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TEACHERS' HEALTH IN MOISTURE-DAMAGED SCHOOLS - A FOLLOW-UP STUDY

National Public Health Institute,
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- A FOLLOW-UP STUDY

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ACADEMIC DISSERTATION

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ABSTRACT

This thesis deals with adverse health effects on teachers in moisture- and mould-damaged schools before and after building remediation. This was an intervention study where bronchial reactivity and immunological responses were measured clinically and subjects filled in symptom questionnaires. Classification into moisture- and mould-damaged buildings and non-damaged buildings was based on technical and microbiological measurements of the building before and after remediation parallel to the health study.

In the first part of the study, the health effects among teachers in a mould-damaged school before, during and after extensive remediation were assessed by collecting health data three times with a self-reported symptom questionnaire from the teachers in that school (n=31) and from a reference group of teachers working in a non-damaged school. The questionnaire included about 70 questions on general and respiratory irritation symptoms, respiratory infections, allergic diseases and medical treatment. At the end of the remediation and two and three years later, spirometry was measured; and at the end of the remediation and two years later mould-specific immunoglobulin G antibodies were determined twice from 26 teachers by enzyme-linked immunosorbent assay (ELISA).

In the second part of the study, teachers (n=52) at the different mould-damaged schools made serial measurements of peak expiratory flow (PEF) three times a day during a three week-period; the second week was winter holiday (non-exposed) week. Three out of four moisture- and mould-damaged schools were selected for the follow-up study, and teachers (n=56) took part in a self-administered symptom survey before and one year after remediation of the buildings. The questionnaire was the same as in the first study.

In the first part of the study, a cluster of asthma was identified, the prevalence of asthma being 26% and three of the cases diagnosed as occupational disease caused by

exposure to fungi. Among the index group symptoms of bronchitis ($p=0.03$), conjunctivitis ($p=0.02$) and fatigue ($p=0.02$) decreased after remediation. During the three-year follow-up, the lung function levels of the index school teachers remained at the same normal level. Nor was there any significant change in IgG-antibody concentrations between index and reference groups or during the follow-up study. However, for ten out of twenty moulds, an association was found between elevated mould-specific IgG antibodies and sinusitis.

As a result of the second part of the study, in the mornings, afternoons and evenings the means of the weekly PEF-levels were found to be slightly, but significantly, reduced between the second holiday week and the third week. In the intervention study, self-reported fatigue (OR=0.2) and headache (OR=0.4) were reported to decrease. Female gender was a risk factor for sinusitis, age over 40 years was a risk for voice problems and more than ten years at the same school was a risk for conjunctivitis and headache.

In conclusion, mould remediation of the school building had positive effects on teachers' health. The effect was seen as a decrease in general symptoms and in respiratory infections. No new cases of asthma were found after remediation. Exposure-induced symptoms appeared to be reversible. Significant risk factors for health outcomes were female gender, age and a working history of more than ten years at the same school. In non-asthmatic teachers, a minor but significant decrease was found in PEF-levels during the exposure period. Based on the results of this study, spirometry was not sensitive enough to detect changes in lung function after mould remediation. Furthermore, IgG-antibodies did not appear to be a useful biomarker for decrease in exposure due to successful remediation of a work environment.

To Petri, Inga-Maria, Iida-Elisa and Iina-Sofia

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Kuopio, March 7th, 2005

A handwritten signature in black ink, appearing to read 'Riitta-Liisa Patovirta', with a long horizontal flourish extending to the right.

Riitta-Liisa Patovirta

ABBREVIATIONS

AARC	American Association for Respiratory Care
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
cfu	colony-forming units
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
FEV1	forced expiratory volume in one second
FEV%	$FEV1/FVC \times 100$
FVC	forced vital capacity
IgE	immunoglobulin E
IgG	immunoglobulin G
IOM	Institute of Medicine
MEF25	maximal expiratory flow at 25% of FVC
MEF50	maximal expiratory flow at 50% of FVC
PEF	peak expiratory flow
RAST	radioallergosorbent-test
SPSS	Statistical Package for Social Sciences
SPT	skin prick test

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by the Roman numerals I-IV.

I Patovirta R-L, Husman T, Haverinen U, Vahteristo M, Uitti JA, Tukiainen H, Nevalainen A. The remediation of mold damaged school – a three-year follow-up study on teachers` health. *Cent Eur J Publ Health* 2004;12:36-42.

II Patovirta R-L, Reiman M, Husman T, Haverinen U, Toivola M, Nevalainen A. Mould specific IgG antibodies connected with sinusitis in teachers of mould-damaged school: a two-year follow-up study. *Int J Occup Med Environ Health* 2003;16:221-230.

III Patovirta R-L, Husman T, Vepsäläinen A, Meklin T, Nevalainen A, Tukiainen H. Peak expiratory flow in teachers exposed to mould during school weeks and a holiday week (submitted).

IV Patovirta R-L, Meklin T, Nevalainen A, Husman T. Effects of mould remediation on school teachers` health. *Int J Environ Health Res* 2004;14:415-427.

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1 INTRODUCTION

Nowadays modern man spends over 90% of his time indoors (Schwab et al. 1992); therefore, good quality of indoor air is a crucial part of a healthy work environment. The relationship between adverse health effects and moisture and mould problems in indoor air has been of public and scientific interest during the last two decades. Recently some international committees of high scientific repute have published reports, confirming that a connection does exist between exposure to moisture and mould in indoor air and adverse health effects, even chronic diseases (Health Canada 2004, IOM 2004). This connection has also been confirmed in the conclusions of recent reviews of scientific literature (Bornehag et al. 2001, Bornehag et al. 2004a). However, the mechanisms behind this complex phenomenon are still largely unknown and more research is needed to clarify the pathophysiological pathway from exposure to the appearance of symptoms and disease.

In Finnish primary and secondary schools, about 51 500 teachers teach children every school day (Statistics Finland 2002). According to a questionnaire study answered by the headmasters of Finnish schools, moisture damage was present in 53% and serious damage, as indicated by visible mould growth or mould odour, in 26% of all school buildings (Kurnitski et al. 1996). In a recent survey of Finnish schools, 27% of the damage was found in floor structures, 19% in partition walls, 15% in upper floors and 8% in the most upper floors. The most common reason for damage, concerning a total of 27% of all damage observations, was technical aging of materials. Other common reasons were related to sources of moisture outside the buildings and to water leaks (Koivisto et al. 2002). The seriousness of this problem could be described by looking at the statistics published by the Finnish Register of Occupational Diseases. During 1995-2002 among Finnish teachers, the number of new cases diagnosed as occupational diseases caused by fungal exposure was 19 - 66 cases per year.

In this thesis, the health of teachers was monitored before and one to three years after remediation of a moisture- and mould-damaged school building. The main interest of the study was the effect of building remediation on health. It was hypothesized that since there is a known connection between this exposure and health effects (IOM

2004), elimination of exposure should have an effect on the health of the building occupants. It was also hypothesized that once improvement of health, as a result of elimination of exposure, could be shown, this would provide evidence of reversibility of the symptoms and other health findings. The information was collected in a symptom questionnaire and by repeated clinical measurements, e.g. mould-specific IgG-antibodies, spirometry and PEF-measurements. Technical investigations and microbial assessment were done parallel to the health survey.

2 REVIEW OF LITERATURE

2.1 Moisture-damaged buildings and microbes in indoor air

Excess water in a building structure, in a structural component or on the surface of the building material may develop into moisture damage. The damage may be a consequence of leaks in the roof or plumbing, condensation due to poor ventilation or insufficient insulation or of capillary movement of water from soil (Haverinen 2002).

Repeated or constant moistening of building material will lead to microbial growth, damage to the materials and release of various potentially harmful agents, such as microorganisms and their spores, volatile organic chemicals and mycotoxins, into the indoor air (Pasanen et al. 1992b, Flannigan and Morey 1996, Rylander 1999). Microorganisms related to excessive moisture on building materials include filamentous fungi (also known as mould), rot fungi, yeasts and bacteria (Flannigan and Miller 1994).

Visible mould or dampness in buildings is often associated with elevated concentrations of fungi in indoor air (Hunter et al. 1988, Li and Kendrick 1995, Garrett et al. 1998, Dharmage et al. 1999, Johanning et al. 1999, Ellringer et al. 2000, Klanova 2000, Hyvärinen et al. 2001, Meklin et al. 2003) and in house dust (Verhoeff et al. 1994). This has also been shown by measuring a chemical marker of fungi, i.e. the ergosterol content in dust (Dharmage et al. 1999). On the other hand, there are also studies where no difference in concentrations of viable fungi between mould-damaged and non-damaged buildings has been found (Strachan et al. 1990, Nevalainen et al. 1991, Pasanen et al. 1992a, Dill and Niggelmann 1996, Garrett et al. 1998). Nor was a difference in the fungal concentrations between severe and mild mould damage found by Miller and co-workers (2000). In spite of these somewhat contradictory results, it is evident that microbial growth in a building acts as a source of microbial aerosols. During demolition of mouldy structures, high levels of fungi have been observed in the working air (Hunter et al. 1988, Rautiala et al. 1996); and a few months after removal of damaged materials, i.e. the source of microbes, the levels had decreased back to the baseline level (Rautiala et al. 1996, Ellringer et al. 2000).

In indoor environments, outdoor air is usually the main source of airborne fungi if no intramural sources, such as microbial growth on building materials, are present (Gravesen et al. 1979, Burge 1990, Levetin 1995). An unusual composition of airborne fungi in non-industrial settings may indicate moisture problems (Hyvärinen et al. 1993). Some types of fungi that do not belong to the normal mycoflora of indoor environment are often found in moisture-damaged buildings; thus they may be called “indicator microbes”. Fungal genera or species that have been suggested to be such indicators or that have been connected with moisture damage in individual buildings are shown in Table 1.

Table 1. Summary of fungal genera related to moisture or mould damage in buildings.

GENUS OR GROUP	FOUND TO INDICATE/ RELATE TO MOISTURE or MOULD DAMAGE
<i>Acremonium</i>	Rand 1999, Meklin 2002
<i>Aspergillus fumigatus</i>	Samson et al. 1994, Flannigan and Morey 1996
<i>Aspergillus versicolor</i>	Samson et al. 1994, Flannigan and Morey 1996, Haverinen et al. 1999a+b, Backman et al. 2000, Lappalainen et al. 2001
<i>Chaetomium</i>	Rand 1999, Flannigan et al. 2001
<i>Eurotium</i> , <i>Exophiala</i> , <i>Fusarium</i>	Samson et al. 1994, Flannigan and Morey 1996
<i>Paecilomyces</i>	Rand 1999
<i>Penicillium</i> , <i>Phialophora</i>	Samson et al. 1994, Flannigan and Morey 1996
<i>Stachybotrys</i> , <i>Trichoderma</i>	Samson et al. 1994, Flannigan and Morey 1996, Robertson 1999
<i>Tritirachium</i>	Hyvärinen 2002
<i>Ulocladium</i> , <i>Wallemia</i> and yeasts (e.g. <i>Rhodotorula</i>)	Samson et al. 1994, Flannigan and Morey 1996

The indoor air of occupied buildings typically has higher levels and a different flora of bacteria than outdoor air (Nevalainen 1989, Otten and Burge 1999). Humans are the most important source of indoor bacteria (Otten and Burge 1999). The concentrations of airborne cultivable bacteria have been reported to be of the same order of magnitude both in mouldy and reference residences (Pastuszka et al. 2000) and in schools (Lappalainen et al. 2001). Actinobacteria, which originate from

environmental sources rather than from humans, are regarded as moisture-indicative bacteria in indoor environments (Samson et al. 1994, Flannigan and Morey 1996). They have been found in mould-damaged houses but not in reference houses (Nevalainen et al. 1991). Microbial growth inside insulated external walls was not found to increase levels of fungi but did increase the levels of actinobacteria (Pessi et al. 2002). A potential trend for such an indication has also been shown in school environments (Lappalainen et al. 2001).

2.2 Occupational exposure to bioaerosols

Bioaerosols are airborne particles that are living or originate from living organisms (ACGIH 1999). They include microorganisms, fragments, toxins and particulate waste products from various sources (e.g. viruses, bacteria, fungi, plants, protozoa and animals such as arthropods, birds and mammals). Microorganisms are widespread in the environment and are often a major component of organic dust. Exposure to bioaerosols can occur via inhalation, ingestion or dermal contact (ACGIH 1999). Health hazards associated with bioaerosols are traditionally encountered in working environments where organic materials are being handled, such as agriculture and waste management, in the food and biotechnology industry and also in health care and other indoor environments (Kotimaa et al. 1984, Johanning et al. 1996, Büniger et al. 2000, Seuri et al. 2000). In addition to infections caused by specific pathogens, health risks associated with bioaerosols are usually assumed to be mediated by different types of pathophysiological mechanisms: e.g. allergy, infections, irritation and toxicity. However, these mechanisms are not yet well known.

Conventionally, in agricultural settings there is a wide range of bioaerosols; and on many occasions concentrations are high. The exposure includes grain dust, fungi, bacteria, mites, animal dander and also several animal, plant and microbial allergens (Schenker et al. 1998). In the working air of barns, cowhouses and swinehouses the concentrations of culturable spores vary from 10^1 to 10^{11} colony-forming-units (cfu)/m³ in the working air of farm barns, cowhouses and swinehouses (Kotimaa et al. 1984, Heikkilä et al. 1988, Karlsson and Malmberg 1989, Pasanen et al. 1989, Dutkiewicz et al. 1994, Hanhela et al. 1995).

Handling of hay, grain and straw raises the airborne levels of biocontaminants for several hours (Pasanen et al. 1989). Common microbes in agricultural environments are *Aspergillus spp.*, *Penicillium spp.*, *Thermoactinomyces vulgaris* and yeasts (Kotimaa et al. 1987). Some microbial components, such as endotoxin and (1-3)- β -D-glucans, have been shown to have a marked immunotoxic potential (Rylander 1989, Fogelmark et al. 1992). Their levels are high wherever microbial concentrations are high, but their role as a causative agent of health effects is still not fully known. Mycotoxins are toxic secondary metabolites of fungi, and several fungal conditions may produce them (Betina 1984, Sorenson 1993, Abbot 2002). Toxins can be found in fungal mycelia and spores as well as in the substrate on which the colony grows (Burge and Amman 1999). When introduced in small concentrations by a natural route (mouth, respiratory system or skin), they are able to initiate a toxic response in vertebrates. The toxic properties and degree of toxicity vary, depending on the administration, chemical structure and concentration (Gravesen et al. 1994).

In many occupational settings where organic materials are stored or used (i.e., waste management, sawmills, furniture factories, food industry) exposure to airborne organic dust, fungal spores, bacteria and microbial components and products have increased and been associated with adverse health effects (Kotimaa et al. 1984, B unger et al. 1999, Eduard 1993, Eduard et al. 1994). In bakeries and in pharmaceutical and textile factories, a specific type of bioaerosol exposure can occur, namely, fungal enzymes that are proteins and have allergenic potential (Houba et al. 1997, Bernstein et al. 1999, Kim et al. 1999).

Workers may also be exposed to bioaerosols in non-agricultural, non-industrial occupational settings. The most important source of exposure in such facilities are mould-damaged constructions, which may cause bioaerosol exposure among employees in, e.g. offices (Johanning et al. 1996, Hodgson et al. 1998, Malkin et al. 1998, Wan and Li 1999), schools (Lappalainen et al. 1999, Meklin et al. 1996, Smedje et al. 1996, Cooley et al. 1998) day-care centres (Ruotsalainen et al. 1995, Li 1997) and hospitals (Wieslander et al. 1999, Seuri et al. 2000). Exposure in moisture problem buildings is not fully known; but it includes biological material, such as microbial spores and cells, the structural components and metabolites of microbes, e.g. toxins, volatile organic compounds and mites, as well as chemical emissions from

moisture-damaged materials, such as phthalates from moist PVC floor coverings (Bornehag et al 2004b). The exposure levels are lower than in the above mentioned industrial or agricultural settings. The concentrations of viable airborne fungi in various indoor environments vary between 10^1 - 10^4 cfu/m³ and those of viable bacteria from 10^1 to 10^4 cfu/m³ (Hyvärinen 2002). These levels are usually not much higher than those in normal conditions. On the other hand, the microbial flora in such indoor environments appears to differ from normal (Meklin et al. 1996, Hyvärinen et al. 1993, Lappalainen et al. 1999, Hodgson et al. 1998, Sudakin et al. 1998, Fung et al. 2000).

An individual's personal exposure to airborne microbes is not necessarily identical to the concentrations measured in homes or in workplaces. In the study of Toivola et al. (2004) it was shown that teachers' personal exposure to microbes was higher than the concentrations measured in homes or in schools. This was explained mainly by the so-called personal cloud, also known from particle exposure studies, which is the result of resuspension of settled particles due to the individual's movements (Toivola et al. 2002). The most important determinants of personal exposure to microbes in wintertime were male gender and age of 27-40 years. Other factors associated with higher bacteria concentrations were moisture damage and visible mould growth indoors and having a spouse with lower occupational status. Living in a family house and condensation on the inside of interior window glass at home were associated with higher fungal concentrations; however, moisture damage or visible mould growth inside did not indicate higher concentrations of fungi (Toivola 2004).

2.3 Health effects of indoor exposure to moisture and mould

During the last twenty years, indoor moisture and mould problems of buildings and adverse health effects have been associated with modern non-agricultural and non-industrial work environments as well as residential buildings during last twenty years (Waegemaekers et al. 1989, Dales 1991, Brunekreef. 1992, Pirhonen et al. 1996, Peat et al. 1998, Koskinen et al. 1999a+b, Norbäck et al. 1999, Engvall et al. 2001a+b, Zock et al. 2002). Bornehag et al. (2001) and Bornehag et al. (2004a) have twice reviewed selected studies on the association between dampness and health. In the first review they found 61 studies that filled their selection criteria. The conclusion was that strong evidence for the association exists, the risk for health effects ranging from

1.4 to 2.2. The latter review confirmed this conclusion. Despite strong evidence of an association, causal relationships between exposing agents and health effects have not been established. These have also been the conclusions of many expert evaluations of the literature, e.g. IOM (2004) and Health Canada (2004). However, it is evident that there is no single “mould syndrome” or disease, but rather many exposing agents and exposure situations and large array of health endpoints (Nevalainen 2002).

Many ongoing studies aim at clarifying the causal connections between exposure to non-infectious microbes and health effects. Recent studies suggest an inflammatory pathway. It has been shown *in vitro* and in animal studies that exposure to microbes and mycobacteria isolated from mouldy buildings can evoke changes in the concentrations of inflammatory markers (Hirvonen et al. 1997a+b, Shahan et al. 1998, Huttunen et al. 2000, Jussila et al. 2001). At the same time, evidence of inflammatory reactions in the upper and lower respiratory system has been found in nasal lavage fluid and induced sputum among mould-exposed occupants (Purokivi et al. 2001). The responses disappeared during absence from the building, which speaks for a link between the observed responses and occupancy in the building. These responses also correlated with self-reported respiratory symptoms of the occupants (Hirvonen et al. 1999, Purokivi et al. 2001). The observed responses were evidently not caused by elevated fungal concentrations as such, since in a study among sawmill workers, exposure to high concentrations of microbes did not cause airway inflammation (Roponen et al. 2002).

There have been several animal studies on the toxic effects of moulds. Nikulin and co-workers (1996, 1997) examined the effects of intranasal exposure of mice to *Stachybotrys atra* spores (10^3 and 10^5) using two strains from *Stachybotrys atra*, one more toxic and the other less so, isolated from houses with moisture damage. According to these studies, severity of changes in lung tissue depended on the concentration and toxic potency of spores. Severe inflammatory changes with hemorrhagic exudates present in alveolar lumina were found after treatment with 10^5 spores of the more toxic strain. Yike and co-workers (2002), who developed a model technique for studying pulmonary toxicity in infant rats, have studied the effects of *Stachybotrys chartarum* spores containing mycotoxins on survival (LD_{50}), growth, lung histopathology, BALF characteristics, and pulmonary function of rat pups.

Intratracheal instillation of high-dose spores was used, and changes in hemorrhaging were found to be dose-dependent. The same technique based on the infant rat model was used when Yike and co-workers (2003) found that the spores of *S. chartarum* could germinate in the lungs of infant rats and form hyphae. Three days after exposure an association was observed between exposure and acute neutrophilic inflammation and intense interstitial pneumonia with poorly formed granulomas.

2.3.1 Irritation and general symptoms

In many epidemiological studies a connection has been found between moisture or mould damage in office buildings and other non-industrial workplaces and increased rates of irritation symptoms, mostly in the respiratory track, as well as with general symptoms (IOM 2004). In Table 2 the wide variety of symptoms that describe the same symptom in different terms has been simplified and put into the same category. As shown in Table 1, similar types of symptoms have been found around the world in moisture- and mould-exposed workers in schools, offices, day care centres, hospitals and other public buildings in different climate conditions. In residential buildings, the same kind of symptom profiles have been reported among adults and children living in moisture- or mould-damaged dwellings (Brunekreef 1992, Pirhonen et al. 1996, Koskinen et al. 1999, Zock 2002, Engvall et al. 2002b). In different studies, throat symptoms have been described with different terms, e.g. dryness, irritation, itching or soreness, hoarseness, etc.

Table 2. Irritative and general symptoms reported among moisture- and mould-exposed employees in non-agricultural and non-industrial work places.

Country	Work environment	Symptoms	Reference
Finland	a) day care centres b) hospital	eye symptoms, respiratory symptoms	a) Ruotsalainen et al. 1995 b) Seuri et al. 2000
Sweden	a) schools b) hospital	respiratory symptoms, eye symptoms, nasal symptoms, throat symptoms, gastrointestinal symptoms, dermatologic symptoms, general symptoms	a) Thörn 1998, Åhman et al. 2000 Rudblad et al. 2001 b) Wieslander et al. 1999
Norway	hospital	ocular symptoms	Smedbold et al. 2001
Danmark	a) schools b) swimming bath	ocular symptoms, nasal symptoms, throat symptoms, dermal symptoms, general symptoms	a) Sigsgaard et al. 2000, Lander et al. 2001 b) Ebbehøj et al. 2002
United States	a) school b) office	respiratory symptoms, ocular symptoms, nasal symptoms, throat symptoms, general symptoms	a) Cooley et al. 1998, Santilli and Rockwell 2003 b) Johanning et al. 1996, Hodgson et al. 1998, Sudakin 1998, Malkin et al. 1998, Jarvis and Morey 2001
Canada	a) office b) courthouse	respiratory symptoms, ocular symptoms, nasal symptoms	a) Menzies et al. 1998 b) Lee 2003
Taiwan	a) offices b) day care centre	respiratory symptoms, eye symptoms, nasal symptoms, throat symptoms, skin symptoms, general symptoms	a and b) Wan and Li 1999, b) Li et al. 1997

The aetiology of irritation symptoms is unknown, but it has been suggested that exposure to endotoxin or $\beta(1-3)$ -glucans may play a role (Rylander 1998, 1999b, Douwes et al. 2003). Microbial volatile metabolites may also have irritative characteristics (Korpi 2001).

2.3.2 Infections

Viruses and bacteria transmitted from person to person evidently cause common respiratory infections like the common cold, sinusitis and bronchitis. However, these

infections have been reported to increase among occupants in moisture- or mould-damaged dwellings (Pirhonen et al. 1996, Koskinen et al. 1999a, Kilpeläinen et al. 2001). This is an interesting finding, but the mechanism behind this phenomenon has not yet been discovered. It has been suggested that impaired ciliary function because of microbial toxins (Pieckova and Jesenska, 1998) or immunological defence mechanisms (Johanning et al. 1996) of the respiratory mucosa are possible explanations for the susceptibility of occupants to common respiratory infections.

Direct infections caused by indoor moulds are highly uncommon in healthy individuals and are mostly restricted to severely immunocompromised patients. The most common pathogen is *Aspergillus fumigatus* (Bennett 1994); and invasive aspergillosis has been reported in haematology wards. In such cases aspergillosis has been associated with increased airborne concentrations of *Aspergillus* spores (Sherertz et al. 1987, Andersson et al. 1996, Loo et al. 1996, Oren et al. 2001). Some cases of community-acquired opportunistic invasive aspergillosis have also been reported (Benoit et al. 2000, Chen et al. 2001).

In allergic bronchopulmonary mycoses, colonization of fungi in the bronchial epithelium occurs in patients with a chronic respiratory disease such as asthma. When it occurs in the nasal cavity, this condition is referred to as allergic fungal sinusitis. *Aspergillus* species are the most common etiologic agents. Eosinophilia and the presence of non-invasive fungal hyphae in sputum or in nasal mucus characterize both conditions (Ponikau et al. 1999).

However, some fungi can infect otherwise healthy subjects, sometimes causing fatal illness. Among such agents are, e.g. *Cryptococcus* associated with bird droppings, *Histoplasma* associated with bat droppings and *Coccidioides*, which is endemic in the soil in southwestern United States. However, these agents are not normally found in offices or residential environments. In principle, such agents can gain entry from outdoors, although there is little evidence that this actually occurs (Hardin et al. 2003).

2.3.3 Allergic diseases

A number of allergic diseases are related to exposure to indoor mould and moisture, and there are allergens that stimulate specific immunological responses. Examples of this kind of disease are allergic rhinitis and allergic asthma, which are associated with IgE-mediated response, and hypersensitivity pneumonitis, also called allergic alveolitis, which is associated with IgG and T-cell responses. About 70 fungal allergens have been listed by the International Allergen Nomenclature Committee (Kurup et al. 2002). For example, exposure to *Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium* species is frequently associated with development of allergic disease (Husman 1996, Pieckova and Jesenska 1999, Kurup et al. 2000).

The prevalence of IgE-mediated fungal allergy will remain unknown until well-defined populations are tested with standardized fungal extracts. At present the estimated prevalence of fungal sensitization and allergy varies from 3 to 30 %, depending on the population studied (Horner et al. 1995, Husman 1996, Norbäck et al. 1999, Kurup et al. 2000). Among asthmatics and atopic individuals, fungal allergy has been reported to be more common than among non-asthmatics or the general population (Norbäck et al. 1999, Kurup et al. 2000). Among atopics, the prevalence of fungal sensitization/allergy is estimated to range from 20 to 30% and in the general population up to 6 % (Kurup et al. 2000).

Hypersensitivity pneumonitis, which is a severe allergic chest disease, can also occur among persons occupying water-damaged mouldy buildings (Jarvis and Morey 2001). In a Swedish case study, allergic alveolitis has been described in a female teacher in a mould-damaged school (Thörn et al. 1996). Allergic alveolitis occurs in industrial or agricultural settings. It is commonly named according to the occupation or environment, e.g. farmer`s lung, wood trimmer`disease, cheese washer`s disease, bird breeder`s lung (Hawksworth et al. 1995).

2.3.3.1 Work-related asthma

In previous studies, the risk of asthma has been related to presence of visible mould or mould odour in work places (Jaakkola et al. 2002a), and clusters of asthma cases have been found in mould-damaged working environments like schools (Smedje et al.

1996), hospital (Seuri et al. 2000) and other buildings (Bornehag et al. 2001). In a Swedish study (Flodin et al. 2004), working in a building affected by dampness and mould brought a significant risk (OR=4.7) for diagnosis of asthma. According to a large international study, sensitisation to moulds seems to increase the severity of asthma (Zureik et al. 2002).

Occupational asthma has been defined as a category of disease “characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace” (Bernstein et al. 1993). In Finland, occupational asthma is considered to be a physician-diagnosed asthma, which is caused by exposure to dust, gases, vapours or fumes present in the workplace (Onikki and Ranta 1998 a+b). The association between symptoms, bronchial variability and exposure must be shown objectively by allergological test, pulmonary function tests in the workplace and/or with either non-specific or specific bronchial-challenge tests (Keskinen et al. 1978). These requirements follow international guidelines published as the Assessment of Asthma in Workplace, ACCP, consensus statement (Chang-Yeung 1995). The main clinical diagnostic criteria for mould-induced occupational asthma include 1) history of fungal exposure, 2) descriptive symptoms (obstruction or wheezing) at work, 3) positive responses in a specific inhalation challenge test or 4) reduced peak flow values during a work shift following additional criteria for levels of specific IgE-antibodies and positive skin prick test reactions (Reijula 1998, 1999).

2.3.4 Toxic effects

Toxicity due to fungal exposure is caused mainly by secondary metabolites produced by moulds. Fungi produce toxic substances (some of them called mycotoxins) in order to provide competitive advantage over other mould species and bacteria. Mycotoxins are typically cytotoxic, disrupting cell membranes and interfering with protein and RNA/DNA synthesis (Sorenson et al. 1987).

Several fungi, such as *Acremonium* spp., *Aspergillus* spp., *Chaetomium* spp., *Fusarium* spp., *Penicillium* spp., *Stachybotrys* spp., and *Trichoderma* spp., can produce mycotoxins (Betina 1984, Sorenson 1993, Abbot 2002). These toxins include

e.g., aflatoxins, ochratoxins, sterigmatocystin and trichothecenes (Betina 1984). Exposure to mycotoxins can occur via inhalation, via ingestion of mould-contaminated food or by skin contact (Kemppainen et al. 1988, Schiefer 1990). It has been found that the potency of the respiratory route is higher than that of the alimentary route. The dose of mycotoxin required to cause particular effects is an order of magnitude less when administered by the respiratory tract than by ingestion (Hendry and Cole 1993).

In an agricultural environment mycotoxins have been related to a disease called organic dust toxic syndrome (ODTS), a non-infectious illness resembling influenza with the major symptoms being fever and malaise (doPico 1986).

According to some studies (Hodgson et al. 1998, Johanning et al. 1999), indoor exposure to mycotoxins produced by *Stachybotrys chartarum* and *Aspergillus versicolor* have been associated with adverse health effects such as disorders of the respiratory system, skin and mucous membrane, and central nervous system. Nevertheless, the role of indoor air mycotoxins as causative agents of health effects is still obscure. Although the US National Academies of Science, Institute of Medicine Committee on Dampness in Indoor Environment, concluded that it is biologically plausible that a causal connection exists, the conclusion of some recent reviews has been that the evidence is still insufficient (Page and Trout 2001, Burge 2003, Chapman et al. 2003).

2.3.5 Registered occupational diseases associated with exposure to microbes

In Finland the Finnish Register of Occupational Diseases (FIOH) has collected all new cases of occupational diseases and injuries into official statistics since 1926. New cases of occupational diseases caused by fungal exposure among Finnish teachers, office workers and farmers during the last eight years are listed in Table 3 (Karjalainen et al. 1996-2001, Riihimäki et al. 2002, 2003). The population of Finland is 5.1 million and the number of cases of occupational asthma caused by fungal exposure has continued to increase, with 79 diagnosed cases in 2002 versus 62 in 2001 and 48 in 2000. In 2002 the number of cases of occupational rhinitis caused by fungal exposure was 15. Allergic alveolitis was diagnosed in 15 cases because of mould problems in the working environment, and in 2002 all except one in nine

diagnosed cases of ODTs were related to microbial exposure in mould-damaged working environments (Riihimäki et al. 2003).

Table 3. New diagnoses of occupational diseases caused by fungal exposure among Finnish teachers, office workers and farmers according to the Finnish Register of Occupational Diseases during 1995-2002.

Year	Teachers Number of cases	Office workers Number of cases	Farmers Number of cases
1995	19	25	66
1996	29	42	65
1997	66	31	68
1998	49	12	53
1999	30	17	130
2000	32	21	42
2001	17	27	59
2002	25	42	39

2.4 Effects of mould remediation on health

There have been few follow-up studies of health effects related to mould remediation among adults in non-industrial and non-agricultural environments (see Table 4). So far Jarvis and Morey (2001) have reported the largest study on remediation, a mould-contaminated 11-story structure with 488 current occupants. Because of the high rates of symptoms of the occupants and also chronic building-related diseases like asthma and hypersensitivity pneumonitis, the whole building was evacuated and remediated. Based on a self-reported questionnaire survey, symptom rates prior to building re-entry were substantially lower than those found before evacuation and remained low after re-occupancy. No building-related illness is known to have occurred after building re-entry. Åhman et al. (2000) made an interview-based study among personnel and pupils of a school before and seven months after remediation. According to their findings, the excess symptoms of the personnel had almost disappeared. An intervention study made with a self-administered questionnaire about rebuilding a mould-damaged school has been reported by Sigsgaard et al. (2000); and after rebuilding of the school, symptoms of mucosal and neurological irritation diminished significantly among employees. Rudblad et al. (2002) made a two-year follow-up study of a group of 26 mould-exposed teachers. Nasal mucosal hyperreactivity seemed to persist for years and decrease slowly, even after successful

remedial measures. With a symptom questionnaire and clinical examinations, Ebbehøj et al. (2002) made a follow-up study among swimming pool staff. Seven months after the intervention the rate of symptoms and variability in mean peak flow fell to normal level. In Sudakin`s study (1998) among office employees, multiple symptoms with a predominance of neurobehavioral and upper respiratory track complaints were significantly less prevalent after relocation from a water-damaged environment.

Table 4. Effects of moisture remediation on health of adults. Summary of reported intervention studies.

	Place/ Number of participants	Methods	Health effects of remediation
Jarvis and Morey 2001	11-story structure n=488	questionnaire	lower symptom rates no new building-related respiratory disease
Åhman et al. 2000	school n=21 teachers n=224 pupils	interview	lower almost “normal” symptom rates
Sigsgaard et al. 2000	school n=43	questionnaire	mucosal and neurological symptoms decreased
Sudakin 1998	office building n=37	interview	decrease in upper respiratory and neurobehavioral symptoms
Rudblad et al. 2002	school n=28	questionnaire nasal provocation test	increased reactivity to histamine in nasal provocation test
Ebbehøj et al. 2002	swimming bath n=25	questionnaire clinical examination 2-week peak flow follow-up	decrease in symptom levels decrease in peak-flow variability

2.5 Assessment of exposure to moisture and mould

To assess the possible health effects of indoor moulds, characterisation of the presence and degree of exposure is essential. For assessing exposure in studies focusing on health effects of moisture and mould, several approaches are available. In many epidemiological studies, a self-reported questionnaire has been used to assess both the exposure and the health effects related to indoor moisture and mould. The questionnaires may include questions about visible signs of dampness, condensation on windows, smell of mould and/or visible mould growth, and thus subjective/

observed assessment of exposure (Ruotsalainen et al. 1995, Li 1997, Cooley et al. 1998, Reijula and Sundman-Digert 2004). Respondents may also be asked to give their personal opinion about their perceived indoor air quality and state of health.

2.5.1 Technical and microbiological assessment

Visual walk-through inspection by a trained expert is a more objective method of detecting moisture and mould problems of the building than information collected only in self-reported questionnaires (Platt et al. 1989, Verhoeff et al. 1995, Williamson et al. 1997, Nevalainen et al. 1998). Surveyors can also be trained to assess the condition of a building using a previously developed protocol and then characterize the moisture status of the building according to defined scale (Williamson et al. 1997, Koskinen et al. 1999a).

Humans` ability to sense air humidity is poor, but certain signs of inappropriate moisture can be observed. Signs that liquid water leaves on materials or changes that can be attributed to excess moisture are usually visual, e.g., peeling of paint. Such perceptions are the basis of most epidemiological studies, in which data on moisture conditions are collected by questionnaire (Brunekreef 1992, Pirhonen et al. 1996, Kilpeläinen et al. 2001).

Mould exposure in indoor air has conventionally been assessed by measuring numbers of fungal spores in the air or by using cultures obtained from a sample of settled dust. These methods are based on cultivation and microscopic identification of fungi (Reponen et al. 1989). The samples can be obtained with volumetric samplers, which collect a known volume of air. These samplers include cascade impactors, slide impactors and liquid impingers (Macher 2001). The most widely used sampling device is the Andersen 6-stage impactor, which collects airborne microbes effectively (Willeke and Macher 1999) and allows identification of air-borne spores and examination of microbes of different size classes. Surface or material samples may be needed to verify the sources of contamination measured in air samples (Reynolds et al. 1990).

Cultivation methods underestimate the total microbial levels of fungi. In dwellings, the number of viable fungi has been observed to be only about 1% of the total spore count (Toivola et al. 2002). However, a good correlation has been shown between viable and total concentrations in indoor environments (Palmgren et al. 1986, DeKoster and Thorne 1995). In the future, PCR-assays for indoor fungi may replace the routine protocol for microbiological methods of assessing the indoor environment (Haugland et al. 1999, Cruz-Perrez et al. 2001a+b, Meklin et al. 2004).

2.5.2 Mould-specific IgG-antibodies

Immunoglobulin G (IgG) antibodies are produced as a normal response of human defence to foreign antigens. The presence of IgG antibodies suggests exposure to the microbes in question but not development of a disease (Erkinjuntti-Pekkanen et al. 1999). IgG concentrations have been used as a marker of mould exposure in occupational environments with massive exposure to mould (10^5 - 10^6 cfu/m³), such as agriculture (Erkinjuntti-Pekkanen 1999, Lappalainen et al. 1998), sawmills (Eduard et al. 1992, Halpin 1994) and handling and treatment of biowaste (Bünger et al. 2000). In these studies an association has been shown between exposure to high concentrations of airborne moulds and development of IgG antibodies.

The biological half-life of IgG-antibodies against different microbes is several weeks (Eduard 1995), and therefore the presence of IgG-antibodies does not indicate the place and time where the foreign antigen was encountered. In the same exposure environment, antibody production against microbes varies considerably between individuals, and even low IgG concentration does not exclude the possibility of mould exposure (Erkinjuntti-Pekkanen et al 1999).

In non-agricultural and non-industrial occupational environments, such as public buildings and also homes, microbial levels are usually in the range 10^1 - 10^3 cfu/m³ (Nevalainen et al 1997, Hyvärinen 2002). Despite this, the association between exposure to indoor moisture and mould and the development of IgG antibodies to microbiological antigens has been shown in adults in occupational environments like hospitals (Seuri et al. 2000), offices (Vojdani et al. 2003) and homes (Vodjani et al. 2003). In a Finnish population-based case-control study an increased risk of

developing asthma in adulthood was significantly related to IgG antibodies to *Trichoderma citrinoviride*, but not to the other seven moulds studied (Jaakkola et al. 2002b). However, there are also some studies in which no or only a weak association has been found between mould exposure and elevated IgG antibodies (Johanning et al. 1996, Malkin et al. 1998, Makkonen et al. 2001, Hyvärinen 2002).

2.6 Determination of the health effects of occupational exposure to moisture and mould in indoor air

Several approaches are available and have been used in health studies of indoor air, such as self reported questionnaires and measurement of lung function.

2.6.1 Questionnaire

Self-reported questionnaires are a relatively easy and inexpensive way to collect information about health and perceived indoor air factors from a large group of occupants. Self-reported questionnaires are widely used in epidemiological studies (Pirhonen et al. 1996). Questionnaires may include health questions about respiratory and non-respiratory symptoms, different kinds of respiratory infections, doctor diagnosed chronic diseases, allergic diseases and prescribed medication. Many questionnaires also include demographic data and information on living habits.

However, one of the weaknesses of questionnaires is a risk of bias in remembering, answering or perception. In the Nordic countries, the MM-questionnaire, which was developed in Örebro, Sweden, is widely used (Andersson et al. 1993, Andersson 1998). This questionnaire has been tested for usefulness, reliability and validity and was standardized in 1989 (Andersson and Stridh 1992). Various versions concerning workplaces, homes, schools and day-care centres are now available. Recently in Finland Reijula and Sundman-Digert (2004) published a study on assessment of indoor air problems at work with a questionnaire in an office environment. More than 11000 office workers from 122 workplaces with some kind of indoor air problems, took part in the survey and filled in the Örebro MM questionnaire. The most common symptoms reported were irritated, stuffy or runny nose, itching, burning or irritation of eyes, and fatigue. If the complaint rate is exceptionally high, this can point to problems in the building and in the air-conditioning system. The basic rule for

prevalence of symptoms (that is, the symptom is work-related and is experienced every week) is that a rate of over 20% is considered higher than normal (Andersson et al. 1993, Andersson 1998). In a Norwegian study, Bakke et al. (2001) have showed that, compared with data obtained in a structured job history interview, self-reported occupational exposure had high sensitivity and lower specificity in subjects with respiratory disorders than in those without symptoms. In the United Kingdom the RSH questionnaire, which focuses on office environments, issued by The Building Research Establishment is used (Raw 1995).

Previous studies have shown that in the same environment women are likely to report more complaints than men are. In addition, persons suffering from atopic disease report a much higher prevalence of skin and mucous-membrane symptoms than non-atopics do (Andersson, 1998, Runeson et al. 2003, Reijula and Sundman-Digert, 2004).

2.6.2 Lung functions

In studies dealing with adverse health effects of indoor air, objective lung-function measurements like spirometry or PEF have been used to evaluate the respiratory effects of mould exposure (Dahlqvist and Alexandersson 1993, Norbäck et al. 1999, Seuri et al. 2000, Dharmage et al. 2002, Ebbehøj et al. 2002, Kilburn 2003, Gunbjörnsdottir et al. 2003).

2.6.2.1 Spirometry

Spirometry, the most basic and frequently performed test of pulmonary function, measures the ventilatory function of the respiratory system. Using a forced expiratory manoeuvre, which is maximal expiration of the total lung capacity to residual volume, spirometry measures volumes and flow rates (ACOEM, 2000). According to 1996 the AARC clinical practice guidelines, indications for spirometry are to detect the presence or absence of lung dysfunction according to medical history or physical signs and symptoms, to quantify the severity of known lung disease, to assess the change in lung function over time or following administration of or change in therapy, to assess the potential effects or response to environmental or occupational exposure

and to assess impairment and/or disability. In occupational medicine, spirometry can play an important role in primary, secondary and tertiary prevention of respiratory diseases in the workplace. For example, primary prevention of occupational respiratory disease also includes research on and monitoring of health status in workers (AARC 1996).

There have been few studies where measurements of lung function have been used in association with moisture- and mould damage in working environments. However, in those studies it has been shown that during work in non-agricultural and non-industrial moisture- or mould-damaged workplaces, the presence of respiratory symptoms seems to be associated with deterioration of pulmonary function. In a Swedish pilot study, during a working week in winter, 13 of 15 school employees with lower-airway symptoms exhibited a fall in FVC during a working week in winter (Dahlqvist and Alexandersson 1993). Also in Swedish study among adults living in damp dwellings, FEV1 was lower in subjects living in a building with floor dampness (Norbäck et al. 1999).

According to a North American study, pulmonary function abnormalities indicating severe airway obstruction that reduces vital capacity and FEV1 were found among a patient series of 65 individuals exposed to mould in indoor air at home. History of atopic background or asthma was not reported. When neuropsychological tests were made for the patient series, 21 of 26 functions tested were abnormal (Kilburn 2003). In females aged 20 - 44 years, after adjusting for bronchial hyperresponsiveness, respiratory symptoms and smoking, skin reactivity to *Alternaria* was associated with a decrease in FEV1 (Sunuyer et al. 2000). On the contrary, a study of Swedish young adults found no difference in FEV1 and FVC measurements between subjects who reported water damage or visible mold or those who did not (Gunnbjörnsdottir et al. 2003).

2.6.2.2 Peak flow measurements

Peak expiratory flow (PEF) is the maximum flow achieved during forced expiration performed during a satisfactory manoeuvre, which requires the maximum possible inspiration followed immediately by a maximally forced expiration. Follow-up of

measurements of peak expiratory flow are commonly used, and the criteria for observed changes in the PEF-measurements are the result of clinical experience (Quanjer et al. 1997). Thus, PEF is utilised for measuring changes that occur in pulmonary function in the work environment, housing conditions or related environmental exposures in diagnosing of occupational diseases as well as in clinical and epidemiological studies (Lebowitz 1991, Rylander et al 1989, Zock et al 1995, Lebowitz et al. 1997). This method has been used to assess the severity of asthma. Diurnal variation (within-day) of PEF-values represents more acute phases of disease, like bronchial lability in asthma; and day-to-day variation represents the chronic state of lung function. Serial measurement of PEF is the most appropriate initial confirmatory test for occupational asthma suggested by a history of asthmatic symptoms that improve on days away from work (Gannon and Burge 1997).

As discussed previously (see 2.3.3.1), occupational exposure to mould and other bioaerosols increases the risk of asthma. It has been shown among asthmatics sensitized to fungi that increased variability in peak flow is significantly associated with both smoking and visible mould (Dharmage et al. 2002); but also among non-asthmatics, PEF variability is higher in subjects with damp floors (Norbäck et al. 1999). In an intervention study made among the personnel of a mould-damaged swimming pool the mean PEF variability was 20% and after remediation, fell to 15% (Ebbehøj et al. 2002).

3 AIMS OF THE STUDY

The aim of this study was to characterize the health effects of changing occupational mould exposure on teachers.

The specific aims were:

1. to assess adverse health effects on teachers by using a symptom questionnaire and measurements of lung function after extensive mould remediation of school buildings.
2. to measure mould-specific IgG-antibodies at the end of the remediation and two years later as a marker of mould exposure.
3. to measure daily PEF-levels during a mould-exposure school week and a holiday week
4. to evaluate possible risk factors for teachers in mould-damaged school buildings

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9 GENERAL DISCUSSION

9.1 Methodological aspects

This study was a follow-up study among teachers from six mould-damaged schools and one reference school. The school buildings were investigated both technically and microbiologically; thus the exposure assessment was based on objective methods. The same two trained civil engineers made the investigations using the same observation protocol before the remediation and one and three years after remediation, using a walk-through inspection that has been used and validated in many studies (Nevalainen et al. 1998). Definition of the school buildings as normal or damaged was based on technical criteria together with microbiological findings.

Health data were collected with a self-reported questionnaire based on two widely used questionnaires, the MM40 and the Tuohilampi questionnaires (Andersson et al. 1998, Susitaival and Husman 1996). All cases of asthma and most respiratory infections could be double-checked from the medical records of the studied individuals or from the local hospital. In the first part of the questionnaire study (I) the response rate was good; 83% answered all three questionnaires. In the second part of the study (IV), 36% of the teachers answered both questionnaires. The main reasons for dropouts was probably the long time period between the questionnaires, during which 25% had retired and 25% had changed jobs. Those individuals who had left the schools could not be reached, and thus we could not determine whether some of them had left because of indoor air problems and symptoms. The strength of this study was the long-term follow-up of the same individuals and the combination of these health data with exposure assessment of the buildings. The teachers were aware of indoor moisture and mould problems, and there may have been some overreporting of the symptoms. Some memory bias is likely in all phases of the study; thus in a follow-up study the effect is minor.

Lung function tests; spirometry (I) and serial measurements of peak expiratory flow (III) are commonly used in clinical and epidemiological studies related to asthma and environmental exposure to bioaerosols (Lebowitz 1991, Rylander et al 1989, Zock et al. 2002). The same experienced specialized nurse made the spirometry measurements

with the same spirometry equipment according to an accepted protocol. Each teacher had a peak expiratory flowmeter of her/his own. A trained doctor gave instructions for the measurements in small groups.

Mould-specific IgG antibodies (II) were analyzed altogether for 20 different microbes including moisture-indicative moulds and also moulds commonly found in water-damaged indoor environments (Samson 1994). The analysis of IgG antibodies has been widely used in Finland since the 1980's, and the sera of more than 14 000 individuals from different occupational exposure environments have been analysed (Reiman et al. 1998).

9.2 Respiratory, skin and general symptoms related to mould exposure in indoor air

The prevalence of symptoms among these teachers in moisture- and mould-damaged schools was high before the remediation (I, IV). Hoarseness (I) was more common among teachers in the index school than in the reference school ($p=0.0040$), and high proportions of exposed teachers complained of fatigue (I, IV) and headache (I). Large numbers of respiratory symptoms and skin irritation were reported (I). Female gender and exposure situations outside school buildings, such as a mould exposure at home and handling of organic materials, e.g. gardening, as well as the number of years at the same school, were related to the increase in symptoms before remediation (IV).

Respiratory symptoms seem to be indications of disease rather than the disease itself (IOM 2004). Numerous studies have been published, and different ones have reported symptoms in different terms and. However, most of the studies confirm the connection between upper and lower respiratory symptoms among children and adults in homes and in non-industrial office-type working places. In different studies and circumstances no single symptom is "mould-specific", but several symptoms or groups of symptom may vary. The conclusions, according to IOM (2004), about the state of scientific knowledge regarding the association between symptoms and indoor environments can be defined in two different ways, "damp" and "mould" (Table 1).

Table 1. Summary of findings regarding the association between health outcomes and exposure to damp indoor environments and health findings and the presence of mould or other agents in damp indoor environments (IOM 2004).

Category of evidence	The association between health outcomes and exposure to damp indoor environments	The association between health outcomes and presence of mould or other agents in damp indoor environments
Sufficient evidence of a causal relationship	no outcomes met this definition	no outcomes met this definition
Sufficient evidence of an association	Upper respiratory (nasal and throat) track symptoms, cough, wheeze, asthma symptoms in sensitized persons	Upper respiratory (nasal and throat) track symptoms, cough, wheeze, asthma symptoms in sensitized persons, hypersensitivity pneumonitis in susceptible persons
Limited or suggestive evidence of an association	Dyspnea (shortness of breath), lower respiratory illness in otherwise healthy children, asthma development	Lower respiratory illness in otherwise healthy children
Inadequate or insufficient evidence to determine whether an association exists	Airflow obstruction (in otherwise healthy children), mucous membrane irritation syndrome, chronic obstructive pulmonary disease, inhalation fevers (non occupational exposures), lower respiratory illness in otherwise healthy adults, acute pulmonary hemorrhage in infants, skin symptoms, gastro-intestinal track problems, fatigue, neuropsychiatric symptoms, cancer, reproductive effects, rheumatologic and other immune diseases	Dyspnea (shortness of breath), airflow obstruction in otherwise healthy people), mucous membrane irritation syndrome, chronic obstructive pulmonary disease, inhalation fevers (non occupational exposures), lower respiratory illness in otherwise healthy adults, rheumatologic and other immune diseases, acute pulmonary hemorrhage in infants, skin symptoms, asthma development, gastrointestinal track problems, fatigue, neuropsychiatric symptoms, cancer, reproductive effects

Fatigue is a non-specific general symptom that is related to many physical and psychiatric disorders. In some studies among adults, however, fatigue is also associated with indoor moisture and mould exposure (Pirhonen et al. 1996, Koskinen et al. 1999a, Lander et al. 2001, Engvall et al. 2002) and children (Waegemaekers 1989). In a case study in Sweden (Thorn and Rylander 1998) inhalation of lipopolysaccharides caused unusual tiredness among volunteer individuals. Indeed, it has been speculated that the outcome might have been mediated by TNF- α activity. Release of TNF- α and other proinflammatory cytokines has been related to exposure to moulds and to symptoms (Hirvonen et al. 1999).

Skin symptoms related to self-reported or researcher-assessed moisture or mould indoor problems such as irritation have been reported in earlier studies (Pirhonen et al. 1996, Li et al. 1997, Wan and Li 1999, Koskinen et al. 1999, Kilpeläinen et al. 2001, Engvall et al. 2002). Skin symptoms have also been connected with odour and water leakage in the preceding 5 years (Engvall et al. 2002). Among the agents of damp indoor environments that may cause irritation are microbial volatile organic compounds (MVOC) (Korpi 2001). Furthermore, one of the mycotoxin groups associated with mouldy indoor environments is the trichothecenes, which are known to be irritative (IOM 2004). However, the role of these subgroups as causative agents of skin symptoms is still unclear.

Most of the symptoms associated with mould exposure are very common and may be related to many other environmental factors or diseases. Therefore, in assessment of possible causal connections, the temporal and spatial relationship between the symptom and the indoor environment in question is essential.

9.3 Infections related to indoor air moisture and mould exposure

In this study, respiratory infections like the common cold (I), sinusitis (I, IV) and conjunctivitis (I, IV) were increased among teachers exposed to indoor moisture and mould compared to the reference group (I) or general population (IV). In addition the sum of all respiratory infections was higher in mould- exposed teachers than in reference subjects (I). This is in accordance with previous studies, where exposure to indoor moisture and moulds seemed to be associated with a variety of infections in airways and also in conjunctivitis (Koskinen et al. 1999, Kilpeläinen et al. 2001).

However, it is not fungi that cause these infections among healthy individuals, but rather the common respiratory viruses and bacteria. Moisture- and mould-damaged indoor environments appear to affect exposed individuals so that they are more prone to respiratory infections. There is some preliminary evidence concerning impaired ciliary functions in the lungs (Pieckova and Jesenska 1999) and the immunosuppressive effects of mycotoxins (Johanning et al. 1996). However, while it is still unclear whether the occupants' exposure leads to the effects suggested by experimental studies, the causes of increased prevalence of infections remain to be verified.

We found a connection between sinusitis and female gender. So far, previous studies have suggested that women are more likely to report complaints than are men in the same environment (Andersson, 1998, Runeson et al. 2003, Reijula and Sundman-Digert, 2004). Sinusitis is not a subjective symptom but is rather a disease usually diagnosed by a doctor, thus strengthening the assumption that women are more prone to adverse health outcomes and that differences between genders is not merely a reporting bias.

9.4 Asthma and allergy related to indoor air moisture and mould exposure

A cluster of asthmatic teachers was observed. Prevalence of asthma in the mould damaged school was 26%, and three of the cases of asthma were diagnosed as an occupational disease caused by fungal exposure (I). This prevalence was exceptionally high, i.e. five times higher than in the normal population. Clusters this big are rare. Clusters or building-related asthma or hypersensitivity pneumonitis among occupants have been reported from a water-damaged Finnish military hospital (Seuri et al 2000) and a large office building in North America (Jarvis and Morey 2001)

Asthma and asthmatic symptoms such as wheezing and cough have been connected to moisture and mould exposure in work places and home environments. Many studies of adults (Smedje et al. 1996, Williamsson et al. 1997) and children (Waegemaekers et al. 1989) have reported odds ratios over 1 for association between exposure to dampness or presence of mould or other exposure agents in damp indoor environments and asthma. As shown in Table 1. there is sufficient evidence for this

connection. Exacerbation of asthmatic symptoms and even onset of asthma, was also observed in our study.

Development of asthma and moisture or mould damage in indoor environments has not been studied intensively but some reports of self-reported indoor mould or mould odour have found a connection to increased risk of asthma (Thorn et al. 2001, Jaakkola et al. 2002). An interesting point has been reported by Jaakkola et al. (2002): increased risk of developing of asthma was related to visible mould or mould odour in work environments but not with such damage in the home.

Asthma can be defined as a reversible airflow disorder of obstruction that may be allergic (IgE-mediated) or non-allergic. According to previous a study by Douwes and Pearce (2003), moulds are known to produce immunoglobulin-E inducing allergens; and higher prevalence of mould sensitization has been found among subjects living in damp buildings (Norbäck et al. 1999) and among severe asthmatics (Black et al. 2000). The role of allergic sensitization is still somewhat unclear.

In Finland, legislation on occupational diseases and the statement of occupational diseases defines the diagnostic criteria for occupational asthma related to moisture and mould exposure. The Finnish Institute of Occupational Health (FIOH) collects and publishes annual statistics on new occupational diseases and injuries. According to these statistics, occupational diseases caused by fungal exposure in indoor air have remained at the top of the list during the last decade. Among the diseases, occupational asthma caused by fungal exposure is increasing. The criteria for diagnosis of occupational disease are relatively strict. The chain of evidence is formed by verified exposure conditions as well as symptoms related to exposure, clinical measurements that confirm symptoms and experimental, controlled exposure to fungal extracts. Because of the strict criteria for diagnosis of occupational-exposure asthma, some symptomatic cases for which there is less evidence might fall outside the official statistics.

9.5 Effects of school-building remediation on the health of teachers

Remediation of the school building led to beneficial effects on health among the teachers. Most changes were found in chronic diseases (I), infections (I) and general

symptoms (IV). During the three-year follow-up no new cases of asthma appeared (I); the sum of the respiratory infections (I) and e.g. self-reported bronchitis (I) and conjunctivitis (I) decreased significantly. In general, symptoms of fatigue and headache decreased (I, IV). In repeated measurements during the three-year period after remediation, spirometry measurements were at normal level. But on the other hand, asthmatic teachers could not give up their medication, and their spirometry measurements did not improve. This suggests that while some of the symptoms may be reversible, this does not apply to asthma.

Few intervention studies have been published concerning the health effects of mould remediation in public buildings. In general, the results show improvement in terms of the reversibility of the health effects related to moisture and mould exposure, but not all the results are so positive. Nevertheless, in all except one intervention study a decrease in respiratory and general or neurobehavioral symptoms was reported after remediation (Åhman et al. 2000, Sigsgaard et al. 2000, Jarvis and Morey 2001, Ebbehøj et al. 2002). A cluster of building-related hypersensitivity pneumonitis and asthma was found in a large office building; but after remediation, no new building-related allergic respiratory disease occurred (Jarvis and Morey 2001). On the other hand, according to one Swedish clinical study among a group of teachers exposed to a school building with moisture and mould problems, the observed nasal mucosal hyperreactivity seemed to persist for years and only slowly decrease after successful remedial measures had been taken (Rudblad et al. 2002).

The results of intervention studies have shown so far positive effects on health. Now the evidence is based on single case studies, not more than 600 hundred exposed individuals, and on the different kinds of study protocols and exposure assessments. There are no large population studies with long follow-up times after repairs up on which strong conclusions and generalisations can be based. The follow-up times have usually been from a few months to two years. This may not be long enough for recovery of the symptoms or, on the other hand, to show all the health effects or indicate whether the remediation is really performed sufficiently and correctly.

9.6 Role of mould-specific IgG-antibodies in exposure to mould in indoor air

In high exposure environments, such as in agriculture or sawmills, determination of IgG antibodies has been used in assessment of exposure to fungi (Eduard 1995). Diagnostic criteria for the disease may also include microbe-specific IgG antibodies (Terho 1986). In recent decades, however, analysis of IgG antibodies has been widely used in occupational health care.

No association was found between mould-specific IgG antibodies in teachers and the presence of indoor air moisture or mould problems in schools. However, a significant association was found between elevated mould specific IgG-antibodies to 10 moulds and episodes of sinusitis (II). An association was also found between allergic rhinitis and IgG-antibodies to two different moulds that were also elevated in sinusitis (II). In the follow-up the total concentration of mould-specific IgG-antibodies to *Tritirachium roseum* was lower and decreased even more in those who had reported sinusitis in the beginning of the study (II). A decrease in IgG antibodies for four moulds were found among mould-exposed teachers with reported episodes of bronchitis and for two moulds among those with a history of atopy (II). Neither mould-specific IgG antibodies nor their changes during the two-year follow-up showed a significant association with asthma or gender (II).

In indoor environments damaged by moisture and mould, the role of mould specific IgG antibody is obscure, because the indoor air concentrations of viable fungi in homes are low and are even lower in public buildings, e.g., schools, compared to the concentrations at sawmills. The question is whether it is enough to stimulate specific IgG production. However, an association between exposure to indoor moisture and mould and the development of IgG antibodies to microbiological antigens has been shown in adults in non-industrial occupational settings (Seuri et al. 2000, Vojdani et al. 2003) and in homes (Vodjani et al. 2003). IgG antibodies to *Trichoderma citrinoviride* have been associated with increased risk of developing asthma in adulthood (Jaakkola et al. 2002). No or only a weak association has been found between mould exposure and elevated IgG antibodies (Johanning et al. 1996, Malkin et al. 1998, Makkonen et al. 2001).

9.7 Peak expiratory flow levels related to mould exposure

A minor but significant decrease in peak expiratory flow levels was found among teachers working in the mould-damaged school after a winter holiday week. The change was seen in all three daily measurement points (III).

According to a recently published committee report of the Institute of Medicine, there is sufficient evidence of the association between cough, wheeze and asthma symptoms and exposure to damp or mould in indoor environment (IOM 2004). In many epidemiological studies, prevalence of asthma is increased in moisture- and mould-damaged environments, and symptoms of asthma are also reported often (Peat et al. 1998, Norbäck et al. 1999, Engvall et al. 2001, Jaakkola et al. 2002). In earlier studies, biochemical markers of inflammation from nasal lavage fluid (Hirvonen et al. 1999) and induced sputum (Purokivi et al. 2001) have also been reported from exposed teachers, which supports the connection between exposure and clinical findings. In environmental studies with low exposure, changes in lung function are seldom found with spirometry (Gunnbjörnsdottir et al. 2003).

In some earlier studies, high variability in peak expiratory flow has been shown among mould-exposed individuals (Norbäck et al. 1999); and after remediation variability has decreased to the normal level (Ebbehøj et al. 2002). Minor functional changes take place in the lungs; and in susceptible individuals serial measurements of peak expiratory flow are one possible way to detect these changes.

9.8 Ethical considerations and future aspects

Moisture or mould damage and its connection to the resulting exposure is complex and, the human response is diverse (Nevalainen and Seuri 2005). To apply proper risk assessment and risk management, the connections between these factors should be known more thoroughly.

To elucidate the links between building damage and health, large controlled studies are needed in which thorough technical, microbiological and health investigations are done parallel to each other (Hirvonen et al. 1999) and induced sputum (Purokivi et al. 2002) could be used in such studies to assess individual exposure. In acute exposure situations, the diagnostic procedure could also include more thorough clinical

investigations. However, on the community level the focus of concern, is in most cases, on problems of construction engineering, repairs, and remediation of the building and even more so, on the prioritization and decision-making concerning the remediation process.

10 CONCLUSIONS

Based on the results of the present study, Teachers` Health in Moisture-Damaged Schools- a Follow-up Study, the following conclusions can be drawn:

1. Mould remediation had a positive effect on the health of teachers. Self-reported fatigue, headache and respiratory infections decreased. No new cases of asthma appeared during the follow-up time and there were no notable changes in spirometry measurements.
2. IgG-antibodies were not a marker of moisture- and mould exposure in the school environment. On the other hand, mould-specific IgG-antibodies were connected with sinusitis, which is a new finding.
3. Lung functions in non-asthmatic teachers, as assessed by serial measurements of peak expiratory flow, increased during absence from the exposure environment.
4. In the moisture- or mould-damaged schools, significant risk factors for sinusitis, voice problems and headache were identified as being female, over 40 years old and having worked more than ten years at the same school, respectively.

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