causal agents and mechanisms can be identified, but for irritation, inflammation, toxic, or immunotoxic reactions, the causal connections and pathophysiology are less evident. The epidemiological and clinical evidence for health effects associated with dampness and mold in buildings, such as upper respiratory tract symptoms, wheeze, cough, and asthma is well established (Kanchongkittiphon et al., 2014; Mendell et al., 2011). However, the so-called hygiene hypothesis has introduced the potential role of microbes as protective agents from allergy in early childhood (Braun-Fahrländer et al., 2002), although in this context, mainly bacterial agents have so far been considered. A clarification of these outcomes will only be possible with a thorough understanding of the microbial exposures in all their complexity, a topic to be discussed next.

Complexity of fungal exposures

The complex nature of fungal exposures poses a major challenge in studying the health effects of indoor fungi. Extensive data on fungal occurrence and its determinants will contribute to the core knowledge unraveling the links between fungal exposures and human health, both in regard to good and bad outcomes. To achieve the goal, it may not be enough to perform isolated analyses on fungi alone; interactions with other agents also need to be addressed. Furthermore, exposure, that is, contact between an individual and an exposure agent, may not only take place via inhalation but also by ingestion or dermal absorption (Bekö et al., 2013). The contribution of various routes of exposure has not received much attention in fungal exposure studies, but from other research fields, it is known that, for example, small children can ingest remarkable amounts of house dust (Stapleton et al., 2005).

Indoor fungi occur in close proximity to bacteria and other organisms, and their ecologies become closely intertwined. Exposure to fungi is similarly connected to exposure to other biological particles. These exposures consist of myriad microbial species, particulate matter, cellular components, microbial products, and other biological and even non-biological material, which can be house dust, hay, animal-related dust, or other matrices depending on the exposure situation (Eduard and Heederik, 1998; Lacey and Crook, 1988; Rintala et al., 2012). Modern sequencing studies have demonstrated that 'our' homes are also 'their' homes, that is, homes house hundreds, even thousands of different fungal and bacterial species that are present in carpets, mattresses,

and the dust layer of indoor surfaces (Adams et al., 2013b; Adams et al., 2013c; Amend et al., 2010b; Pitkäranta et al., 2011). Even indoor air, which is usually not heavily loaded with microbial particles, contains a wide diversity of microbial agents as shown in studies assessing bacterial communities (Hospodsky et al., 2012; Kembel et al., 2014). Thus, exposures to environmental fungi are virtually never exposures to single fungal species or even to only fungi.

While environmental fungi and bacteria have fundamental differences in their biology, they share many characteristics as exposure agents. Both have similar sources in nature and are able to exist in air. Both microorganisms are capable of inducing inflammatory reactions (Douwes, 2005; Heumann and Roger, 2002), and certain species show infectious and allergenic characteristics. They produce secondary metabolites while growing in indoor environments (Täubel et al., 2011). It is tempting to speculate that whenever health effects are caused by indoor microbial agents, these two types of microorganisms may be acting together. Interactions between fungi and bacteria are known from microbial ecology, for example, from studies on biocontrol research (Whipps, 2001) but have been less extensively addressed in the paradigm of human health and exposure studies. Some interactions have been already observed: For example, endotoxin, the compound present in Gram-negative bacteria, has been shown to enhance the biological activity of some mycotoxins (Islam et al., 2007; Kankkunen et al., 2009). Interactions in experimental settings have also been demonstrated between bacteria and fungi (Markkanen et al., 2009) and between fungi and amoebae (Yli-Pirilä et al., 2007) isolated from moldy indoor environments. One great challenge to be tackled in exposure- and health-related research is to learn more about these kinds of interactions.

Fungal infections and allergies

While pathogenic bacteria and viruses are the main infectious agents that cause disease in humans, infections may also be caused by pathogenic or opportunistic fungi (Falvey and Streifel, 2007). Fungal infectious agents that spread by the airborne route, for example, *Aspergillus fumigatus*, pose a definite risk in hospital environments. Patients with immunodeficiencies are particularly vulnerable to acquire fungal infections, and these infections are often difficult to treat (Rocchi et al., 2014; Vonberg and Gastmeier, 2006).

Allergies are conditions where the contact to the allergen triggers an immunological reaction via an IgE-mediated pathway in the exposed individual, leading to symptoms of varying severity. Around 150 individual allergens from approximately 80 fungal genera have been isolated over a 20-year period (Green et al., 2006; Simon-Nobbe et al., 2008). The most extensively characterized allergenic fungi are probably *Alternaria alternata*, *Aspergillus fumigatus,* and *Cladosporium herbarum* (Horner et al., 1995). The roles of fungi as allergens and allergies have been reviewed in several publications (Burge and Rogers, 2000; Horner et al., 1995; Salo et al., 2009; Simon-Nobbe et al., 2008). It is noteworthy that not all the health effects associated with fungi develop through allergy-mediated mechanisms although the symptoms may resemble allergic reactions (Dales et al., 1991; Taskinen et al., 1997; Taskinen et al., 1999).

Occupational diseases associated with fungal exposures

To put the health effects associated with microbial exposures into perspective, it must be noted that many respiratory diseases occur in occupational environments where there are heavy loads of airborne microbes and other biological particles. There are several examples of such diseases, for example, allergic alveolitis or hypersensitivity pneumonitis (farmer's lung), occupational asthma, and organic dust toxic syndrome (ODTS), all of which are occupational diseases that are associated with agricultural work (doPico, 1986; Kotimaa et al., 1984; Lacey and Crook, 1988; Malmberg et al., 1993). One etiological factor for the development of these diseases is the massive exposure to biological dusts; the concentrations of culturable fungi and other biological particles may be as high as 10^5–10^7 cfu/m^3, that is, orders of magnitude higher than concentrations in residential indoor air. Similar occupational disease and exposure situations are also found in other environments such as food processing (Dutkiewicz et al., 2002; Skorska et al., 2005; Tsai and Liu, 2009), sawmills (Dutkiewicz et al., 2001; Park et al., 2010), and waste handling and processing (Durand et al., 2002; Eduard and Heederik, 1998). Work situations with heavy exposures to airborne fungi and other biological particles also include the dismantling of structures associated with mold remediations (Rautiala et al., 1996) and cleanup tasks after hurricanes and floods (Johanning et al., 2014; Rao et al., 2007).

Health effects associated with dampness and mold

The health outcomes associated with moisture, dampness, and mold of buildings have been extensively documented and evaluated by working groups of the World Health Organization (WHO, 2009) and the Institute of Medicine (2004) of the US National Academies of Science. The epidemiological findings have been critically reviewed (Mendell et al., 2011). The health effects best documented in large population studies include irritant effects on the respiratory system and mucous membranes, increased and prolonged respiratory infections, and increased risk of asthma.

Both exacerbation of symptoms of previous asthma and onset of new asthma have been reported in children (Pekkanen et al., 2007) and adults (Jaakkola et al., 2002). Clusters of asthma cases in adults have been observed in moisture-damaged schools (Patovirta et al., 2004), offices (Iossifova et al., 2011), and a hospital (Seuri et al., 2000). Other, less strongly documented effects include allergic alveolitis (Iossifova et al., 2011), otitis media (Pettigrew et al., 2004), sarcoidosis (Park and Cox-Ganser, 2011; Tercelj et al., 2011), and autoimmune diseases including rheumatic conditions (Myllykangas-Luosujärvi et al., 2002). There is no convincing evidence that would support the opposite finding; that is, that dampness and mold are not a risk of health.

Although the association between health outcomes and building mold has been extensively documented, the causative agents and mechanisms of the health effects are insufficiently understood (Institute of Medicine, 2004; WHO, 2009). Fungal particles, cellular components such as glucans, and metabolic products such as MVOC compounds and mycotoxins have all been postulated to be involved as contributing causal agents, but none of these agents can be said to exert a conclusive role (Jacobs et al., 2014). The concentrations of fungi in indoor environments are low from a traditional toxicological point of view (Eduard, 2009), and little is known on the effects of exposure to such low levels. Possible interactive effects have been even less extensively explored. Intervention studies have shown that most of the symptoms linked with mold are reduced when the exposures are lowered by means of building renovation (Haverinen et al., 1999; Haverinen-Shaughnessy et al., 2008; Kleinheinz et al., 2006; Meklin et al., 2005; Patovirta et al., 2004; Roponen et al., 2013; Rylander, 1997; Sauni et al., 2013). However, also a lack of improvement has been reported in the respiratory health of office employees after remediation (Iossifova et al., 2011). More studies will be needed to verify whether such ineffective interventions are due to inadequate reduction in exposure (Meklin et al., 2005) or whether the symptoms may be of an irreversible nature.

In indoor air sciences, fungi are often associated with the Indoor Air Quality problems caused by dampness, moisture, and mold growth. Those problems indeed represent an extensive concern both from the health point of view (Fisk et al., 2007; Fisk et al., 2010; WHO, 2009) and also due to their economic consequences (Mudarri and Fisk, 2007). There is a general consensus that moisture and mold problems of buildings should be remediated and the associated exposures eliminated. Guidance for management of problem situations has been issued by WHO and, more specifically, by many countries. While no numerical health-based guideline values can be provided, the basic principles of recognition and remediation of the mold problem are similar. The importance of adequate building investigations, including the functioning of ventilation and the building structures, observations of mold, dampness, and moisture, and suitable sampling and measurements are emphasized (Federal Environment Agency (UBA) Innenraumlufthygiene-Kommission des Umweltbundesamtes, 2008; Health Canada, 2007; New York City Department of Health and Mental Hygiene, 2008; Umweltbundesamt Innenraumlufthygiene-Kommission des Umweltbundesamtes, 2005; US EPA, 2013a).

The paradox of protective and adverse health effects

Population studies in different countries have revealed one consistent observation: Farming children suffer less allergy than urban children (Ege et al., 2008; Ege et al., 2011; von Mutius and Vercelli, 2010). It has been assumed that the more extensive and diverse microbial exposure in the farming environment could be a protective factor by challenging the developing immune system of infants with natural microbial materials. The study by Ege et al. (2011) linked a more diverse fungal flora—the determination of which was based on a few fungal genera in cultivation—with reduced risk of development of asthma. As the exposures associated with adverse health effects of damp and moldy indoor environments and with the beneficial protective effect in farming environments are to some extent comparable, there seems to be an interesting paradox, even when factors such as timing and duration of exposure are considered. In both these domestic environments, microbial levels are elevated and their diversity increased compared to 'normal' urban homes (Dannemiller et al., 2014; Ege et al., 2011; Hyvärinen et al., 2001; Schram-Bijkerk et al., 2005). Yet, in those homes that have observations of dampness, moisture, or mold, there is a risk of adverse health effects (Mendell et al., 2011), while in the farming homes, a protective effect from allergies is seen (Genuneit, 2012). Interestingly, the farming environment does not protect from adverse effects of exposure to moisture damage (Karvonen et al., 2009). The paradox cannot be explained with present knowledge. Likely, it is the case that quantitative microbial measurement approaches—including sampling and microbial analyses—applied so far in indoor environmental studies are simply not specific enough to differentiate exposure situations that relate to either farming or moisture damage in buildings.

Do fungal concentrations in indoor air associate with health effects?

The issue of the dose dependency of symptoms in relation to airborne fungal concentrations has been the target of many studies. The fungal concentrations in homes of symptomatic and non-symptomatic

individuals have been compared, but the results have only rarely revealed any notable differences (Belanger et al., 2003). In some studies, for example, in Singapore, fungal levels were higher in day care centers of children with allergic symptoms (Zuraimi et al., 2009). A multicenter study in European schools showed that in schools where concentrations were >300 cfu/m^3, children had an elevated risk of dry cough at night, rhinitis, and persistent cough (Simoni et al., 2011). However, most studies have come to the negative conclusions, that is, no statistically significant difference is observed in fungal concentrations between patients' homes and control homes (Dotterud et al., 1996; Flores et al., 2009; Jovanovic et al., 2004; Su et al., 2001). The respiratory symptoms and nocturnal cough recordings in Canadian elementary schoolchildren were not related to the concentrations of airborne ergosterol or to viable fungi in dust, but they were related to the reported mold (Dales et al., 1999). As a general conclusion, it seems that fungal concentrations in either indoor air or house dust do not correlate with respiratory symptoms, asthma, or atopy (Jovanovic et al., 2004). This means that while a higher fungal concentration indicates poorer Indoor Air Quality of the building (Simoni et al., 2011), the connection between measured fungal exposures and health outcomes is more complex (Jacobs et al., 2014).

Conclusions and future vision

Our present knowledge on indoor fungi is extensive, and it involves four major themes: (i) information on the occurrence and airborne behavior of fungi indoors, the determinants of the variations in concentrations, and their relationship with their outdoor counterparts; (ii) awareness of problems that link dampness, evident moisture, and mold growth in buildings with its consequences to health, well-being, Indoor Air Quality, and public health; (iii) the role of fungi as allergens and opportunistic pathogens; and (iv) the growing evidence that microbial exposures, especially in farming environment, may be protective from allergies. Research on indoor fungi is a multidisciplinary task, and even more such collaboration between disciplines will be needed in the future.

We still lack a profound understanding needed to answer many fundamental questions. As human well-being in indoor spaces is one of the basic cornerstones of indoor air sciences, the most evident gaps of knowledge are linked to health. The road ahead may depend on identifying better ways to characterize health-relevant exposures and to understand the mechanisms by which exposure-influenced health effects develop. One can predict that the progress will rely greatly on novel methodologies that can describe the fungal microbiomes in all their richness, as well as target a multitude of fungal products. New methodological approaches are further needed to find out not only 'which microbes are there' but also 'what they are doing there' by the tools of proteomics, lipidomics, and other molecular-level approaches.

The wealth of documentation that has revealed the symptoms and diseases associated with fungi growing indoors shows a main direction toward which the health-related studies should proceed. The majority of reported health outcomes are conditions of respiratory health, and therefore, the factors that affect the actual personal exposure via indoor air, or dose, should be addressed in health-related research. Examples of such factors are particle size and interactions of various agents. We also need knowledge on the synergistic effects of co-exposures to multiple fungal and bacterial agents, a situation that is almost invariably the case, and the understanding can only be achieved by adopting toxicological and immunotoxicological approaches. The role of fungal exposures in contributing to protective effects on health must also be further explored. Many research questions will undoubtedly emerge from these studies, and they cry out for efficient collaboration between several disciplines.

From the perspective of indoor air practices, the problem of mold growth is simple: It must be avoided. However, a more profound risk assessment of indoor fungi and fungal products broadens the scope of the challenge by several orders of magnitude. We should recognize here the great opportunities to use multidisciplinary approaches in resolving these challenges. Real progress will be made through research that can be applied in everyday practice. With modern scientific tools and the wide international expertise available, this is a challenge that will be tackled with success.

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