Asthma in damp indoor work environments

Kirsi Karvala

People and Work
Research Reports 97

Finnish Institute of Occupational Health
Helsinki, Finland

Hjelt Institute, Department of Public Health
University of Helsinki
Helsinki, Finland

DOCTORAL DISSERTATION

Supervisors: Henrik Nordman, Adjunct Professor
Finnish Institute of Occupational Health
Helsinki, Finland

Jukka Uitti, Adjunct Professor
Finnish Institute of Occupational Health
Tampere, Finland

Reviewers: Terttu Harju, Adjunct Professor
University of Oulu and
Oulu University Hospital
Oulu, Finland

Professor Kimmo Räsänen
University of Eastern Finland
Kuopio, Finland

Opponent: Professor Tari Haahtela
University of Helsinki
Helsinki, Finland

ABSTRACT

Indoor dampness and mold in work environments are associated with adverse respiratory health effects, of which asthma is the most frequently diagnosed disease. According to the Finnish Register of Occupational Diseases, indoor-air molds have been the most frequently reported cause of occupational asthma (OA) since 2001. The diagnostics are not straightforward, mainly due to difficulties in identifying the specific causative agent and demonstrating the relationship between asthma and this unknown factor. Respiratory ill-health and multiple non-specific symptoms related to building dampness are usually transient, but persistent symptoms appear to be common for some persons, even despite building repairs or a change to an alternative work environment.

One aim of this thesis was to assess and develop methods for the diagnosis of OA induced by indoor dampness and mold. Another aim was to determine whether prolonged asthma-like symptoms appearing in relation to workplace dampness and mold lead to the development of asthma later. The objective was also to evaluate long-term outcomes with respect to the quality of life (QOL) and work ability among workers with asthma or respiratory symptoms previously related to damp indoor work environments.

The study population was 2200 patients examined at the Finnish Institute of Occupational Health (FIOH) from 1995 through 2004 because of a suspected occupational respiratory disease. All of the patients had experienced work-related respiratory symptoms that manifested in damp and moldy indoor environments. At the time of the exposure, most of the patients had worked in office-like surroundings, schools, hospitals, or children day-care centers. In 2007 (3–12 years after the baseline ex-

aminations), the patients were followed up with a questionnaire survey. Altogether 1295 (61%) of the 2114 persons participated.

At the time of the study, specific inhalation challenge (SIC) tests with commercial mold extracts were a routine procedure with which to confirm OA, and the patients for the analyses were selected from the 694 patients who underwent this test. The clinical investigations had included the assessment of specific sensitization to molds and serial peak expiratory flow (PEF) measurements at and away from work.

A retrospective review of the medical files was conducted of the patients who had been suspected of having occupational asthma. An evaluation of each patient's exposure at work was assessed by classifying the intensity of microbial exposure on the basis of the available information in the medical files. The information included technical reports on building-structure damage and microbial measurements. For these analyses, the patients were divided into three categories according to the probability of OA consistent with the international diagnostic criteria for OA.

An OA diagnosis was considered as probable for 156 patients. The diagnosis was based on verified mold exposure, work-related asthma symptoms with onset after entrance into the workplace, lung function changes compatible with asthma, and objectively demonstrated work-relatedness of asthma by work-related changes in serial PEF monitoring or positive SIC tests with mold extracts or both. Specific immunoglobulin (Ig) E sensitization to molds was found for 20% of the patients classified as probable OA. The agreement between the serial PEF measurements and the SIC tests (both being either positive or negative) was 56%. For the patients with a positive SIC test, the agreement with the serial PEF monitoring was 78%.

The study contributed some new information pertaining to the diagnostics of OA induced by workplace dampness and molds. An individual exposure assessment can be based on descriptions of the extent and location of the moisture and mold damage in the building structures and on microbial measurements. Serial PEF monitoring can be regarded as an applicable method in the clinical evaluation of OA induced by indoor dampness and molds. This in particular considering the flaws of the SIC, for example due to the complex exposure situation. Unlike SIC testing, the serial PEF records reflect the entire exposure at the workplace. The

major weakness is that they do not accurately differentiate between work-exacerbated asthma (WEA) and OA. Specific IgE-mediated sensitization to molds occurs, but in a small proportion of cases only. The mechanisms of dampness-induced asthma remain largely unknown. The results support the epidemiological evidence that indoor dampness and mold induce new-onset adult asthma.

Of the 483 patients who participated in the questionnaire study and who had had asthma-like symptoms (cough, dyspnea, wheezing) but lung function within a normal range at baseline, 62 (13%) reported having developed physician-diagnosed asthma during the follow-up period. Continued exposure to a damp work environment was associated with a more than fourfold increase in the risk of asthma. Working in a non-remediated environment at follow-up was the strongest risk factor for developing asthma. The remediation of damp buildings seemed to be associated with a decrease in the risk of asthma.

Preventive measures to avoid further exposure seem to be relevant in order to prevent the development of asthma. In practice, such measures would involve the remediation of moisture and mold damage or the relocation of workers with asthma-like symptoms to a non-moisture damaged environment. In the interpretation of the results, the limitations of the data collection by questionnaire must be taken into account. Follow-up at occupational health services is recommended for patients with respiratory symptoms related to workplace dampness.

A high proportion of patients with OA caused by indoor dampness and mold had an impaired QOL 3–12 years after their initial diagnosis when the patients were compared with those with WEA and those with no asthma but with symptoms related to the exposure. Not working was a strong determinant of deteriorated QOL. As estimated by the use of asthma medication, the asthma symptoms of the OA patients were both more persistent and more severe than those of the WEA patients. Greater use of asthma medication was a determinant of a worse QOL physical component.

The diagnosis of OA was associated with a strong, nearly sixfold risk of withdrawal from work due to early retirement or unemployment, in a comparison with a reference group with upper-respiratory symptoms only. A perceived poor social climate at work and poor experiences with the supervisor's cooperation at an early stage of symptoms were determi-

nants for impaired self-assessed work ability and early withdrawal from work. In addition, multiple, persistent, indoor-air symptoms at follow-up increased the risk of poor self-assessed work ability. The results are in accordance with the widely recognized fact that the causes of disability are multifactorial and are not associated with medical conditions only.

The results of this study corroborate the clinical impression that a proportion of patients with asthma in relation to exposure to moisture- and mold-damaged workplaces has long-standing limitations in everyday life and remains symptomatic and unable to work. Patients diagnosed with OA had worse outcomes than did patients with WEA or only respiratory symptoms without asthma at baseline. The reasons for this phenomenon remain to be elucidated. Acknowledgement of, and compensation for, dampness-induced asthma as an occupational disease does not seem to be beneficial in preventing disability. More apt measures, for example, early support and workplace management practices concerning work ability, are required.

YHTEENVETO

Työpaikan kosteus- ja homevaurioiden on osoitettu olevan yhteydessä haitallisiin hengitystievaikutuksiin, joista yleisin diagnosoitavissa oleva sairaus on astma. Työterveyslaitoksen Työperäisten sairauksien rekisterin mukaan vuodesta 2001 alkaen kosteusvauriohomeet ovat olleet yleisin ammattiastman aiheuttaja Suomessa. Kosteusvaurioympäristöstä johtuva ammattiastma on vaikea todeta, koska täsmällistä ammattiastman aiheuttajaa ei tiedetä. Tavallisesti kosteusvaurioympäristöön liittyvät hengitystie- ja yleisoireet menevät ohi, kun rakennuksen vauriot korjataan. Osalla potilaista oireet kuitenkin pitkittyvät rakennuksen korjaustoimenpiteistä tai työpisteen vaihdosta huolimatta.

Väitöskirjan tavoitteena oli arvioida ja kehittää kosteusvaurioympäristöstä aiheutuvan ammattiastman diagnostiikkaa. Toisena tavoitteena oli arvioida kosteusvaurioympäristössä ilmenevien astmankaltaisten oireiden merkitystä astman riskitekijänä. Tavoitteena oli myös selvittää työpaikan kosteusvaurioihin liittyvän hengitystiesairauden pitkäaikaisvaikutuksia elämänlaatuun ja työkykyyn.

Tutkimusaineistona oli 2 200 Työterveyslaitoksella ammattitautiepäilyn takia vuosina 1995–2004 tutkittua potilasta, joilla oli ollut työpaikan kosteusvaurioon liittyviä hengitystieoireita. Suurin osa potilaista oli työskennellyt toimistossa, koulussa, sairaalassa tai päiväkodissa. Seuranta toteutettiin kyselytutkimuksella vuoden 2007 alussa 3–12 vuotta Työterveyslaitoksen tutkimusten jälkeen. Kyselyyn vastasi 1 295 henkilöä (61 %).

Tutkimusjakson aikana ammattiastman osoittamiseen käytettiin hengitysteiden spesifistä altistuskoetta homeuutteilla. Yhteensä 694 potilaalla oli epäilty olevan kosteusvauriohomeiden aiheuttama ammattiastma, minkä vuoksi heille oli tehty altistuskoe. Tutkimuksiin oli kuulunut

myös PEF-työpaikkaseuranta sekä homeherkistymisen toteamiseksi ihopistokokeita ja seerumin IgE-määrityksiä.

Väitöskirjatutkimusta varten potilaiden sairauskertomustietoja tarkasteltiin jälkikäteen. Potilaiden altistuminen kosteusvauriomikrobeille luokiteltiin voimakkuudeltaan kolmiportaisesti sen mukaan, kuinka laajoja työpaikan kosteusvauriot olivat, ja mitä mikrobianalyyseissä löydettiin. Tiedot kerättiin potilasasiakirjoihin liitetyistä työpaikan rakennusteknisistä ja sisäilmatutkimusraporteista. Ammattiastman todennäköisyys arvioitiin kansainvälisten ammattiastman kriteerien mukaisesti.

Ammattiastman arvioitiin olevan todennäköinen 156 potilaalla. Diagnoosi perustui siihen, että työpaikalla oli todettu kosteus- ja homevaurioita, astmaoireet liittyivät työhön ja ne olivat alkaneet kosteusvaurioympäristössä, keuhkojen toimintakokeissa oli astmalle tyypillisiä muutoksia ja yhteys työpaikan altisteisiin oli osoitettavissa joko PEF-työpaikkaseurannalla tai altistuskokeilla. Ammattiastmapotilaista 20 %:lla todettiin IgE-välitteinen herkistyminen homeille. PEF-työpaikkaseuranta ja spesifiset hengitysteiden altistuskokeet olivat yhdenmukaisia (molemmat tutkimukset olivat joko myönteisiä tai kielteisiä) 56 %:ssa tapauksia. Kun altistuskoe oli positiivinen, yhdenmukaisuus PEF-työpaikkaseurannan kanssa oli 78 %.

Tutkimus antaa uutta tietoa kosteusvaurioympäristön aiheuttaman ammattiastman diagnostiikkaan. Altistumisen arvioinnin perusteena voidaan käyttää kuvauksia työpaikan kosteus- ja homevaurioiden laajuudesta ja sijainnista sekä mikrobimäärityksiä. Yhteys altistumisen ja astman välillä voidaan osoittaa PEF-työpaikkaseurannalla, joka kuvastaa työpaikan altistumistilannetta kokonaisuudessaan toisin kuin altistuskoe. Heikkoutena on, että PEF-työpaikkaseurannalla ei voida luotettavasti erotella ammattiastmaa ja työssä pahenevaa astmaa. IgE-välitteistä homeherkistymistä esiintyy vain osalla ammattiastmapotilaista. Kosteusvaurioympäristön aiheuttaman astman syntymekanismit ovat edelleen pääosin tuntemattomia. Tutkimus vahvistaa epidemiologista tutkimustietoa kosteusvaurioympäristön ja astman yhteydestä.

Kyselytutkimukseen osallistui 483 potilasta, joilla oli ollut kosteusvauriotyöpaikkaan liittyviä astmankaltaisia oireita (yskää, hengenahdistusta tai vinkunaa), mutta astman diagnostiset kriteerit eivät olleet täyttyneet Työterveyslaitoksen ammattitautitutkimuksissa. Vastaajista 62 (13 %) ilmoitti, että seuranta-aikana lääkäri oli todennut heillä ast-

man. Jos nykyisessäkin työpaikassa oli kosteusvaurio, astmariski oli yli nelinkertainen verrattuna vastaajiin, jotka ilmoittivat, ettei työpaikalla ole kosteusvaurioita. Entisissä, korjaamattomissa kosteusvauriotiloissa työskentelyyn liittyi merkittävä astman kehittymisen riski. Kosteusvaurioiden korjaaminen näytti vähentävän astmariskiä.

Tutkimustulokset viittaavat siihen, että kosteusvaurioiden korjaamisella tai oireilevan työntekijän siirtämisellä pois kosteusvaurioituneista tiloista voidaan vaikuttaa astmariskiin. Tulosten tulkinnassa on huomioitava kyselytutkimuksen rajoitukset. Työterveyshuollon seuranta on tarpeen työntekijöille, joilla on kosteusvaurioympäristöön liittyviä hengitystieoireita.

Elämänlaatu oli 3–12 vuoden seurannan jälkeen huonompi ammattiastmadiagnoosin saaneilla verrattuna potilaisiin, joilla oli työssä paheneva astma tai hengitystieoireita ilman astmaa. Työelämän ulkopuolelle jääminen oli myös yhteydessä heikentyneeseen elämänlaatuun. Potilaat, joilla oli diagnosoitu ammattiastma, käyttivät enemmän astmalääkkeitä kuin muut astmaa sairastavat. Runsas astmalääkkeiden käyttö oli yhteydessä heikentyneeseen elämänlaatuun.

Ammattiastmadiagnoosiin liittyi lähes kuusinkertainen riski ennenaikaiseen poistumiseen työelämästä (työkyvyttömyyseläkkeen, tapaturmaeläkkeen tai työttömyyden takia), kun ammattiastmadiagnoosin saaneita verrattiin potilaisiin, joilla oli hengitystieoireita ilman astmaa. Huonoksi koettu esimiehen toiminta ja huonoksi koettu työilmapiiri aikaisemmassa kosteusvauriotyöpaikassa olivat yhteydessä alentuneisiin työkyvyn indikaattoreihin. Myös mitä enemmän pitkittyneitä sisäilmaoireita seurannassa ilmoitettiin, sitä huonommaksi työkyky koettiin. Tulokset sopivat aikaisempaan tietoon, että työkyvyn alenemisen syyt koostuvat monesta tekijästä eivätkä johdu pelkästään terveydellisistä syistä.

Tutkimus toi esille kosteusvaurioympäristöön liittyvän astman yhteyden heikentyneeseen elämänlaatuun, huonoksi koettuun työkykyyn ja ennenaikaiseen poistumiseen työelämästä. Ammattitautilainsäädännön suomista etuuksista huolimatta ammattiastmaa sairastavien elämänlaatu ja työkyky olivat huonompia kuin muuta astmaa sairastavilla tai hengitystieoireisilla potilailla, joilla ei ollut astmaa. Syyt jäävät pohdinnan ja jatkoselvitysten varaan. Työkyvyn tukemiseksi tarvitaan varhaisia ja aikaisempaa tehokkaampia toimia työpaikalla ja työterveyshuollossa.

ACKNOWLEDGEMENTS

This dissertation is the result of my work in the Finnish Institute of Occupational Health (FIOH) in 2006–2012. I have been privileged to carry out the study in the scientific atmosphere of the Institute, and I appreciate the resources and other facilities provided by it. The following persons are acknowledged for contributing to this dissertation, and I extend my sincere gratitude to them all.

Above all, both of my supervisors, Henrik Nordman, Adjunct Professor, and Jukka Uitti, Adjunct Professor, for their encouraging and constructive guidance: the former particularly for generating the idea for the study, for his genuine enthusiasm on the topic, for his great expertise and advice in scientific writing, and for our numerous intelligent discussions throughout the years; and the latter for helping me through the most strenuous moments, for always being available, for offering insightful comments on the manuscripts, and for offering firm support, which was essential in helping me finish this dissertation.

My other co-authors: Ritva Luukkonen, PhD, for guiding me patiently in statistics, for her tireless planning and handling of the analyses and without doubt, owing to her vast knowledge in scientific research, always helping me achieve a better outcome; Sanna Lappalainen, PhD, for her expertise in indoor-air investigations, for her immense efforts in wading through the technical and microbiological documents, and for making the very best of the assorted retrospective material; Elina Toskala, Adjunct Professor, for her positive and energetic attitude towards research and this study, which was valuable in the beginning of the project.

Professor Kari Reijula for infusing spirit into my work during the last year and for using his great expertise in the field to help me find the perspective from which to initiate the writing of the dissertation.

The official reviewers of this dissertation, Professor Kimmo Räsänen and Terttu Harju, Adjunct Professor, for their constructive and accurate comments, which greatly improved the text, and for performing the review process in a prompt yet meticulous manner.

Georgianna Oja, ELS, for her high-quality revision of the English language and for being easily approachable and flexible with the timetables.

All my present and former superiors for providing me with excellent working facilities and for their interest in my research, namely, Professor Helena Taskinen; Professor Kaj Husman; the present Head of the Centre of Expertise "Health and Work Ability" Jorma Mäkitalo, MD, PhD; and chief physicians Ari Kaukiainen, Adjunct Professor, Heikki Koskinen, MD, PhD, and Markku Vanhanen, MD, PhD, to whom I am also deeply grateful for providing trustworthy comments on the manuscript.

All of my colleagues and other co-workers in the Occupational Medicine Clinic and in many of the teams within FIOH for their encouragement, support, and counseling regarding varying questions throughout the years; especially Ulla-Maija Hellgren, MD, Irmeli Lindström, MD, and Hille Suojalehto, MD, for their valuable peer support.

Several persons in the Nursing and Support Services Team for their assistance in different stages of the study, especially Ms Tuula Suomela for searching the patient information.

Matti Mero, MD, PhD, for encouraging me throughout my work and for sharing his enormous amount of knowledge in insurance medicine.

The respondents of the questionnaire study for their valuable contribution, for their patience in filling out the extensive questionnaire, and for making this study possible.

The Finnish Work Environment Fund for financing the study and for granting me a personal scholarship that helped me finalize the dissertation.

Finally, my family, close friends, and relatives for sharing both setbacks and advances with me. My warmest thanks go to my parents, my sister, and my brother and his family for their constant support and caring. It has been a tremendous joy and source of happiness to follow the growing of my lively nephew as a reminder of life outside the research chamber.

Helsinki, October 2012
Kirsi Karvala

ABBREVIATIONS

ABPA	allergic bronchopulmonary aspergillosis
BRS	building-related symptoms
cfu	colony-forming unit(s)
CI	confidence interval
COPD	chronic obstructive pulmonary disease
ERS	European Respiratory Society
FEV1	forced expiratory volume in 1 second
FIOH	Finnish Institute of Occupational Health
FROD	Finnish Register of Occupational Diseases
ICF	International Classification of Disability, Functioning and Health
Ig	immunoglobulin (E and G)
IOM	Institute of Medicine
MCS	multiple chemical sensitivity
MMVF	man-made vitreous fiber
mVOC	microbial volatile organic compound
OA	occupational asthma
ODTS	organic dust toxic syndrome
OR	odds ratio
PAR	population attributable risk
PEF	peak expiratory flow
QOL	quality of life
RADS	reactive airways dysfunction syndrome
RR	relative risk
SBS	sick building syndrome
SCHER	Scientific Committee on Health and Environmetal Risks
SD	standard deviation
SF-12	Short Form Health Survey 12-Item Questionnaire
SIC	specific inhalation challenge
SPT	skin prick test
VAS	visual analogue scale
VCD	vocal cord dysfunction
VOC	volatile organic compound
WEA	work-exacerbated asthma
WHO	World Health Organization
WRA	work-related asthma

LIST OF ORIGINAL PUBLICATIONS

I Karvala K, Toskala E, Luukkonen R, Lappalainen S, Uitti J, Nordman H. New-onset adult asthma in relation to damp and moldy workplaces. Int Arch Occup Environ Health 2010;83(8):855–65.

II Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H. Prolonged exposure to damp and moldy workplaces and new-onset asthma. Int Arch Occup Environ Health 2011;84(7):713–21.

III Karvala K, Uitti J, Luukkonen R, Nordman H. Quality of life of patients with asthma related to damp and moldy work environments. Scand J Work Environ Health Published Online First: 11 March 2012.

IV Karvala K, Nordman H, Luukkonen R, Uitti J. Asthma related to workplace dampness and impaired work ability. Submitted 20 June 2012.

TABLE OF CONTENTS

1 INTRODUCTION

Problems associated with indoor environments are one of the most common environmental health issues that most clinicians face (Redlich et al. 1997). Typically, the patient reports symptoms that worsen while in the building of concern and improve when away from it. Occasionally, it is easy to find the cause of the complaints, for example, when there is obvious moisture and mold damage, but quite often the situation is far more complex (Reijula and Sundman-Digert 2004). Moisture problems often occur simultaneously with several other factors that may impair indoor-air quality, such as inadequate ventilation, material emissions, or dustiness. Specific etiological agents cannot always be identified.

Asthma is the most common diagnosable disease that is connected with damp indoor environments. The patients often seem to have a wider variety of symptoms than merely those that belong to the clinical picture of asthma. Epidemiological data indicate with increasing plausibility that indoor dampness and mold play a role as risk factors for the exacerbation of asthma and new-onset asthma, as well as for respiratory infections and symptoms (reviewed by Mendell et al. 2011). Measured microbiologic agents have shown less consistent associations with health effects than qualitative assessments like visible dampness or mold odor. However, in clinical practice, evaluating relationships between indoor dampness, or dampness-related factors, and suspected building-related health effects is difficult for multiple of reasons. A major limitation is the inability to equate environmental measurements directly to personal exposure. There are no health-based guideline values for indoor dampness, microbes, or other indoor-air contaminants in nonindustrial environments. These factors typically occur at low levels in normal indoor and outdoor environments. In addition, clinical evaluations are hampered by the facts that

the conceivable exposures are complex, the exact causative factors and mechanisms behind the health effects are seldom known, the symptoms are non-specific in nature and overlap with other conditions, and also the available medical tests are not specific enough (Andersson 2008; Bernstein et al. 2008; WHO 2009).

Even though there are gaps in the basic scientific knowledge related to dampness problems, a great deal of existing research has enabled some recommendations to be made for managing such problems. According to a World Health Organization (WHO) expert group, the prevention and remediation of indoor dampness and mold are likely to reduce health risks (WHO 2009). Good practices for the indoor-air quality evaluation have been developed for buildings (Salonen 2009). Case studies suggest that problems can be handled efficiently if a multiprofessional team is involved in the renovating process at a workplace, and both the physical and psychosocial environment is focused on (Lahtinen et al. 2009). However, there are only a few intervention studies available on the effects of repairing buildings damaged by dampness and mold on respiratory health, and more research is needed to find the most effective ways to minimize respiratory hazards (Sauni et al. 2011).

Another challenge that clinicians face is the persistent disability experienced by some patients. They seem to develop sensitivities to many environmental factors with symptoms that persist despite improvements in the initial environment (Redlich et al. 1997). As the patients react to factors that are ubiquitous in the environment, avoiding these factors completely is usually impractical and very limiting for the patient (GINA 2011). It seems that the intensity of subjective symptoms often correlates only poorly with the degree of impairment, as defined by organ dysfunction (Hodgson 2002). Due to a lack of a specific diagnosis, the patients may get the impression that physicians do not listen to their concerns. A better understanding of the origin of such symptoms is needed if the ability to manage the condition effectively and prevent disability is to be improved.

2 REVIEW OF THE LITERATURE

2.1 Indoor work environments and health

2.1.1 Overview

Many people associate adverse health effects with non-industrial, indoor work environments where there are no traditional health hazards. It has been suspected that building design, operation, and maintenance can significantly affect workers' health. WHO reported its concern about indoor-air quality as early as the 1970s, and this concern has led to the organization of numerous task forces for the management of the problem (WHO 1983). Now, over 30 years later, a great deal of effort has been made to improve non-industrial indoor environments in order to create healthier conditions, even though the reporting of symptoms has not ceased.

First, the problem manifested itself in the form of case reports for office buildings in which up to 30% of the employees reported building-related symptoms, a higher prevalence than in the general population (WHO 1983). The term "sick building" was used to describe such buildings. Primarily the reports were from the Scandinavian countries and the United States (WHO 1983). Later, similar symptoms were reported in work environments such as hospitals, schools, and children day-care centers. The buildings were investigated in an attempt to find causative factors, and sometimes the problems could be attributed, for example, to inadequate ventilation, emissions from furnishings or construction materials, or moisture damage with mold growth in the structures of the building (Redlich et al. 1997; Thörn 1999; Burge 2004).

As building occupants typically report that the symptoms occur while in the building and diminish when away from the building, the symptoms can be referred to as building-related symptoms (BRS) (Mendell 2003). The concept "sick building syndrome" (SBS) was first used and is still more often used to describe this non-specific symptom complex with often an unclear cause (WHO 1983; Thörn 1999; Norbäck 2009). The term is confusing and is not approved by all researchers, as it is the workers rather than the building that are sick and suffer from the symptoms (Burge 2004). Furthermore, indoor environment complaints are not only common in "sick buildings", but also can be found in "healthy buildings" with no obvious indoor environment problems (Bakke et al. 2007; Brightman et al. 2008; Brauer and Mikkelsen 2010).

The variety of symptoms includes upper- and lower-respiratory symptoms, a combination of general symptoms, as well as symptoms involving the mucosal membranes and skin as follows (WHO 1983; Thörn 1999):

- Irritation of the eyes, nose and throat; cough
- Experience of dry skin, rash, pruritus
- Fatigue, headache, lack of concentration
- High frequency of respiratory tract infections
- Hoarseness, wheezing, shortness of breath
- Nausea, dizziness
- Enhanced or abnormal odor perception

The list is of limited value to clinicians, as the symptoms are non-specific and may refer to many clinical conditions. In addition, there is a lack of objective biomarkers that would help relate symptoms with indoor environmental exposures (Bernstein et al. 2008). Both the types and severity of symptoms can vary greatly among people within the same building. The symptoms, although not life-threatening, can be very unpleasant and disruptive, causing absence from work, reduced productivity, and disability (Redlich et al. 1997; Niemelä et al. 2006). Distress about more serious health risk is also common (Redlich et al. 1997).

In a Finnish survey from the 1990s, the Indoor Air Questionnaire of the Finnish Institute of Occupational Health (FIOH) was used to determine the symptoms related to the indoor environment of 11 154 employees from 122 workplaces (Reijula and Sundman-Digert 2004).

In all of the workplaces, indoor-air problems had been suspected before the survey was conducted. The most common symptoms that had occurred every week during the past 3 months were irritated, stuffy or runny nose (20%), eye symptoms (17%), fatigue (16%), skin symptoms (15%), or hoarse, dry throat (14%) (Reijula and Sundman-Digert 2004). The symptom spectrums were similar in Finnish surveys conducted in the 2000s in office environments (Salonen et al. 2009a) and hospitals (Hellgren et al. 2011).

Norbäck (2009) has divided human reactions to indoor-air pollution into the following three main categories: 1) the most common effects are complaint reactions due to poor subjective indoor-air quality (e.g., thermal discomfort, complaints of stuffy air, dry air or malodors); 2) diseases or specific building-related illnesses that may be caused by factors in the indoor environment (e.g., building-related asthma, allergic alveolitis and legionellosis); and 3) medical symptoms with an unclear cause, but with a possible relation to the indoor environment. In this grouping, the latter constitutes SBS. Norbäck regards SBS as a group phenomenon rather than as a syndrome, as it is normally defined in medicine and considers individual diagnostics as a difficult issue. The difference between a building-related illness and SBS is not always clear, and the two may overlap (Crook and Burton 2010).

2.1.2 Risk factors for building-related symptoms

Building-related symptoms, or SBS, are regarded as being multi-factorial in origin (Redlich et al. 1997). One factor or a combination of several factors may be responsible for the symptoms and complaints of the occupants, and different types of symptoms and health outcomes may appear in individuals depending on personal susceptibility (Jaakkola and Jaakkola 2010). The simplified model presented in Figure 1 illustrates several types of relations that exist between environmental determinants and health outcomes (Jaakkola and Jaakkola 2010). The outer circle illustrates a non-industrial work environment, which is divided into physical and social environments. The worker, in the inner circle, is viewed as having two different domains, one belonging to physical phenomena and the other belonging to psychological phenomena. The model describes how environmental determinants

can affect human health and well-being and can cause both physical and mental outcomes, and how a disease or health state can have both physiological and psychological underlying mechanisms and manifestations (Jaakkola and Jaakkola 2010).

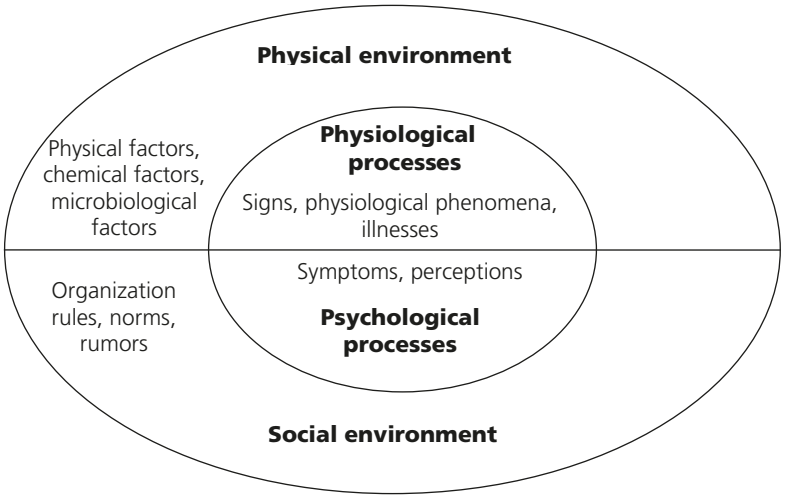


Figure 1. The office environment model (Jaakkola and Jaakkola 2010).

Risk factors in the physical environment

Indoor air may contain chemicals, particles, and biological materials with potential health effects (SCHER 2007). Table 1 lists the main indoor pollutants and exposures in physical non-industrial work environments, as well as their typical sources and associated health effects. Inadequate ventilation is one of the most important factors contributing to indoor-air quality (SCHER 2007). Many other factors also influence air quality (e.g., cleaning conditions, properties of buildings, moisture damage, products used in indoor areas, and outdoor air). The compositions and concentrations of the different components vary widely, and the different types of pollutants may give rise to combined effects (SCHER 2007). The indoor concentrations of the pollutants in non-occupational environments are generally orders of magnitude below occupational threshold limits (Wolkoff et al. 2006). In addition, the absence of dose–response

data is common to these indoor-air pollutants (Wolkoff et al. 2006). Very little information is available regarding permissible exposure levels that would be health-based (Bernstein et al. 2008).

Ventilation is necessary to remove indoor generated pollutants from indoor air or dilute their concentration to acceptable levels (Seppänen and Fisk 2004). Low ventilation rates generally increase risks of building-related symptoms in offices, whereas higher ventilation rates reduce symptoms (Sundell et al. 2011). Some studies suggest that indicators of inflammation, rates of respiratory infections, the frequency of asthma and allergy symptoms, and rates of short-term sick leave increase with lower ventilation rates (Sundell et al. 2011). Low ventilation rates, as well as carbon dioxide concentrations in indoor air, have also been found to be associated with low task performance and productivity (Seppänen and Fisk 2004). On the average, the prevalence of building-related symptoms is higher in air-conditioned buildings than in naturally ventilated buildings (Seppänen and Fisk 2004). In relation to requirements in guidelines and standards, poor ventilation conditions have been shown to be common in many buildings, especially in schools, according to Swedish studies (Sundell et al. 2011). Ventilation standards are based primarily on data that pertain to occupants' perceptions of indoor-air quality rather than to risk-related aspects of indoor-air pollutant exposure (Sundell et al. 2011). Low-level ventilation may lead to moisture accumulation in building structures and materials, which may, in turn, lead to increased dust mite populations and microbial growth (Seppänen and Fisk 2004). In the case of moisture damage due to other reasons, inadequate ventilation may increase the level of moisture-related pollutants in indoor air (Bornehag et al. 2005).

Dustiness and man-made vitreous fibers (MMVFs), formerly called man-made mineral fibers, are commonly found in office environments (Schneider 2008a). In indoor air, MMVFs are airborne fibers, typically glass wool and mineral wool, released by thermal and acoustic insulation products. MMVFs with diameters of >5 μm have the potential to cause skin irritation, and coarse fibers at high airborne concentrations may also irritate mucous membranes of the eyes and respiratory tract, but a diameter dependence is not known (Schneider 2008a). In 258 examined office buildings with a background of indoor-air problems in the Helsinki area, over 60% of the surface dust and almost 90% of the

samples collected from supply air ducts contained MMFVs. In buildings where workers reported irritation of the upper-respiratory tract, eyes, and skin, the occurrence of MMVFs was nearly 70% (Salonen et al. 2009b).

As potential causes of the reporting of indoor-air symptoms, attention has focused on the emission of volatile organic compounds (VOCs) from building materials and products (Wolkoff et al. 2006). New building materials may contribute substantially to the indoor concentrations of VOCs, and temporarily high concentrations are also obtained during many human activities and processes, such as cleaning and using copying machines (Wolkoff et al. 2006). More than 900 VOCs have been identified at detectable levels in indoor air, but normally the number identified in one air sample varies from 20 to 150 (Salonen et al. 2009a). In a study of 176 Finnish office buildings, acetic acid, ethylacetate, 2-ethyl-1-hexanol, and xylene had the highest irritation potency of the VOCs (Salonen et al. 2009a). Mainly sensory irritation of the eyes and respiratory tract (occurring from stimulation of receptors on trigeminal nerves) has been found to be associated with VOCs, but the available evidence on VOCs in causing health effects in indoor environments is not conclusive (SCHER 2007). Several studies have reported associations between VOCs and asthma symptoms (SCHER 2007). According to a review article, there is no consistent association between indoor VOC exposures and new-onset asthma (Nielsen et al. 2007). Odor thresholds for VOCs are generally much lower than sensory irritation thresholds, and the reported sensory irritation may be the result of odor annoyance (Wolkoff et al. 2006). Low relative humidity may exacerbate the sensory irritation impact (Wolkoff et al. 2006). Formaldehyde is a strong irritating chemical substance, and it has been found in indoor-air at concentrations capable of irritating mucous membranes and causing respiratory tract symptoms (Salonen 2009).

Phthalates are common contaminants in indoor environments, and polyvinyl chloride flooring material is among the most important sources (SCHER 2007). Phthalates are not skin or respiratory sensitizers. Polyvinyl chloride and different surface material have been found to be associated with respiratory effects in epidemiological studies (Jaakkola et al. 2006a), but there is no consistent evidence indicating that phthalates should be of high concern as chemicals in indoor-air (SCHER 2007; Jaakkola and Knight 2008).

Table 1. Varied indoor-air pollutants and factors in non-industrial work environments and associated health effects.

Pollutant / factor	Typical sources	Associated health effects
Low ventilation rates	Building and its services	Symptom reporting
Too high or low temperature	Building and its services	Discomfort
Low relative humidity	Building and its services	Skin symptoms, eye irritation, nasal dryness
Mold and other dampness-related factors	Building moisture damage	Respiratory symptoms, asthma, allergic alveolitis, symptom reporting
Particles	Outdoor air, ETS, combustion, room dust, moisture damage	Respiratory and cardiovascular effects
Man-made vitreous fibers	Building materials	Eye, skin, and respiratory tract irritation
Allergens	Occupants' clothing (e.g. from pets)	Allergic airway symptoms
Viral infections	Occupants	Asthma and respiratory tract symptoms
VOCs	Building materials and furnishings, office equipment, cleaning products	Sensory irritation, asthma symptoms
Formaldehyde	Furnishings, insulation, consumer products, office equipment	Eye and respiratory tract irritation
Radon	Diffusion through soil	Lung cancer

ETS=environmental tobacco smoke; VOCs=volatile organic compounds.

Individual risk factors

In several studies, female gender has been found to be associated with a higher prevalence of several kinds of SBS symptoms (Björnsson et al. 1998; Brasche et al. 2001; Runeson et al. 2006; Bakke et al. 2007). The gender difference has been suggested to be a reflection of a general excess of psychosomatic symptoms among women (Stenberg and Wall 1995) or of the fact that women more often hold occupations that predispose to them to SBS than men do (Björnsson et al. 1998). It has also been

claimed that men and women perceive psychosocial work conditions differently and may react differently to job stressors (Runeson et al. 2006).

No consistent association between age and SBS has been found in different studies (Norbäck 2009).

Self-reported allergy has been shown to be associated with a higher prevalence of SBS (Norbäck 2009). Atopy was found to be associated with SBS symptoms in a study in which atopy was defined as a positive skin prick test (SPT) to common environmental allergens and tested in a population sample (Björnsson et al. 1998). In another study, specific immunoglobulin (Ig) E, total IgE, familiar allergy, and ever eczema were not associated with mucosal symptoms (Bakke et al. 2008).

Psychological factors have been investigated in several studies. Björnsson et al. (1998) found an association between anxiety and depression and SBS symptoms. In addition, a tendency towards somatization has been shown to be associated with reports of SBS symptoms (Berglund and Gidlöf Gunnarsson 2000). Of the personality traits, neuroticism (or negative affectivity, meaning tendency to experience negative mood states) seems to be associated with the reporting of SBS symptoms (Gomzi et al. 2007). One experimental study has suggested that, for women high in negative affectivity, stress-inducing conditions are more important predictors of distress in response to poor indoor-air quality than the indoor-air quality itself (Fiedler et al. 2008). Several other personality factors have been shown to be related to a high occurrence of SBS symptoms (Runeson et al. 2004; Runeson and Norback 2005). In addition a low sense of coherence has been shown to be associated with SBS (Runeson et al. 2003).

Brauer and Mikkelsen (2010) investigated the perception of the indoor environment among 3281 employees in 39 randomly selected Danish non-industrial workplaces. Only non-problem buildings were included. They found that persons with an increased tendency to report symptoms were more likely to complain about the indoor environment (Brauer and Mikkelsen 2010).

Risk factors in the psychosocial environment

In principal, both work and home environments can be sources of adverse psychosocial factors (WHO 1985). The effect of work conditions on

SBS were studied already in the 1980s and 1990s, and, according to the studies, psychosocial factors are strongly associated with SBS (Lahtinen et al. 1998). Several factors have been shown to be associated with SBS symptoms, for example, work stress, work dissatisfaction, poor climate of co-operation at work, lack of support from supervisors, heavy workload, and conflicting demands in work (Lahtinen et al. 1998). In the studies reviewed by Lahtinen et al. (1998), the associations were similarly confirmed in the buildings that were, beforehand, defined as problem cases and also in those with no previous information on their status.

Associations have also been found in more recent studies. Using the demand–control–support model by Karasek and Theorell, a Swedish community-based study measured the psychosocial work conditions of 532 office workers. It was found that SBS is influenced by a combination of low social support and either a passive or strained work situation. The lowest symptom score was recorded in a relaxed work situation, irrespective of social support. The authors concluded that the demand–control–support model can predict symptoms compatible with SBS (Runeson et al. 2006).

Stress load, as measured by a non-verbal drawing test, proved to be a predictor of SBS symptoms in a questionnaire study (Runeson et al. 2007).

The Whitehall II study, which is an ongoing longitudinal study of civil service office workers in the United Kingdom, showed that the physical environment appears to be less important than the psychosocial work environment in explaining differences in symptom prevalence (Marmot et al. 2006). Altogether 4052 participants were included in this part of the study. The physical environment included exposure to airborne fungi with a limit of 500 colony forming units per m^3 (cfu/m^3) air. High job demands and low support at work were associated with higher symptom reporting. The ability of people to exert control over the environment of their local workstation was related to a lowering of reported symptoms (Marmot et al. 2006).

In the aforementioned study by Brauer and Mikkelsen (2010), psychosocial work environment factors at the individual level, but not at the workplace level, were associated with the individual perception of the indoor-air. Variables such as job demands, job support, effort–reward imbalance, workloads, social climate at work, motivation, stressful

work, stimulating work, and satisfaction with work were studied. There were large differences between individuals in the same building, and these differences, the authors concluded indicated that some occupants of a building perceive problems in the indoor environment even in the absence of a general indoor-air problem (Brauer and Mikkelsen 2010).

2.2 Indoor dampness and mold

2.2.1 Prevalence

Moisture and microbial growth are present in all buildings (IOM 2004). It is evident that there are situations in which the presence of moisture can be regarded as normal, as well as situations in which the material contains excess moisture that is potentially harmful and there is a need to make a distinction between the two (Haverinen 2002).

The term indoor dampness has been used to define a variety of moisture problems in buildings, including high relative humidity, condensation, and signs of excess moisture (IOM 2004). The severity of dampness varies widely, from occasional minor condensation on windows to the wetting of a large portion of a building due to water leaks. There is no agreed-on basis for determining the severity of damage from either the engineering or the health point of view (IOM 2004). The term moisture damage is used to describe damage caused by dampness in a building structure or on a surface of a material (Haverinen 2002). Moisture damage is any visible, measurable, or perceived outcome caused by excess moisture (or dampness). Common sources of moisture damage are sources outdoors (condensation through cold gaps or faulty insulation from outdoor air humidity or moisture in the ground), wet construction materials (e.g., fresh concrete structures, timber), leaking services (e.g., burst pipes, defective pipe joints), spillage (e.g., cleaning and washing activities), and flooding (Haverinen 2002).

Microbial growth starts in building materials and structures when the conditions are favorable. Moisture is the only limiting factor for mold growth in indoor environments; usually there is enough light, oxygen, nutrients, and warmth for such growth (Haverinen 2002). Therefore, excess moisture on almost all indoor materials leads to the growth of

microbes, such as mold, fungi and bacteria, which subsequently emit spores, cells, fragments, and volatile compounds into indoor air (WHO 2009). Microbes differ in their needs for conditions for optimal growth. The materials used in the building determine the type of microbes whose growth will be favored (IOM 2004). Some microbes are hydrophilic, requiring substrates with a high moisture content, while some are xerophilic, growing in relatively dry environments (Haverinen 2002). The time it takes for microbes to grow varies depending on the conditions. The growth can start in a day in optimal conditions, or it can take several weeks or months (IOM 2004).

As there is no gold standard for building dampness, the exact prevalence of indoor dampness cannot be established. Reports by occupants and inspectors indicate that it is likely to be on the order of 10%–50% in developed countries (WHO 2009). According to studies from 31 European countries, dampness or mold problems can be expected to occur in one of every six dwellings in Europe (Haverinen-Shaughnessy 2012). In the 1990s, a random sample of 450 houses surveyed by trained civil engineers revealed that approximately 55% of Finnish private houses were in need of repair or more thorough inspection due to moisture problems (Nevalainen et al. 1998). The severity of the moisture damage was only minor in 94% of the cases, and the faults were estimated to be repairable at a reasonable cost.

Systematic surveys assessing the prevalence of dampness and mold in school buildings, offices, institutional buildings, and other non-industrial workplaces are sparse. In a survey evaluating the state of Finnish hospital buildings in 2003–2005, altogether 15% of the total area of the studied hospital buildings was found to need immediate repair according to thorough investigations of 10 central hospitals by construction engineers and indoor-air experts (Hellgren et al. 2008). The most common causes of the need for immediate repairs were dampness problems in moist facilities, found in 80% of the targeted hospitals. Other typical problems causing a need for immediate repairs were moisture damage in the foundation structures or intermediate floors and damage in outer walls, which included, for example, contaminated and moist insulation in buildings without a crawl space (Hellgren et al. 2008).

According to the "Work and Health in Finland 2009" survey (based on interviews of 2355 respondents), one in five employees in the health,

social, or education sector reported the smell of mold indoors at work (Reijula 2010).

Globally, climate change and its effects on the weather (i.e., storms and heavy rainfall) have been predicted to further increase the proportion of buildings with damp problems (WHO 2009).

2.2.2 Microbial and non-microbial factors associated with indoor dampness

Mold growth is usually accompanied by bacterial growth. Many specific components of mold and bacteria may be responsible for health effects: spores and hyphal fragments of fungi, spores and cells of bacteria, allergens of microbial origin, structural components of fungal and bacterial cells, and such products as microbial volatile organic compounds (mVOCs) and mycotoxins. In more advanced damage, also protozoa and higher organisms such as mites and insects are present. Moisture may also trigger the degradation of building materials and contribute to the release of non-microbial chemicals into the indoor air (IOM 2004). No specific measure of microorganisms or microbial substances has resulted in a more specific or sensitive exposure assessment relevant to health effects; in other words, specific causal agents have not been identified conclusively (WHO 2009). Microbial exposure is often suggested to play a causal role (WHO 2009).

Many of the bacterial and fungal species detected in damp environments are the same as those detected in normal indoor air, but their concentrations may be higher (SCHER 2007). There are also species that are normally not present in indoor air, but typically exist in moisture-damaged environments and are called indicator species of the dampness problem. Low concentrations of these species can be found also in non-moisture-damaged buildings (Salonen et al. 2007). The spectrum of microbes varies according to time and space. The material, its moisture contents, and other circumstances regulate the microbial profile, and also the toxicity. There is geographic and also building-to-building variation. Several lists of indicator species have been cited by different laboratories. The indicator species most commonly presented to describe Finnish circumstances are *Stachybotrys, Trichoderma, Aspergillus versicolor, Aspergillus fumigatus, Chaetomium, Phialophora, Fusarium*, and

actinomycetes (mainly *Streptomycetes*) (STM 2003). However, the most common fungi detected in indoor air and settled dust samples in Finnish offices are *Penicillium*, yeasts, and *Cladosporium*, both in mold-damaged and non-damaged buildings (Salonen et al. 2007). These species are also typical outdoors. *Penicillium*, *A. fumigatus,* and yeasts have been the best indicators of mold damage (Salonen et al. 2007).

Many fungi and some yeasts replicate by producing numerous spores that are well adapted to airborne dispersal. Spores can stay airborne for long periods. Fungi also release smaller fungal fragments, which are derived from broken spores and hyphae. Fungal spores, hyphae, and fragments are known to contain allergens, many of which are glycopeptides with enzymatic properties (WHO 2009). The viability of spores is important for allergenic expression, and non-viable fungal spores and fungal fragments also contain potentially harmful compounds such as (1– >3)-β-D-glucans and mycotoxins (WHO 2009). Both spores and fungal components may be involved in mold-related adverse health effects.

Many fungi and bacteria are able to produce compounds called secondary metabolites, depending on the growth conditions and the substrate. Many secondary metabolites are toxic or otherwise biologically active, among them, mycotoxins and bacterial toxins, some of which are toxic to animals and human beings (WHO 2009). Some fungal species may produce various mycotoxins. Typical toxigenic fungi found in buildings or building materials are *Stachybotrys*, *A. versicolor, A. fumigatus, Aspergillus flavus, Penicillium, Trichoderma, Fusarium,* and *Chaetomium* (IOM 2004). The mycotoxins that have received the most attention are the trichothecenes, produced by *Stachybotrys chartarum*. Of the bacteria, *Streptomycetes* are among the potentially toxic types (IOM 2004). Microbial toxins are not volatile, but they may be carried by spores. Mycotoxins and bacterial toxins have been shown to be present in indoor environments (Tuomi et al. 2000; Peltola et al. 2001; Brasel et al. 2005; Täubel et al. 2011).

Endotoxins are components of the outer membrane of gram-negative bacteria and are composed of proteins, lipids, and lipopolysaccharides (WHO 2009). The term endotoxin refers to a toxin on the bacterial cell wall, which is liberated as a result of cell lysis. Airborne endotoxins are usually associated with dust particles or aqueous aerosols (WHO 2009).

Endotoxin exposure has been found to be associated with occupational lung disease among workers exposed at high levels of endotoxins (e.g., in farming) (IOM 2004). The terms endotoxins and lipopolysaccharides are often used interchangeably in the scientific literature (WHO 2009).

(1–>3)-β-D-glucans are non-allergenic, water-insoluble, structural-cell wall components of most fungi and some bacteria (Douwes 2005). Methods exist with which to analyze (1–>3)-β-D-glucan concentrations in dust or air samples. Observational and experimental studies suggest that some association exists between indoor (1– >3)-β-D-glucan exposure, airway inflammation, and symptoms. However, the results are mixed, and specific symptoms and potential underlying inflammatory mechanisms associated with exposure can not yet be identified (Douwes 2005).

Mite allergen concentrations have been shown to be higher in houses with mold damage than in non-damaged houses (van Strien et al. 2004). In a Finnish study estimating mite exposure in moldy buildings, mites were found (counted and identified microscopically) both in moisture-damaged buildings and non-damaged buildings, somewhat more often in moisture-damaged buildings however (Pennanen et al. 2007). Mites, especially storage mites, were found in workplaces and homes in a total of 26% of the dust samples but seldom at high concentrations (Pennanen et al. 2007). In addition, amoebae have been shown to be present in more than 20% of the building material samples taken from moisture-damaged buildings (Yli-Pirilä et al. 2004).

VOCs emitted from microbial growth (mVOCs) include those that are known as mold odor. mVOCs are often similar to common industrial chemicals, and more than 200 of these compounds derived from different fungi have been identified (WHO 2009). Few of these compounds are specific to fungi; therefore measuring mVOCs is of limited use in attempts to identify indoor fungal growth (WHO 2009).

Damp concrete floors have been shown to increase the chemical degradation of the plasticizer in floor coatings and adhesives made of polyvinyl chloride, resulting in emissions of VOCs, like 2-ethyl-1-hexanol and 1-butanol (Tuomainen et al. 2004, Wieslander 2010). Induced by dampness, the self-leveling flooring compound used in Europe in the late 1970s and early 1980s may emit ammonia (WHO 2009). The off-gassing of formaldehyde from composite wood products has been shown to increase as the relative air humidity increases (WHO 2009).

2.2.3 Exposure assessment

Exposure is defined as an event during which people come into contact with a pollutant at a certain concentration during a certain length of time (WHO 2009). The interpretation of concentrations is a difficult question, as there are no health-based exposure limits for indoor biological agents (WHO 2009). It is likely that the major route of the exposure to dampness-related agents is via the airways. Exposures to fungal agents may occur through dermal contact and the incidental ingestion of house dust as a consequence of hand-to mouth activity, but the significance of these routes is probably low with respect to adults (IOM 2004). At present, there is a lack of valid, quantitative methods for assessing exposure to microbial and other agents associated with indoor dampness (WHO 2009). Therefore, indicators of exposure are used to estimate the microbial exposure of occupants and to find abnormal sources of microbes.

The methods used to estimate exposure include 1) information from occupants and their perceptions in the form of inquiries or questionnaires, which elicit occupants' perceptions of conditions such as marks of water leaks or moldy odors and which are used in most epidemiological studies; 2) visual inspection of buildings or a more specific investigation of building construction, which may include structural openings; and 3) environmental sampling (Salonen 2009; WHO 2009).

When moisture damage is suspected in a building, a technical investigation is performed, and the ventilation system is inspected. The aim is to recognize and localize the sources and mechanisms of the moisture damage in order to remediate the mold damage and repair structures, and then to insure that recurrence is prevented.

Traditional microbial exposure assessment is based on culturing. In cold climates, the presence of visible mold is unusual, and therefore sampling is needed to demonstrate mold (Nevalainen et al. 1998).

Bulk sampling from building materials is a principal sampling method if mold growth is suspected in constructions (Salonen 2009). The results of material samples help to locate the microbial contamination and indicate the need for remediation. The results are expressed as concentrations of culturable microbes per gram of material (cfu/g). By measuring air pressure differences between spaces or locating air leaks with tracer gases, it is possible to verify whether pollutants migrate from

spaces with moisture-damaged structures to working spaces (Haverinen-Shaughnessy et al. 2008).

Airborne concentrations of microorganisms can be studied from air samples or settled dust samples (WHO 2009). They can be used to clarify hazard identification when the results of a "walk-through" inspection reveal no significant moisture or mold damage in constructions (Salonen et al. 2007) and the cause of symptoms among occupants is unclear. Generally, a so-called six-stage impactor is used to collect air samples. As the collecting time is short, usually 15 minutes, air sampling represents a momentary situation. The result is expressed in colony forming units per cubic meter of air (cfu/m^3). As indoor microbial concentrations in air vary temporally and spatially, the representativeness of the sampling improves when several samples are taken. A low concentration of microbes in one sample does not exclude the presence of an abnormal microbial source in structures. For example, for school investigations, 10–12 indoor-air samples per building are recommended (Meklin et al. 2007). The outdoor air is a major source of indoor microbes. In subarctic countries like Finland, the outdoor concentrations of microbes vary seasonally and are very low in winter, when the ground is covered with snow. Therefore, outdoor air sampling is needed as a reference for indoor-air sampling from spring to late autumn, when the earth is not frosted. Settled dust samples reflect long-term exposure conditions, but the microbial concentrations and flora may differ from those in the indoor air (Salonen 2009).

Several other aspects must also be considered in the interpretation of microbial measurements. Both concentrations and fungal genera are assessed. Proper interpretation of indoor measurements requires detailed information about sampling and an awareness of the problems associated with these procedures (WHO 2009). The methods used must be taken into account, as the detected microbial concentrations are method specific. Reference values have been suggested for Finnish home environments (STM 2003), school environments (Meklin et al. 2007), and office environments (Salonen et al. 2007). Higher levels of fungi and bacteria exist in homes than in non-industrial work environments, as homes have diverse natural sources of microbes, like pets, firewood, and foodstuff. The recommended levels are not health-based, but they can be used for identifying abnormal indoor sources of microbes. In other words, they should not be used for evaluating health risks.

Cultivation methods may underestimate the real exposure to fungi, because only viable microbes can grow on culture media. New methods of collecting fungi have been presented, but the experience with them is limited (WHO 2009). Quantitative polymerase chain reaction has proven to be a feasible method for revealing unusual microbial concentrations in house dust from moisture-damaged buildings (Lignell et al. 2008). The method has, however, not yet been well validated; hence normal levels are not known (Haverinen-Shaughnessy et al. 2008). Most methods for measuring microbial constituents (e.g., endotoxins, fungal allergens, (1– >3)-β-D-glucans, ergosterol, and muramic acid) are experimental and do not differentiate between moisture-damaged and non-damaged buildings (WHO 2009). The same is true for the measurement of mVOCs and non-volatile secondary metabolites (e.g., toxins). The presence of microbial toxins has been found in the indoor air of environments with microbial contamination (Brasel et al. 2005). This measurement method has, however, not yet been validated and is thus far not practicable. Measuring general toxicity in dust or air samples is an experimental method that is being tested for its usefulness.

2.2.4 Risk assessment

The expert group of the Scientific Committee on Health and Environmental Risks (SCHER) of the European Committee recommends using the basic paradigm for toxicological risk assessment in indoor-air risk assessment (SCHER 2007). Risk assessment consists of 1) hazard identification, 2) dose–response assessment, 3) exposure assessment evaluating the duration and concentration of exposure, and 4) risk characterization (SCHER 2007). A hazard implies the potential to cause harm, and a risk specifies the likelihood and seriousness of the occurring harm. Thus risk assessment involves deciding on whether a given level of exposure is or is not associated with some risk of adverse effects on health (Maynard 2010).

Currently, there is a lack of valid, quantitative methods for assessing exposure to microbial and other agents associated with indoor dampness, and this lack seriously hampers risk assessment (WHO 2009). Although some studies suggest that respiratory symptoms increase with increasing severity of moisture damage (Haverinen et al. 2001; Hellgren et al.

2008), dose–response data are not available for the setting of health-based criteria for exposure. SCHER demands flexible use of the risk assessment paradigm; when it is not possible to compare the exposure with relevant health-based guidelines, a scientifically based hazard characterization should be attempted (SCHER 2007). However, it should be taken into account that complaints and diseases related to indoor exposures may have a complex cause–effect relationship (SCHER 2007).

When unacceptable indoor conditions, like extreme heat, a lack of ventilation, excessive dirtiness, or excessive microbial growth and dampness are present and there are diseases or a risk of diseases, symptoms, or complaints obviously related to these conditions, risk management can be carried out directly without further detailed risk assessment (SCHER 2007). Regarding building dampness and mold, tools for assessing risk and planning the remediation processes require an overall evaluation using available exposure assessment methods (see Section 2.2.3) and a simultaneous assessment of the symptoms and complaints of the occupants (Reijula and Sundman-Digert 2004; Haverinen-Shaughnessy et al. 2008; Schneider 2008b; Lahtinen et al. 2009, STM 2009). Clinical guidelines on the recognition of health effects are sparse (Majvik 1998; Storey et al. 2004; Majvik 2007). Often a multiprofessional approach to risk assessment is necessary, and technical experts, the workplace, and occupational health professionals have their own roles to play (Lahtinen et al. 2008).

Risk communication should be added as an essential component of risk management (Maynard 2010). The success of the technical remedies is the first priority, but investment in information, communication, and cooperation help to attain the confidence of the occupants in order to succeed in solving the indoor-air problem (Lahtinen et al. 2009).

2.3 Health effects related to indoor dampness and mold

Many epidemiological studies have found associations between evident indoor dampness or mold and respiratory health effects on children and adults in many geographical regions (Bornehag et al. 2001; Bornehag et al. 2004; IOM 2004; Fisk et al. 2007; Antova et al. 2008; WHO

2009; Fisk et. al 2010; Mendell et al. 2011). The evidence is not strong enough to document causal relationships, and this lack of strength is likely attributable to an uncertainty about the causal agents and a lack of valid exposure assessment methods for these unknown agents (WHO 2009, Mendell et al. 2011). A WHO expert group has concluded that, although not established conclusively, it is plausible that heavy exposure to indoor mold or other microbial agents plays a causal role (WHO 2009). However, conventional quantitative exposures to mold or other microbiological exposures, such as culturable airborne fungi, have shown less consistent associations with health effects than have qualitative assessments of visible dampness or mold, or mold odor (Mendell et al. 2011). It has been suggested that visible mold may better represent long-term exposure to molds than direct measurements during a short sampling time do (Antova et al. 2008).

The studies have also other limitations. The methods assessing exposure and health outcomes vary. Many of them have used subjective reports for assessing exposure or health and thus have a potential for reporting bias (WHO 2009). The microbial measurements used in many studies may not target actual causal factors. For example, although glucans and endotoxins have been shown to cause inflammation, they have also been suggested to have health protective associations, and this possibility is consistent with the hygiene hypothesis that postulates that growing up in a more microbiologically hygienic environment early in life may increase the risk of atopy and allergic disease (von Hertzen and Haahtela 2004; Mendell et al. 2011). However, there is no indication that living or working in a damp building with heavy exposure to mold prevents the development of allergies and respiratory disease (WHO 2009). They seem only to increase rather than decrease the development of respiratory disease, both in allergic and non-allergic persons (Mendell et al. 2011).

The scientific literature concerning the health effects of indoor dampness and mold has been reviewed by several groups. The reviews NORDDAMP (Bornehag et al. 2001) and EUROEXPO (Bornehag et al. 2004) cover the literature up to 2000. The expert group of the Institute of Medicine (IOM) has reviewed the literature up to 2003 (IOM 2004) and that of WHO up to 2007 (WHO 2009). The latest review on the epidemiological evidence concerning respiratory and allergic health effects was carried out by Mendell et al. (2011); it covers the literature

up to 2009. In addition, three meta-analyses have been published that combine data of multiple studies with qualitative dampness and mold factors into quantitative summaries of the association between dampness or mold and specific respiratory outcomes (Fisk et al. 2007; Antova et al. 2008; Fisk et al. 2010).

IOM focused its review on epidemiological studies. The quality of the evidence concerning a relation was classified into the following five categories: 1) sufficient evidence of a causal relationship, 2) sufficient evidence of an association, 3) limited or suggestive evidence of an association, 4) inadequate or insufficient evidence to determine whether an association exists, and 5) limited or suggestive evidence of no association (IOM 2004). The expert group of WHO separately reviewed the epidemiological evidence and the clinical and toxicological evidence.

Table 2 shows how, based on the epidemiological evidence, the level of confidence of associations (using the IOM classification) between indoor dampness and related factors has increased over the years (IOM 2004; WHO 2009; Mendell et al. 2011). For none of the outcomes, is there sufficient evidence of a causal relationship. Table 2 also shows that there is epidemiological evidence only for respiratory health outcomes. For other effects, like effects related to skin, eyes, fatigue, nausea, headache and insomnia, the WHO report notes that only limited research has been reported (WHO 2009), and therefore the associations are not assessable.

Clinical studies provide evidence for rare outcomes, for which the epidemiological approach is not reasonable due to difficulties in defining exposure. The WHO report (2009) also weighed the evidence of clinical studies. These studies were based on small groups, or are case reports, and both the exposure and outcomes are characterized better than in the epidemiological studies (WHO 2009). The WHO experts concluded that clinical evidence indicates that associations exist between mold and other dampness-associated microbiological agents and allergic alveolitis in susceptible persons (reviewed in more detail in Section 2.3.5), mold infections in immune-suppressed or otherwise susceptible persons (see Section 2.3.7), and humidifier fever (from contaminated humidifiers) and inhalation fevers (from the handling of moldy material) (see Section 2.3.6).

Toxicological studies provide an understanding of the pathological processes and are needed in consideration of the biological plausibility of potential causal associations (see Section 2.3.9).

Table 2. The level of confidence of associations between indoor dampness or dampness-related agents and health outcomes, based on epidemiological evidence according to systematic literature reviews. NA, not assessed.

Outcome	IOM conclusion (2004)	WHO conclusion (2009)	Conclusion by Mendell et al. (2011)
Asthma exacerbation	Sufficient evidence	Sufficient evidence	Sufficient evidence (strongly suggestive of causation)
Asthma development	Limited or suggestive evidence	Sufficient evidence	Sufficient evidence
Cough	Sufficient evidence	Sufficient evidence	Sufficient evidence
Wheeze	Sufficient evidence	Sufficient evidence	Sufficient evidence
Dyspnea	Limited or suggestive evidence	Sufficient evidence	Sufficient evidence
Upper respiratory tract symptoms	Sufficient evidence	Sufficient evidence	Sufficient evidence
Allergic rhinitis	NA	Limited or suggestive evidence	Sufficient evidence
Respiratory infections	NA	Sufficient evidence (except otitis media)	Sufficient evidence
Bronchitis	NA	Limited or suggestive evidence	Sufficient evidence
Allergic alveolitis	(Association based on clinical evidence)	(Association based on clinical evidence)	Inadequate or insufficient evidence
Organic dust toxic syndrome (ODTS)	Inadequate or insufficient evidence	Inadequate or insufficient evidence	NA
Gastrointestinal tract problems	Inadequate or insufficient evidence	NA	NA
Fatigue	Inadequate or insufficient evidence	NA	NA
Neuropsychiatric symptoms	Inadequate or insufficient evidence	NA	NA
Cancer	Inadequate or insufficient evidence	Inadequate or insufficient evidence	NA
Rheumatological and other immune diseases	Inadequate or insufficient evidence	Inadequate or insufficient evidence	NA
Reproductive effects	Inadequate or insufficient evidence	Inadequate or insufficient evidence	NA

2.3.1 Respiratory symptoms

The increasing evidence from the 1990s to the 2000s provides convincing certainty for the associations of dampness and mold with cough, wheezing, and dyspnea, as well as with upper-respiratory symptoms (Table 2) (Bornehag et al. 2001; Bornehag et al. 2004; IOM 2004; WHO 2009). Fisk et al. (2007) have reported an odds ratio (OR) of 1.52 (95% confidence interval [95% CI] 1.18–1.96) as a summary effect estimate for adult cough, an OR of 1.39 (95% CI 1.04–1.85) for adult wheezing, and an OR of 1.70 (95% CI 1.44-2.00) for upper-respiratory tract symptoms in adults and children. The meta-analyses by Antova et al. (2008) included only studies on children.

2.3.2 Development of asthma

The IOM (2004) concluded that there is limited or suggestive evidence of an association between exposure to a damp indoor environment and the development of asthma (for the definition of asthma, see Section 2.4.1). For the presence of mold, the existing evidence of an association had been inadequate or insufficient (IOM 2004).

Fisk et al. provided quantitative summary estimates of associations between qualitatively assessed dampness or mold in residences. The meta-analysis concerning asthma development was based on four studies (Yang et al. 1998; Thorn et al. 2001; Jaakkola et al. 2002; Jaakkola et al. 2005) and ended up with an OR of 1.34 (95% CI 0.86–2.10).

WHO (2009) reviewed the epidemiological evidence up to 2007 and concluded that there is sufficient confirmation of an association between factors related to indoor dampness and asthma development.

The most recent review, by Mendell et al., identified five new studies on asthma development (Rönmark et al. 2002; Hyvärinen et al. 2006; Park et al. 2008; Cox-Ganser et al. 2009; Iossifova et al. 2009) that were not included in the IOM or WHO reports (Mendell et al. 2011). The authors ended up with the same conclusion as the authors of the WHO report (WHO 2009).

Torén et al. (2010) ended up with a different conclusion in their systematic review on asthma development in adults. They questioned whether the results of studies conducted on children can be generalized to

adults, as the mechanisms for asthma development may be different (e.g., allergy may be more important among children). The authors reviewed the epidemiological literature up to 2009 and did not find evidence to support the hypothesis that indoor dampness and mold would increase the risk of asthma development in adults (Torén et al. 2010).

Table 3 summarizes the epidemiological evidence of the studies on the association between asthma development and dampness-related factors among adults. Altogether six of the studies on asthma development have been conducted on adults, and the other eleven studies concerned children (presented in Appendix 1). Workplace dampness was the focus of three of the studies (Jaakkola et al. 2002; Park et al. 2008; Cox-Ganser et al. 2009).

In the so-called Pirkanmaa study, 521 new-onset adult asthma cases and 932 controls were examined in a population-based study (Jaakkola et al. 2002). An association with an OR of 1.54 (95% CI 1.01–2.32) was found between self-reported visible mold or mold odor at the workplace and new-onset asthma. The study controlled for gender, age, parental atopy or asthma, education, smoking, environmental tobacco smoke, pets, work indoors, self-reported occupational exposures, and signs of dampness or water damage (Jaakkola et al. 2002).

Park et al. (2008) found associations between physician-diagnosed post-occupancy-onset asthma and fungal exposure among employees in an office building with a long history of water damage. The study population comprised 200 respiratory cases, of which 49 involved current asthma with a post-occupancy physician diagnosis, and 152 asymptomatic referents. Dust samples collected from floors and chairs were analyzed for culturable fungi, ergosterol, and endotoxin. Post-occupancy-diagnosed asthma showed statistically significant associations with exposure to hydrophilic fungi in models adjusted for age, gender, race, smoking status, building occupancy time, ergosterol, and endotoxin levels. The OR for hydrophilic fungi in floor dust was 2.09 (95% CI 1.15–3.79), and for chair dust it was 1.79 (95% CI 1.79 (1.12–2.85) (Park et al. 2008).

A cross-sectional study of 1171 workers from a water-damaged hospital and a nearby hospital without indoor-air problems showed that post-hire asthma was positively associated with an observational assessment score of workplace dampness (Cox-Ganser et al. 2009). Of

Table 3. Studies on associations of asthma development with dampness, mold, or agents associated with dampness among adults (adapted from IOM 2004 and Mendell et al. 2011). Risk estimates presented as odds ratios with 95% confidence intervals, unless indicated otherwise.

Reference	Subjects	Outcome	Dampness or mold measure	Exposure self-reported (S)/ observed (O)	Exposure at work (W)/ at home (H)	Risk estimate
Population-based nested case–control studies						
Thorn et al. 2001	174 adults aged 20–50 years from Sweden with asthma diagnosed in the last 15 years; 870 referents	Physician-diagnosed asthma after age 16	Visible dampness at or before asthma diagnosis	S	H	1.3 (0.9–2.0)
			Visible mold growth at or before asthma diagnosis	S	H	2.2 (1.4–3.5)
			Dampness or visible mold growth at or before asthma diagnosis	S	H	1.8 (1.1–3.1) (prevalence)
Jaakkola et al. 2002	521 newly diagnosed adult cases from Pirkanmaa, Finland; 932 controls	New physician-diagnosed asthma	Visible mold or odor	S	W	1.54 (1.01–2.32)
			Damp stains or paint peeling	S	W	0.84 (0.56–1.25)
			Water damage	S	W	0.91 (0.60–1.39)
			Visible mold or odor	S	H	0.98 (0.68–1.40)
			Damp stains or paint peeling	S	H	1.02 (0.73–1.41)
			Water damage	S	H	0.90 (0.61–1.34)
Prospective studies						
Matheson et al. 2005	845 adults aged 20–45 years from the southeastern suburbs of Melbourne	Doctor-diagnosed asthma	Ergosterol in floor dust	O	H	1.50 (0.68–3.30)
			Total fungi, culturable airborne	O	H	0.89 (0.60–1.34)
			Cladosporium, culturable airborne	O	H	0.96 (0.72–1.27)
			Other fungi, culturable airborne	O	H	0.99 (0.73–1.36)
Retrospective studies						
Gunnbjörnsdottir et al. 2006	15 995 persons aged 20–44 years, who had participated in the European Community Respiratory Health Survey (ECRHS I)	Asthma onset	Damp homes	S	H	1.13 (0.92–1.40)

Cross-sectional studies

Park et al. 2008		Current asthma with post-occupancy, physician diagnosed	Total culturable fungi in floor dust in total fungi models	O	W	1.46 (0.88–2.44)
			Total culturable fungi in chair dust in total fungi models	O	W	1.60 (0.99–2.58)
			Ergosterol in floor dust in total fungi models	O	W	1.22 (0.71–2.11)
			Ergosterol in chair dust in total fungi models	O	W	1.48 (0.82–2.67)
			Endotoxin in floor dust in total fungi models	O	W	1.05 (0.53–2.08)
			Endotoxin in chair dust in total fungi models	O	W	0.87 (0.51–1.48)
			Hydrophilic fungi in floor dust in hydrophilic fungi models	O	W	2.09 (1.15–3.79)
			Hydrophilic fungi in chair dust in hydrophilic fungi models	O	W	1.79 (1.12–2.85)
			Ergosterol in floor dust in hydrophilic fungi models	O	W	1.19 (0.68–2.07)
			Ergosterol in chair dust in hydrophilic fungi models	O	W	1.47 (0.81–2.63)
			Endotoxin in floor dust in hydrophilic fungi models	O	W	1.02 (0.51–2.05)
			Endotoxin in chair dust in hydrophilic fungi models	O	W	0.87 (0.51–1.47)
Cox-Ganser et al. 2009	1171 workers in sentinel cases hospital or nearby control hospital in western US	Post-hire onset, physician diagnosed asthma, from occupant questionnaire	Dampness score from researcher observation, range –20:			Positive dose response*:
			0–2	O	W	1.0
			3–5	O	W	approx. 1.6 (0.8–4.3)
			6–20	O	W	approx. 2.2 (1.1–5.8)
			Airborne – fungi, bacteria and endotoxin	O	W	no significant association
			Floor and chair dust – endotoxin, beta-glucan, ergosterol, culturable fungi, culturable bacteria, ECP *Pen/Asp*	O	W	no significant association

* The ORs and CIs presented graphically in the article.

the participants, altogether 79 workers had asthma with post-hire onset. The researchers assessed building dampness for selected areas, so that the dampness scores could be linked to 834 participants. For the highest dampness score, the OR of post-hire onset asthma was approximately 2.2 with the lower limit of the 95% confidence interval above zero (presented graphically) (Cox-Ganser et al. 2009).

Studies conducted with children have found associations between asthma development and dampness-related factors with the OR ranging from 0.63 to 6.16 (Appendix 1). The studies have had varying study designs and measures of dampness. A well-designed incident case–control study conducted in the Kuopio Hospital District (Pekkanen et al. 2007) has been found to provide some of the strongest evidence that dampness-related exposures may cause asthma development in infants and children (WHO 2009; Mendell et al. 2011). The study showed an association between the risk of developing new asthma among children aged 1–6 years and the presence of visible mold in the main living quarters, but not in other areas of the home (Pekkanen et al. 2007). Multivariate analyses showed dose–response relations, as the risk of asthma increased as the severity of moisture damage and the maximum severity of the damage increased, as assessed by civil engineers (Pekkanen et al. 2007).

2.3.3 Exacerbation of asthma

The latest systematic review (by Mendell et al. 2011) found 31 studies on dampness and mold and asthma exacerbation and considered the evidence sufficient to document an association, the ORs consistently exceeding 1.0 for adults. In retrospective studies, they ranged from 1.7 to 2.6, and in cross-sectional studies they varied from 1.02 to 4.2 (Mendell et al. 2011). For children, the ORs were notably higher. On the basis of a well-designed intervention study by Kercsmar et al. (2006), the review concluded the evidence to be strongly suggestive of a causal association between indoor dampness and mold and exacerbations among children with asthma (Mendell et al. 2011). Comprehensive removal of dampness sources and visible mold caused dramatic reductions in the occurrence of asthma exacerbations among children (Kercsmar et al. 2006).

2.3.4 Respiratory tract infections

Respiratory tract infections include upper (common cold, pharyngitis, and sinusitis) and lower (pneumonia, acute bronchitis, and acute exacerbation of chronic bronchitis) respiratory tract infections and otitis media. These infections are generally viral or bacterial in origin, except chronic bronchitis which is non-infectious.

The IOM review in 2004 drew no conclusions about the associations between dampness or mold and respiratory tract infections (IOM 2004). The review by WHO concluded that there is sufficient evidence of an association between indoor dampness-related factors and respiratory infections, but only limited or suggestive evidence of an association with bronchitis (WHO 2009).

The results of quantitative meta-analyses, performed by Fisk et al. (2010), indicated that dampness and mold in residences are associated with moderate but statistically significant increases in respiratory infections and bronchitis. Altogether 23 studies were selected for inclusion in the meta-analyses. For the two primary outcomes, bronchitis (13 studies) and respiratory infections (19 studies, including otitis media), the OR estimates were 1.45 (95% CI 1.34–1.56) and 1.44 (95% CI 1.32–1.58), respectively. The construction of a separate, overall respiratory infection group model for adults led to a similar OR, 1.50 (95% CI 1.22–1.83) (Fisk et al. 2010). The authors concluded that the results of the meta-analyses were consistent with the WHO findings for respiratory infections (WHO 2009), but implied more strongly that dampness and mold are associated with bronchitis. They also concluded that the reported statistical associations do not prove that dampness and mold are causally related to bronchitis and respiratory infections (Fisk et al. 2010).

A meta-analysis published earlier analyzed pooled data from 12 European cross-sectional studies of visible mold in residences and bronchitis in children; the result was an OR of 1.38 (95% CI 1.29–1.47), which is comparable with the results reported by Fisk et al. (Antova et al. 2008).

2.3.5 Allergic alveolitis

Allergic alveolitis, also known as hypersensitivity pneumonitis or extrinsic allergic alveolitis, is an interstitial, granulomatous, cell-mediated lung

disease, which is caused by repeated inhalation exposure to antigens from microorganisms or other sources. The primary site of the allergic response is alveolar or bronchiolar tissue and the interstitium of the lung. The occurrence of allergic alveolitis in the general population is rare.

The disease was originally recognized in adults with high antigen exposures in agricultural and industrial settings. For farmers, allergic alveolitis has been found to be associated with high exposure levels, the spore concentrations exceeding 10^9 spores/m^3 (Malmberg et al. 1993). In a Finnish study, the level of exposure to fungi varied from 10^4 to 10^7 cfu/m^3 in the handling of hay and grain (Kotimaa et al. 1987). In moisture-damaged office buildings, the concentrations of viable airborne fungi are generally lower (10^1–10^4 cfu/m^3) (Salonen 2009).

Only 1%–15% of those exposed develop allergic alveolitis (Bourke et al. 2001), although a larger portion of exposed persons may be sensitized. This pattern implies that, in addition to exposure to external antigens, genetic susceptibility must play a significant role (WHO 2009; Park and Cox-Ganser 2011). Host risk factors have been poorly characterized (Bourke et al. 2001). In susceptible persons, the exposure leads to a combined type III allergic reaction of Gell and Coombs and a type IV lymphocytic reaction (Bourke et al. 2001).

Sporadic case reports of allergic alveolitis in damp non-industrial indoor environments have been published, often in connection with the use of humidifiers (WHO 2009). "A summer-type hypersensitivity pneumonitis", which is caused by seasonal mold contamination in the home environment, has been documented clinically and epidemiologically in Japan and some other countries with a similar climate (Ando et al. 1995). Seuri et al. (2000) described a respiratory disease outbreak, including one case of allergic alveolitis, among workers in a seriously water-damaged military hospital building. The case of allergic alveolitis was confirmed by inhalation provocation with *Sporobolomyces salmonicolor* from the hospital (Seuri et al. 2000). A case study from the United States reported a case of allergic alveolitis for a resident of a home contaminated by fungi found in water-damaged carpet and insulation materials (Apostolakos et al. 2001). Another case study from the United States reported restrictive lung disease suspected as chronic allergic alveolitis in a worker with repeated exposure to fungi in a water-damaged hotel (Trout et al. 2001). A report from Spain described two cases with allergic alveolitis caused

by domestic exposure to molds (Enriquez-Matas et al. 2007). A recent case study from Japan reported allergic alveolitis in a 75-year-old man, caused by fungi in his house (Katayama et al. 2008).

In a questionnaire study involving an office building with a long history of water damage, eight participants among 888 reported physician-diagnosed hypersensitivity pneumonitis, 5 of which had post-occupancy onset (Cox-Ganser et al. 2005). The authors concluded that the rarity of allergic alveolitis in the general population suggested a building-related etiology for this cluster, although causal antigens and medical bases for the diagnoses were not reported (Cox-Ganser et al. 2005).

Both IOM and WHO concluded that the clinical evidence indicates that associations exist between mold and other dampness-associated microbiological agents and allergic alveolitis among susceptible persons (IOM 2004; WHO 2009). There is no adequate epidemiological evidence however (Mendell et al. 2011).

2.3.6 Organic dust toxic syndrome

Organic dust toxic syndrome (ODTS), also known as inhalation fever, toxin fever, or toxic pneumonitis, is the result of substantial exposures to airborne organic dusts or aerosols, principally fungi (Iversen 2002). ODTS does not depend on immunological sensitization; therefore it can occur during or immediately after the first exposure (Iversen 2002). Exposure to organic dust causing ODTS is usually heavy. In studies of farmers, the measured concentrations of mold spores that led to ODTS have been shown to be notably higher than those that induce allergic alveolitis (Malmberg et al. 1993). In addition to farming, every occupation associated with the handling of organic material poses some risk. The clinical picture is an influenza-like reaction with fever (38.5–40.0°C) and myalgias, often accompanied by chest tightness, cough, headache, and nausea (Iversen 2002). The symptoms are self-limiting; they rarely persist beyond 1 or 2 days after the cessation of exposure, and there are no long-term consequences even with recurring episodes (Iversen 2002).

The report of IOM (2004) concluded that concentrations of organic dust consistent with the development of ODTS are very unlikely to be found in homes or public buildings, and the authors did not recognize studies in which ODTS should have been explored as a possible explana-

tion of symptoms experienced by some occupants of highly contaminated indoor environments (IOM 2004). ODTS has been described for a museum worker who handled books covered with mold (Kolmodin-Hedman et al. 1986).

2.3.7 Infection with mold

Serious respiratory infections with *Aspergillus spp.* or *Fusarium spp.* are well-known complications among patients who undergo cancer chemotherapy or organ transplantation, or are otherwise immune compromised (IOM 2004, WHO 2009). No studies have been conducted to link such infections to mold associated with the presence of moisture problems (WHO 2009). Rather, a susceptible person is a suitable host for the opportunistic molds that are ubiquitous (WHO 2009).

There are some other clinical disorders in association with which patients become infected with *Aspergillus*, and which have some features in common. They depend on the status of the host's immune system, and it is usually not clear whether the exposure to *Aspergillus* occurred in the indoor environment or outdoors. These are allergic bronchopulmonary aspergillosis (ABPA), sinus disease secondary to the presence of *Aspergillus*, and pulmonary aspergilloma (tumor in a lung cavity consisting of conglomerations of *Aspergillus* hyphae) (IOM 2004; Bush et al. 2006). ABPA affects patients with cystic fibrosis and less frequently those with asthma. The at-risk individuals have ongoing exposures caused by the ubiquitous nature of the fungi involved (Bush et al. 2006).

2.3.8 Other health disorders

Two case studies of clusters of rheumatic diseases associated with dampness and mold have been reported, one in an office building (Myllykangas-Luosujärvi et al. 2002) and another at a health center (Luosujärvi et al. 2003). The authors concluded that the underlying reasons for the accumulation of the rheumatic diseases remain elusive (Luosujärvi et al. 2003). An experimental study on human chondrocytes suggests that endotoxins may play a role in the pathogenesis of rheumatic diseases (Lorenz et al. 2006).

Sarcoidosis, a granulomatous lung disease of unknown etiology, has been linked to exposure to microbial agents by some researchers (Park and Cox-Ganser 2011). A cluster of six cases of sarcoidosis was reported in a moisture-damaged office building with 1327 occupants (Laney et al. 2009).

Neither the report by IOM (2004) nor that by WHO (2009) found studies on the effects of exposure to building dampness and mold on reproductive health. The ingestion of mold-contaminated fodder has been shown to have reproductive toxicity in animals however.

Some mycotoxins are classified as carcinogenic or possibly carcinogenic to humans on the basis of evidence on exposure through dietary consumption of, for example, mold-contaminated grain, maize, or nuts (IARC 1993; IARC 2002). There is no scientific evidence for an association between the inhalation route of exposure to microbial agents indoors and cancers in humans (IOM 2004; WHO 2009).

2.3.9 Mechanisms of health effects

The WHO expert group concluded that no single mechanism can explain the wide variety of effects associated with dampness and mold (WHO 2009). For the most part, the mechanisms through which adverse health effects develop are mainly unknown, although much toxicological research has been carried out. In vitro and in vivo studies have found diverse inflammatory, cytotoxic, and immunosuppressive responses after exposure to the spores, metabolites, and components of microbial species that appear in damp buildings. In addition, interactions between various microbial agents have been suggested by some studies. When the results of studies on experimental animals are being interpreted and attempts are being made to extrapolate the results to human exposures indoors, differences in relative doses should be considered. The exposures used for experimental animals may be orders of magnitude higher than those found in indoor environments (WHO 2009).

Inflammatory, non-allergic responses have been considered to play a central role in the development of health effects in damp buildings (Wolff 2011). The explanation is biologically plausible as health effects manifest as inflammation-related diseases, like asthma (WHO 2009). Increased levels of inflammatory mediators have been found in nasal

laval fluid and induced sputum from occupants of damp buildings (WHO 2009). The role of mycotoxins as a potential explanation for inflammatory responses has been studied. In a murine model, exposure to *Stachybotrys chartarum* induced lung inflammation characterized by the infiltration of neutrophils and lymphocytes, which was regulated by proinflammatory cytokines and leucocyte-attracting chemokines (Leino et al. 2003). The inflammatory responses were stronger in allergic mice and enhanced by *S. chartarum* exposure, the result suggesting that health effects associated with exposure to damp building molds may depend on the immunological status of the exposed person (Leino et al. 2006). Trichothecene mycotoxins (produced by *S. chartarum*), together with lipopolysaccharides, could synergistically activate inflammatory responses mediated by interleukin IL-1β and IL-18 in human macrophages (Kankkunen et al. 2009).

Many fungal species produce type I allergens, and IgE sensitization to the most common outdoor and indoor fungal species, like *Alternaria*, *Penicillium*, *Aspergillus,* and *Cladosporium* spp., is known to be strongly associated with allergic respiratory disease, especially asthma (Jaakkola et al. 2006b; WHO 2009; Knutsen et al. 2012). Fungal sensitization, particularly to *A. fumigatus*, is reported to be common in patients with severe asthma (Knutsen et al. 2012). SPTs and specific serum IgE tests are used to determine sensitization to various fungi (Knutsen et al. 2012). Depending on the climatic conditions, 2.4%–12.6% of the general population and up to 39.4% of atopics have been shown to have IgE antibodies to *Alternaria alternata* (Leino 2006; Simon-Nobbe et al. 2008). IgE sensitization to molds occurs generally in atopic persons as part of polysensitization (Bush et al. 2006; Simon-Nobbe et al. 2008). The occurrence of IgE-mediated sensitivity to common fungal allergens has been found to be rare, up to 2.8%, in Finnish patients with symptoms that suggested allergy (Reijula et al. 2003). Of the those exposed to damp buildings, only a small percentage develops allergies to molds (Immonen et al. 2001). In a study of the occupants of a water-damaged building, persons with post-occupancy onset asthma had a lower prevalence of positive reactions to molds in SPTs than persons with pre-occupancy onset asthma (Cox-Ganser et al. 2005). Fungi are also well-known sources of type III (or IgG-inducing) allergens. At high concentrations, fungi may be involved in combined type III and IV allergic reactions,

including allergic alveolitis (WHO 2009). A WHO expert group has concluded that one of the mechanisms underlying the health effects of exposure to indoor microbial agents may be IgE-mediated allergic responses (WHO 2009).

Whether mold or mycotoxin exposure can induce disorders of immune regulation has also been considered. The increased frequency of respiratory infections observed in some studies suggests immunosuppressive effects (WHO 2009). Several microbes or toxins have been shown to have immunosuppressive effects in vitro, and those of mycotoxins have been confirmed in experimental animals (WHO 2009). No toxicological data are available on autoimmune responses caused by microbes or microbial substances found in damp buildings (Bush et al. 2006; WHO 2009).

Many factors in indoor air in damp buildings are potentially irritative and many of the respiratory tract symptoms appear as irritative in nature. Some authors have suggested a link between exposure to dampness and excess mold growth and the development of aeroirritant symptoms (Hope and Simon 2007). Especially, a strong association between VOCs and mucous-membrane irritation has been suggested by several studies (SCHER 2007; Salonen 2009). It has been reported that, except for a few known airway irritants like formaldehyde, the typical concentrations of VOCs and mVOCs cannot explain the reported complaints in non-industrial work environments (Wolkoff et al. 2006). However, there are large differences in the sensitivities to VOCs between persons (Salonen 2009).

The role of toxigenic mold species as a cause of health effects in damp indoor environments has remained controversial thus far (Yike and Dearborn 2011). The existing scientific information does not offer sufficient evidence that could lead to a better understanding of the problem. Efforts have been made to find measurements to serve as suitable biomarkers of toxic mold exposure (Yike et al. 2006). Many animal studies on the pulmonary effects of a toxigenic mold, *S. chartarum*, have been published. In addition to inflammation, the common finding has been lung injury (Yike and Dearborn 2011). Recently, the remodeling of pulmonary arteries in mice has been described as a result of inhalation exposure to the spores of *S. chartarum* (Nagayoshi et al. 2011). It is known that molds growing indoors are capable of producing toxins. The question is whether exposure to mycotoxins via inhalation occurs

in sufficient levels indoors to cause adverse health effects in humans. No study has thus far shown it (WHO 2009). The mechanisms are likely to be complex and multifactorial (WHO 2009).

2.4 Asthma and its association to work

2.4.1 Overview of asthma

According to an international definition (GINA 2011), asthma is a chronic inflammatory disorder of the airways, which involves several inflammatory cells, like mast cells, eosinophils, and T-lymphocytes, as well as multiple mediators like chemokines and cytokines. In ways that are still not well understood, this pattern of inflammation is associated with airway hyper-responsiveness and recurrent episodes of asthma symptoms (wheezing, breathlessness, chest tightness, and coughing) particularly at night or in the early morning (GINA 2011). These episodes are usually associated with widespread, but variable, airway obstruction within the lung that is often reversible either spontaneously or with treatment (GINA 2011). Since the pathogenesis of asthma is not clear, much of its definition is descriptive, and the clinical spectrum varies. Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms. The former include host factors (which are primarily genetic), and the latter are usually environmental factors, like allergens, infections, and tobacco smoke. Occupational sensitizers belong in both categories (GINA 2011).

There is good evidence that the global burden of asthma was rising until 1990, while some recent findings suggest that the previous upward trend in asthma prevalence has reached a plateau in Western Europe (Bjerg et al. 2011). A survey from Helsinki, Finland, showed that the prevalence of physician-diagnosed asthma was 6.8% in 1996 and 9.4% in 2007 (Pallasaho et al. 2011). The annual incidence rate of asthma from 1996 to 2007 was 3.7/1000 a year, being significantly higher for women (4.3/1000 a year) than for men (2.8/1000 a year) (Pallasaho et al. 2011).

2.4.2 Asthma attributable to work

A recent review, based on longitudinal studies, indicated that a population attributable risk (PAR), also referred to as the population attributable fraction or the etiological fraction, for adult-onset asthma caused by occupational exposures is 16.3% (Torén and Blanc 2009). An attributable risk refers to the proportion of a disease that would not have occurred without a specific exposure. The range of estimates in single studies varies widely, but the authors of the review considered the most accurate range of the likely population burden of asthma attributable to occupational exposures to be at least 15% and potentially as high as 20% (Torén and Blanc 2009). The evidence underscores the potential for prevention and the need for actions to reduce the occupational exposure likely to lead to asthma.

A study covering all 25- to 59-year-old employed Finns without pre-existing asthma followed three temporal cohorts for five (or three) years (Karjalainen et al. 2001). The onset of asthma was determined through the Medication Reimbursement Register of The Social Insurance Institution of Finland so that the cases had clinically well-established asthma. There were 49 575 incident cases of asthma. Exposure was defined on the basis of occupational titles and dichotomized into occupational categories. The incidence rate ratios of asthma were estimated on the basis of a comparison between non-administrative work and administrative work. The incident asthma PAR associated with occupational exposure (non-administrative work) was 29% for the men and 17% for the women (Karjalainen et al. 2001). In a study based on the same material, an excess risk of asthma among men was found in occupations with no generally recognized risk, for example, among shoemakers (relative risk [RR] 2.79, 95% CI 1.58–4.93), smiths (RR 2.37, 95% CI 1.51–3.74), and chimney sweeps (RR 2.34, 95% CI 1.61–3.41) (Karjalainen et al. 2002). In other population-based studies, an increased risk of asthma has also been found not only for occupations with exposure to traditional sensitizers, but also for occupations with exposure to respiratory irritants like cleaning products (Kogevinas et al. 2007), construction and textile mill dusts, welding fumes, solvents, and other chemicals (Arif et al. 2002).

2.4.3 Work-related asthma

At the individual level, asthma is work-related when there is an association between symptoms and work. Work-related asthma (WRA) is the broad term that includes the following two categories: work-exacerbated asthma (WEA) which is exacerbated by inhalation exposures in the workplace, and occupational asthma (OA) which is induced by them (Tarlo et al. 2008; Baur et al. 2012) (Figure 2). The different types of WRA should be distinguished between, since the implications for the worker and the occupational health management of the disease differ (Nicholson et al. 2005).

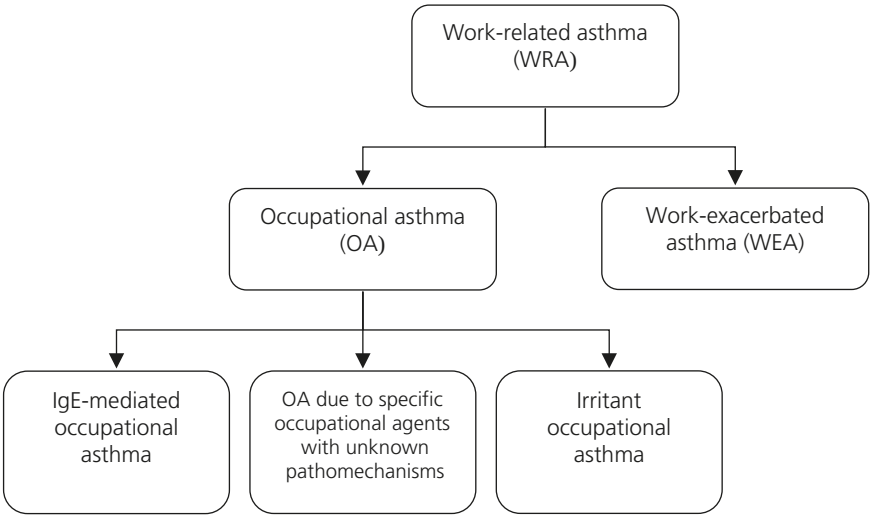


Figure 2. Work-related asthma and its subgroups (Baur et al. 2012).

2.4.4 Occupational asthma

OA is the most common chronic occupational lung disease in most industrialized countries (Nicholson et al. 2005). It is defined as asthma that is caused by a specific workplace exposure to certain substances and not to factors outside the workplace (Bernstein et al. 2006a). OA involves IgE-mediated asthma after a latency period; asthma due to specific occupational agents with unknown pathomechanisms, which

also frequently show a latency period; and irritant asthma with or without a latency period, including reactive airways dysfunction syndrome (RADS), which results from high exposure(s) (Baur et al. 2012) (Figure 2). Almost 90% of the cases of OA have a particular type of latency period (Nicholson et al. 2005), being either the outcome of sensitization to an inhaled protein (high-molecular-weight agent, e.g., flours, animal-derived proteins, or enzymes) or chemical (low-molecular-weight agent, e.g., di-isocyanates, anhydrides, or cleaning agents) (Tarlo et al. 2008). Sensitization to proteins is typically IgE-mediated, whereas, for a large number of chemicals, the mechanisms of induction remain unknown and some induce asthma through an IgE mechanism (Bernstein et al. 2006a). The published literature includes between 300 and 400 agents recognized to have caused OA, and many new agents are reported each year (Malo and Chan-Yeung 2009).

In many industries or occupations workers are exposed to multiple agents, to several high-molecular-weight agents, low-molecular-weight agents, and irritants (Malo and Chan-Yeung 2009). Typical such industries are health care, hairdressing, and farming (Malo and Chan-Yeung 2009).

OA, as well as asthma in general, is a complex disease that results from multiple interactions between environmental factors and host susceptibilities. Atopy has shown to be an important risk factor for OA induced by high-molecular-weight agents. There is some evidence that genetic factors, such as leukocyte antigen class II alleles, are associated with an increased risk of OA (Vandenplas 2011).

Disease definitions vary from country to country, tending to reflect medical practices and medico-legal considerations (Henneberger et al. 2011). Countries with well-developed occupational health care systems tend to have a broader coverage, and this diversity likely leads to higher estimates of occurrence (Jaakkola and Jaakkola 2012). The estimates from the incidence of OA from national surveillance systems range from 20–23 cases per million people in countries such as France, the United Kingdom, and the United States, to around 200 cases per million in Finland (Kogevinas et al. 2007). The data from a population-based survey (European Community Respiratory Health Survey) produced an estimate of 250–300 cases of new-onset asthma per million people as a result of occupational exposures (Kogevinas et al. 2007).

Case definition of occupational asthma

In every adult whose asthma begins or worsens while working, the possibility of WRA should be considered and evaluated (Tarlo et al. 2008; Baur et al. 2012). Due to the multitude of agents that are encountered by a worker, it can be very difficult to confirm OA and demonstrate causation by a specific agent (Bernstein et al. 2006b). The investigation of OA has been compared to an investigation by Sherlock Holmes (Rioux et al. 2008).

Several international guidelines for the diagnostics of OA have been published (EAACI 1992; Nicholson et al. 2005; Fishwick et al. 2008; Tarlo et al. 2008; Baur et al. 2012), of which the evidence-based guidelines by the European Respiratory Society (ERS) Task Force are the most recent (Baur et al. 2012). The ERS Task Force report is intended to supplement other work-related asthma guidelines. It provides evidence-based statements and recommendations for each diagnostic test, grading the level of evidence (Baur et al. 2012). Diagnostics is usually carried out in a stepwise fashion using an algorithm (Tarlo et al. 2008).

The ERS Task Force report reasons that, in the diagnostics, the degree of proof required depends on the consequences of OA development for the individual worker (Baur et al. 2012). If the worker is likely to lose his or her job, the specific agent causing OA should be identified, and, accordingly, if it is possible to relocate the worker away from exposure without economic losses, a precise diagnosis is less important (Baur et al. 2012). The ERS Task Force recommends that OA be confirmed by objective physiological tests and, in cases of allergic pathogenesis, by immunological tests (Baur et al. 2012). The diagnostic tools are presented in Figure 3.

Asthma is confirmed through the demonstration of bronchial obstruction in spirometry, of non-specific bronchial hyper-reactivity, or of increased diurnal variability in the peak expiratory flow (PEF) rates (GINA 2011). Sputum eosinophilia and exhaled nitric oxide may be helpful to confirm asthma. All of these tests may be normal in those with OA confirmed with specific challenge tests (Baur et al. 2012).

Respiratory symptoms that improve on days away from work or during holidays are the best screening method for possible OA (Baur et al. 2012). Improvement in symptoms typically occurs in times away from work and worsens on days with regular or intermittent exposures at work

(Tarlo et al. 2008). The symptoms include cough, wheezing, dyspnea, and chest tightness, and they may be accompanied by or preceded by symptoms of rhinitis or conjunctivitis (Tarlo et al. 2008). The history should also identify detailed information about work status and exposure characteristics (Figure 3). The factors or exposures that worsen asthma symptoms should be assessed (Tarlo et al. 2008).

Measuring lung function in relation to work exposure is the best method of confirming OA (Baur et al. 2012), of which the serial measurement of PEF on days at and away from work is the best validated method (Moore et al. 2010). It should be the first confirmatory test, as it can only be done when the patient is still exposed to the suspected cause of the symptoms (Baur et al. 2012). Acceptable PEF series can be obtained for around two-thirds of those for whom a diagnosis of OA is being considered (Nicholson et al. 2005). The sensitivity and specificity of serial PEF measurements is high in the diagnosis of WRA (Moore et al. 2010; Baur et al. 2012). Workplace challenges are an alternative, but they are not standardized and lack external validation (Rioux et al. 2008).

Changes in non-specific bronchial hyper-responsiveness at and away from work have only moderate sensitivity and specificity for the diagnosis of WRA, nor are pre- to post-shift changes in lung function (by spirometry) recommended (Baur et al. 2012). There is only limited evidence for the use of measuring airway inflammation (induced sputum cell counts or exhaled nitric oxide) in the investigation of WRA (Tarlo et al. 2008; Baur et al. 2012).

The specific agent can be identified either by immunological testing or testing with a specific inhalation challenge (SIC) (Figure 3). Sensitization to occupational agents is investigated with immunological tests, either SPTs or serum measurements of specific IgE (Tarlo et al. 2008). For many low-molecular-weight agents, specific IgE measurements are not available. The ERS Task Force has stated that the presence of specific IgE in a worker with confirmed OA from workplace measurements is sufficient to identify the specific cause (Baur et al. 2012).

SIC testing is regarded as the gold standard for confirming the specific cause of OA (Vandenplas et al. 2006; Baur et al. 2012). The ERS Task Force has stated that SIC is the best method for confirming a specific cause of OA when workplace measurements are not possible or specific IgE measurements are not available (Baur et al. 2012). The tests consist

of exposing a worker in a laboratory to a possible offending agent and monitoring the airway caliber (Vandenplas et al. 2006). False negative SIC tests do occur (Rioux et al. 2008); therefore a negative test for a worker with otherwise good evidence of OA is not sufficient to exclude the diagnosis (Nicholson et al. 2005). In addition, false positive reactions are possible; there are individuals who have been shown to have non-specific reactions to SICs at concentrations likely to be found in the workplace (Nicholson et al. 2005).

1. Assessing asthma
- Medical history
- Symptoms – onset / nature / timing
- Spirometry and bronchodilator response
- Bronchial hyperresponsiveness (histamine or methacholine challenge test)
- Diurnal variation in peak expiratory flow
- Sputum eosinophilia
- Exhaled nitric oxide

2. Assessing exposures / factors that can cause or exacerbate asthma
- Occupational history
  - allergens, irritants at work
  - exertion, cold, infections
  - type of work process / setting
  - ventilation / use of respiratory protection
  - material safety data sheets
  - co-workers – symptoms
  - magnitude / timing of exposures
- Environmental history
  - pets, hobbies, home exposures, ambient air pollution

3. Assessing relationship between asthma and work
- Tests that identify the workplace as the cause of respiratory symptoms
  - Respiratory symptoms that improve on days away from work or during holidays
  - Serial PEF monitoring
  - Bronchial hyper-responsiveness / spirometry / assessment of airway inflammation (induced sputum, exhaled nitric oxide) – changes related to work
  - Workplace challenges
- Tests that identify the agent causing work-related asthma
  - Immunological tests (specific IgE, skin prick tests)
  - Specific inhalation challenge tests (SIC)

Figure 3. Diagnostic tools for the evaluation of work-related asthma, adapted from the American College of Chest Physicians Consensus Statement (Tarlo et al. 2008) and the European Respiratory Society Task Force report (Baur et al. 2012).

2.4.5 Work-exacerbated asthma

The term WEA refers to asthma triggered by various work-related factors in workers with pre-existing or concurrent asthma (Tarlo et al. 2008) (Figure 2). Instead of WEA, some authors use the term work-aggravated asthma (Baur et al. 2012).

Exacerbations of asthma symptoms are common and belong to the natural course of asthma (Enriquez-Matas et al. 2007; GINA 2011). While exacerbation is often attributed to viral infections or failures in therapy, environmental conditions also make a substantial contribution. A wide variety of conditions at work can exacerbate asthma symptoms, like dusts, irritant chemicals, second-hand smoke, common allergens that are not specific to the work environment, low or high temperatures, strong emotions, stress, odors, and physical exertion (Henneberger et al. 2011).

In a Finnish population-based, cross-sectional, questionnaire survey, 21% of the 969 asthmatics that were currently employed reported WEA symptoms at least weekly during the past month (Saarinen et al. 2003). A recent review resulted in a median prevalence of 21.5% for WEA among adults with asthma, on the basis of epidemiological studies involving general populations (Henneberger et al. 2011).

Although WEA is probably common, it has received much less systematic study than OA (Tarlo et al. 2008). Interest has been increasing in the 2000s, however. It has been discovered that the socioeconomic impacts of WEA (in terms of unemployment, reduction in income, productivity loss) and the clinical characteristics (level of severity, medication needs) are at least as severe as those of OA (Henneberger et al. 2011). The recent American Thoracic Society statement summarizes that, compared with asthma unrelated to work, WEA is associated with more symptomatic days, a greater utilization of health-care resources, and a lower quality of life (Henneberger et al. 2011). It has also been suggested that WEA may be associated with higher rates of symptoms and exacerbations than asthma unrelated to work (Vandenplas and Henneberger 2007).

Case definition of work-exacerbated asthma

Confirming WEA depends on 1) clarifying that a person has asthma and 2) demonstrating a relationship between work exposures and asthma exacerbations, most commonly documented by changes in symptoms or medication use temporally related to work (Tarlo et al. 2008; Henneberger et al. 2011). Improvement in asthma symptoms while off work or on vacation is however not specific to WEA (or OA), as patients with other asthma can also feel better when not at work (Tarlo et al. 2008). For a more accurate diagnosis, more objective tests are needed.

Identification of a specific causative agent for WEA is often not possible, and mixed exposures are common (Henneberger et al. 2011). Identification is however important not only for confirming WEA, but also for reducing or eliminating harmful conditions to prevent future problems for the index case worker and co-workers (Henneberger et al. 2011).

In clinical practice, WEA can be identified as a ”byproduct” of OA investigations after OA has been excluded. In settings where SIC is commonly used, a case is classified as OA if the test results are positive and as WEA if the results are negative (Henneberger et al. 2011). In a Canadian study, more than half of the WEA (SIC negative) cases had serial PEF measurements that were more variable for work than for away from work (Chiry et al. 2007). Immunological tests and assessments of work-related changes in spirometry or metacholine responsiveness may be helpful in the diagnostics (Tarlo et al. 2008).

2.4.6 Asthma-like symptoms

Clinics investigating occupational asthma have often found that workers referred for suspected WRA turn out to have respiratory symptoms only, without asthma. In a Canadian study conducted in a clinic specialized in the field of WRA, 57.5% of the patients with work-related respiratory symptoms did not have asthma (Chiry et al. 2009). A high proportion of both those with work-related symptoms and WRA were employed in work environments with respiratory irritants such as dust, vapors, solvents, and welding fumes (Chiry et al. 2009). In a British study, the corresponding figure was 40.4% (Fishwick et al. 2007).

In addition to asthma, several recognizable causes of chronic lower respiratory symptoms, such as chronic obstructive pulmonary disease (COPD), infections, lung cancer, sarcoidosis, idiopathic pulmonary fibrosis, and heart failure, will be obvious after clinical examinations (Pavord and Chung 2008). Other common conditions to be considered are, for example, gastroesophageal reflux disease, medication with angiotensin-converting enzyme (ACE), chronic sinusitis or rhinitis, and postnasal drip syndrome (also called upper-airway cough syndrome) (Pavord and Chung 2008). A spectrum of clinical responses may occur after exposure to occupational and other environmental irritants and odors (Tarlo et al. 2008).

Vocal cord dysfunction (VCD) is one of the work-related laryngeal syndromes important in the differential diagnostics of asthma. VCD can be difficult to clinically differentiate from asthma, and the conditions co-exist. It has been reported that 33%–56% of patients have VCD accompanying asthma. The syndrome is characterized by paroxysms of glottic obstruction due to vocal cord adduction primarily during inspiration, resulting in symptoms like dyspnea, cough, and hoarseness. The diagnosis is confirmed with laryngoscopy, but it often remains unrecognized. A psychological origin for VCD has been established, but it may be also induced by, for example, gastroesophageal reflux disease, nonspecific airway irritants, chemicals, odors, and exercise (Morris and Christopher 2010). A recent review of work-related laryngeal syndromes highlights the fact that occupational exposures such as upper-airway irritants may be associated with the onset of symptoms of VCD (Hoy 2012). A broader term, work-associated irritable larynx syndrome, including VCD, dysphonia due to laryngeal muscular tension, globus, and chronic cough, has also been introduced (Hoy et al. 2010). The symptoms are often provoked by odors that would not usually be associated with asthma exacerbation, they usually start immediately on exposure, and they are not usually controlled by asthma medication, even at high doses (Hoy et al. 2010). People with this syndrome are more likely to be female (Hoy et al. 2010).

Exposures to irritants or odors can lead to asthma-like symptoms with cognitive complaints similar to those of multiple chemical sensitivity (MCS), also known as idiopathic environmental intolerance (Tarlo et al. 2008; Dalton and Jaen 2010). The symptom variety is broad and can

be divided into three groups, those affecting the central nervous system, those affecting the respiratory system, and those affecting the gastrointestinal system. The symptoms overlap with several symptom complexes, for example, the chronic fatigue syndrome, fibromyalgia, and also SBS (NICNAS and OCS 2008). The sufferers of MCS attribute it to exposure to low levels of a wide variety of environmental chemicals, which are well-tolerated by most of the population. The efforts for chemical avoidance limit their access to environments where such exposures may occur, such as grocery stores, libraries, community meetings, and offices (Gibson and Lindberg 2011). Therefore, it may be a difficult problem to manage in the workplace (Dalton and Jaen 2010). The available reports suggest that there is no typical dose–response reaction following exposure to triggering agents. No medical consensus exists on whether MCS symptoms are due to a psychological response to perceived chemical toxicity or to a physiological–pathological interaction between the chemical agents and organ systems. The most credible physiological mechanism is sensitization of the olfactory, limbic, mesolimbic, and related pathways in the central nervous system (NICNAS and OCS 2008). The prevalence in the general population varies between 0.2% and 4% in studies that have reported the prevalence of medically assessed MCS, whereas the prevalence range is 15%–36% in studies that have reported the prevalence of chemical sensitivity or reactions to chemicals. There are no international diagnostic criteria, even though several attempts have been made to establish diagnostic criteria for MCS (NICNAS and OCS 2008). The diagnosis is currently based on self-reported symptoms.

The term airway sensory hyper-reactivity has been used to describe patients with pronounced airway sensitivity to environmental irritants like odorous chemicals and scents, but without asthma or allergy, and who have increased sensitivity to inhaled capsaicin (Millqvist 2011). A suggested explanation for the condition is hyper-reactivity of the sensory nerves of the entire airways. It is regarded as a discrete entity from MCS and is reported to affect more than 6% of the adult population of Sweden (Millqvist 2011).

In some studies, lower respiratory symptoms, cough, wheezing, and dyspnea, as well as chest tightness in the absence of lung function disturbances compatible with asthma, have been called asthma-like inflammation and even pre-asthma (Haahtela 1999; Rytilä et al. 2008). Patients

suffering from this condition run a markedly increased risk of developing asthma (Puolijoki and Lahdensuo 1987; Remes et al. 1998). In particular, recurrent or persistent cough has been considered a harbinger of future asthma (Puolijoki and Lahdensuo 1987; Dicpinigaitis 2006).

2.4.7 Prevention of work-related asthma

OA is unique in that it is the only type of asthma that is readily preventable (Nicholson et al. 2005). In fact, as all WRA is potentially preventable, better prevention efforts are needed to diminish the burden of WRA worldwide (Tarlo et al. 2008). Prevention can be classified as primary, secondary, or tertiary. Primary prevention consists of reducing hazards before disease or damage has occurred, secondary prevention is aimed at preventing advanced disease by intervening early in the course of the disease (e.g., at a preclinical or very early stage), and tertiary prevention provides treatment for advanced disease (Tarlo et al. 2008).

The reduction or elimination of work exposures can be accomplished in several ways and can contribute to all levels of prevention (Henneberger et al. 2011). The actions include modifying, isolating, or enclosing the process to eliminate the asthma trigger or asthmogen, substituting a new agent for common causative ones, improving ventilation, educating workers about avoidance maneuvers, and finally, using respiratory personal protective devices (Tarlo et al. 2008; Henneberger et al. 2011). There is much evidence to indicate that exposure elimination is the strongest preventive approach to reducing the disease burden of WRA (Baur et al. 2012). Therefore it is the preferred primary prevention approach (Baur et al. 2012).

From the perspective of secondary prevention, the ERS Task Force recommends early recognition and diagnosis of WRA, as there is evidence that a shorter symptomatic period after diagnosis is associated with a better outcome (Baur et al. 2012). Medical surveillance at high-risk worksites plays an important role in secondary prevention by identifying cases early (Henneberger et al. 2011).

The guidelines for clinical practice recommend that further exposure to the cause be avoided as soon as OA has been diagnosed (Nicholson et al. 2005; Tarlo et al. 2008). A Cochrane Collaboration Review Group recently concluded that both the removal and reduction of exposure

reduces asthma symptoms significantly when compared with continued exposure (de Groene et al. 2011). Total removal from exposure led to the disappearance of asthma symptoms and job loss or an appreciable loss of income significantly more often than the reduction of exposure did (de Groene et al. 2011). Most data were available for low-molecular-weight agents, and the quality of the reviewed studies was considered low (de Groene et al. 2011). In addition, another systemic review found evidence that the reduction of exposure is associated with a less beneficial effect on asthma outcome than complete avoidance is (Vandenplas et al. 2011).

OA is usually a persistent disease once it has developed. A systematic review of 39 original publications with a median follow-up of 31 months suggested that only one-third of patients with OA recover completely from their asthma despite avoiding exposure to the initiating agent (Rachiotis et al. 2007).

While the best option for managing OA has been shown to be complete avoidance of exposure, it is recommended that the management of WEA focus on reducing work exposures and optimizing standard medical management. If these measures are not successful, a change of job may be an option (Henneberger et al. 2011).

According to the ERS Task Force, the pharmacological treatment of WRA should be adapted to the level of asthma control, in accordance with the general recommendations for asthma (Baur et al. 2012). One study found that regular treatment with inhaled corticosteroids seemed to prevent respiratory deterioration over a 3-year period among patients with OA still exposed to the work environment cause of their disease (Marabini et al. 2003).

2.4.8 Compensation practices for occupational asthma in Finland

In Finland, employers must insure their employees against work accidents and occupational diseases through the statutory accident insurance system (TVL 2011). Those self-employed often have voluntary insurance. The statutory accident insurance is defined by law and is operated by 13 private insurance companies, with the exception of insurance for farmers, which is provided by the Farmers' Social Insurance Institution and that for state employees, which falls under the sphere of the State Treasury.

Compensation for occupational diseases takes priority over other forms of social insurance (TVL 2011). Because the cost liability through the insurance belongs to the employer, it is regarded as an incentive for preventive activities enhancing occupational safety (Tola 2004).

According to the Occupational Diseases Act, an occupational disease is a disease that is probably primarily due to physical, chemical, or biological factors associated with work done during a period of employment, and it therefore must be compensated in accordance with accident insurance legislation (Ammattitautilaki 1988). The Occupational Diseases Ordinance gives a sample list of causative factors and typical forms of the diseases they may cause (Ammattitautiasetus 1988). In addition diseases not on the list can be compensated, as a general clause system is in use according to which any disease that can be proven to be due in all probability to work can be considered an occupational disease (TVL 2011).

The compensation benefits include medical examinations, costs of treatment, medical rehabilitation, inconvenience allowance and, in cases of work disability, vocational rehabilitation, and compensation for loss of earnings in connection with the disease (Tola 2004, TVL 2005). The costs of the medical examinations needed to establish the existence of an occupational disease are paid in full, even when the examinations do not prove the disease to be occupational. The examination must, however, be based on a suspicion of an occupational disease by a physician who knows the work conditions, and the employee must be exposed at work to an agent capable of causing the occupational disease in question. If the disease is accepted for compensation, the benefits are usually better than they would be for a non-occupational disease covered by general social security (Tola 2004). Medical treatment expenses (e.g., medicines and medical examinations) are compensated up to their full amount without one's own risk, and without a time or cost limit. Benefits for vocational rehabilitation are also good and the system facilitates rapid initiation of rehabilitation measures. A change of occupation may be supported with, for example, a work trial or retraining, during which full accident pension (or daily allowance, if not more than one year has passed since the disease occurred) is paid. When the worker transfers to another, more suitable job without harmful exposure, but with a lower salary, 85% of the difference is compensated. Only a 10% reduction in work capacity is required to get compensation for income loss due to an

occupational disease (compared with a requirement of at least a two-fifth reduction to get a partial disability pension due to a non-occupational disease). The pension for total disability is 85% of the former annual earnings of the worker, and 70% after the age of 65. In comparison, in general social insurance, the pension is usually no more than 60% of the former annual earnings. If the disease results in permanent functional impairment, an inconvenience allowance is paid. Various injuries and illnesses are grouped into 20 disability categories according to their seriousness. In categories 1–10, the allowance is a lump sum, and, in higher categories, the worker can choose between continuous and lump sum compensation (Tola 2004, TVL 2011).

In Finland, compensation benefits for OA are paid if a specific agent at work is the probable main causative factor of asthma. Proving causality means extended examinations, including exposure assessment and medical history. In practice, the relationship between the specific agent and asthma is usually identified by SIC testing or, sometimes alternatively, by demonstrating sensitization to a known sensitizer and serial PEF measurements (Nordman et al. 1999; Piipari and Keskinen 2005).

2.5 Recognition of occupational asthma induced by indoor dampness and mold

Estimates of work-related asthma, including OA, come from population-based studies. Another approach with which to obtain estimates of the incidence of OA is to use the existing national surveillance systems, which are based on reporting by physicians or data from compensation schemes, or a combination of these (Finland), or on self-reporting by individuals (Sweden). Great differences exist in the reported incidences between countries. The comparability of the reports is poor, as the reporting of data is influenced by diverse national legislation and compensation systems and no common definition of OA or classifications for occupations and causative agents have been used (Nordman et al. 1999).

Eurostat (the statistical office of the European Union) collects data on recognized cases of occupational diseases from national authorities in the European Union (European occupational diseases statistics). However, data are not yet available as a means for matching the quality criteria

for coverage and comparability (Eurostat 2011). The differences in the reporting level and national compensation practices have a remarkable impact in these data, and the figures observed are influenced not only by the real incidence of the diseases, but also by other factors (Karjalainen and Niederlaender 2004).

2.5.1 Occupational asthma induced by indoor dampness and mold in Finland

The coverage of the Finnish occupational reporting system is regarded as one of the most complete in the world, producing high incidence rates of OA, namely, 174 new cases per million workers yearly (years 1989–1995) (Karjalainen et al. 2000). The high incidence of reported OA in Finland is likely to be a consequence of comparatively good compensation levels (Karjalainen et al. 2000). Each new recognized or suspected case of an occupational disease is registered by the Finnish Register of Occupational Diseases (FROD), which is maintained by FIOH. The data come from the compensation system (the Federation of Accident Insurance Institutions and the Farmers' Social Insurance Institution). The OA cases are diagnosed and notified by central hospitals, as well as FIOH (Piipari and Keskinen 2005).

According to FROD, the most common causative agent for OA has been molds since 2001 (Piipari and Keskinen 2005). Until then, about half of the cases of OA were reported among farmers, the causative agents being animal epithelia, hair and secretions, or flours, grain and fodders (Karjalainen et al. 2000). The OA cases in farming decreased after Finland joined the European Union in 1995, when the number of active farms began to dramatically decrease (Piipari and Keskinen 2005). Figure 4 shows the annual numbers of OA induced by molds and the total number of OA cases in 1992–2010. From 1995 on, an increased number of OA cases caused by molds has been notified. The increased figures represent white-collar employees without exposure to traditional work-related sensitizing agents, but who work in moisture-damaged buildings (Piipari and Keskinen 2005). Due to changes in the data collection and principles regarding compensation (following the renewal of the Accident Insurance Act), the data for 2005–2010 should not be directly compared with earlier FROD data (Oksa et al. 2010;

Oksa et al. 2011). Therefore, trends cannot be reliably assessed for OA induced by molds. Due to the arrangements regarding changes in data collection, FROD did not register cases in 2003 and 2004.

The annual numbers of OA cases caused by molds have been higher since from 2005 than earlier, probably due to the aforementioned reasons. Earlier, the insurance companies only received OA notifications of verified cases from hospital pulmonary clinics. Since 2005, the hospitals have been able to invoice the insurance companies for the costs of medical examinations (Lehtinen and Rahkonen 2004), and this change in procedure has probably increased the activity of notifying cases, including suspected ones. In recent years, the quality of the data coming to FROD has improved and therefore has allowed a better classification of the cases (Oksa et al. 2011). As a result, some of the cases that had earlier been classified in the group ”others” have been classified as OA in recent statistics (Oksa et al. 2011). This development explains the substantial rise in OA cases in 2009, which is reflected in both the total and mold-caused figures (Oksa et al. 2011).

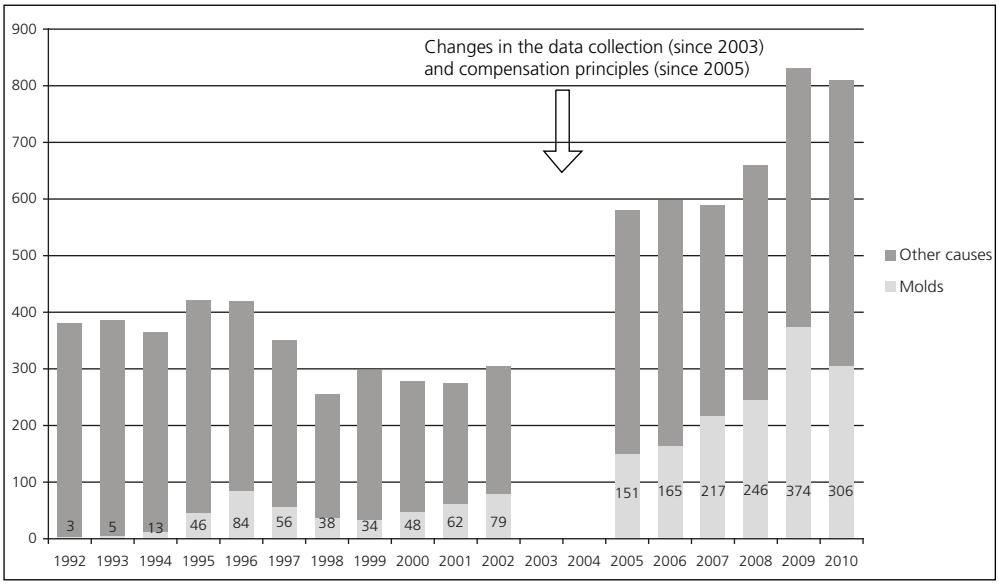


Figure 4. The recognized and suspected cases of occupational asthma caused by molds listed in the Finnish Register of Occupational Diseases (FROD) in 1992–2010. The figures for the years 2003–2004 are not available. The data for 2005–2010 should not be directly compared with earlier FROD data (Source: FROD).

In 2008–2010, FROD published the number of cases approved for compensation by the insurance companies. Of all suspected OA cases, 105 (16%) were compensated in 2008 (Oksa et al. 2010), 150 (18%) in 2009 (Oksa et al. 2011), and 102 (13%) in 2010 (Oksa et al. 2012). Of the cases suspected of being caused by molds, 40 (16%) were compensated in 2008, 73 (20%) in 2009, and 27 (9%) in 2010 (source: FROD; unpublished data). It can be calculated that, in 2008, 38% of all the compensated OA cases were caused by exposure to molds, the corresponding figures being 49% for 2009 and 26% for 2010.

2.5.2 Occupational asthma induced by indoor dampness and mold in other countries

From a clinical case series of occupational health clinics in New York State, poor indoor-air quality or molds were suggested as causative agents in over one-fifth of the cases of new-onset OA (Fletcher et al. 2006). The material comprised altogether 214 cases in 1988–1999 in an area with 8.4 million employed adults. The diagnosis of OA was based on a health-care professional's diagnosis of asthma and an association between symptoms of asthma and work, and, in addition, either workplace exposure to an agent or process previously associated with asthma or objectively verified work-related changes in lung function or airway responsiveness (Matte et al. 1990).

The data from the Sentinel Event Notification System for Occupational Risks (SENSOR) Program from four states in the United States – California, Massachusetts, Michigan, and New Jersey – indicated that, in a list of the 10 most frequently reported agents associated with new-onset OA and RADS in 1993–2003, indoor pollutants were on top, with 1047 cases (Bernstein et al. 2006c). In the four SENSOR states, the educational services industry was the third most frequently reported industry associated with WRA in 1993–2000 (Mazurek et al. 2008). New-onset OA was diagnosed for 182 persons, caused by indoor-air pollutants in 64 cases and by molds in 32 cases (Mazurek et al. 2008). The cases were ascertained using the same criteria as described earlier. Workers' compensation claim data were not used. The objectives of the SENSOR Program are to identify potentially harmful sentinel cases in various occupational settings, and, consequently, to initiate investigations

and implement preventive interventions in such workplaces, and not primarily to estimate disease frequency (Matte et al. 1990).

In Quebec, Canada, the diagnostics resemble those of Finland in that OA diagnoses are ascertained with a high degree of probability, often with an SIC test (Piipari and Keskinen 2005; Bernstein et al. 2006c). Molds were not among the recognized causative agents of compensated OA in Quebec in 1988–2002 (Bernstein et al. 2006c).

In a Belgian survey, new-onset cases of OA were gathered by voluntary reporting from pulmonary and occupational specialists during a period of three years (2000–2002) (Vandenplas et al. 2005). Seven cases of a total of 260 were reported to be caused by molds, but the source of the molds was not described (Vandenplas et al. 2005). The "Observatoire National des Asthmes Professionnels" (ONAP) program in France is a monitoring system for OA that is based on voluntary reporting of occupational and chest physicians, who reported 24 cases of OA suspected to be induced by molds, of a total of 2359 cases in 1996–1999 (Ameille et al. 2003). Likewise, as in the Belgian report, there was no indication of building-relatedness to mold (Ameille et al. 2003).

The data on OA frequency from national surveillance schemes of other European countries, found in a literature search, indicate that indoor-air factors or mold are not among the most frequently reported causative agents of OA (Leira et al. 2005; McDonald et al. 2005; Orriols et al. 2006; Paris et al. 2012). Statistics on occupational diseases in Norway are based on physicians' notifications to the Labour Inspection Authority, obliged by law, and 1508 cases of OA in 1995–1999 were reported (Leira et al. 2005). In the United Kingdom, the Surveillance of Work-Related and Occupational Respiratory Disease (SWORD) scheme receives reports on new occupational lung diseases from specialists in occupational or respiratory medicine all over the country, and, for 1992–2001, the result was an annual average number of cases of OA cases of 604 (McDonald et al. 2005). From Catalonia, Spain, a total of 174 cases of OA were reported during one year (2002) by the voluntary reporting of occupational and chest physicians and other specialists (Orriols et al. 2006). The French national network of occupational health surveillance and prevention (comprising 32 occupational health departments located in university hospitals) reported 2914 cases of WRA in 2001–2009, with no differentiation between OA and WEA (Paris et al.

2012). None of the aforementioned reports referred to molds or other indoor-air factors (Leira et al. 2005; McDonald et al. 2005; Orriols et al. 2006; Paris et al. 2012).

2.6 Symptom persistence after exposure to building dampness and mold

According to clinical experiences, non-specific, building-related symptoms usually improve or disappear when people are away from the building, but long-lasting symptoms appear to be common for some people (Edvardsson et al. 2008; Al-Ahmad et al. 2010). There are otherwise no known long-term adverse health effects. However, little has been published about the long-term health effects of exposure to building dampness and mold. The same facts that hamper the gathering of evidence on health effects in general also hamper the gathering of evidence on long-term health effects, for example, difficulties in defining exposure, the non-specific nature of symptoms that overlap other conditions, and also the lack of objective biomarkers that show a relation between symptoms and indoor exposures. In a Swedish study, long-lasting, building-related symptoms were found 1–13 years after the diagnosis (Edvardsson et al. 2008). The researchers followed a total of 189 patients, 92% of whom were female and who had been examined at an occupational and environmental clinic because of building-related symptoms. Almost half of the patients had been exposed to environments with visible water damage, and the rest to environments with other indoor-air quality problems. Nearly half of the patients claimed that their symptoms were unchanged after 7 years or more, despite actions taken at the workplace. The symptoms were often aggravated by different situations in everyday life, such as visiting a shop or using public transportation. One-fifth of the patients were on disability pension due to persistent symptoms. On the basis of their findings, the authors concluded that a subgroup of patients who are clinically diagnosed as having a non-specific building-related illness had long-lasting symptoms that had a significant impact on their social life (Edvardsson et al. 2008).

A Canadian group followed a total of 32 adult patients seen in Toronto Western Hospital asthma, allergy, or occupational lung disease

clinics (Al-Ahmad et al. 2010). The patients had asthma or asthma-like symptoms attributed to exposures to mold, including *S. chartarum*, 88% of them having symptoms at work. Seventeen patients, six of whom had previous asthma, returned questionnaires after a mean follow-up of 3.1 (SD 0.5) years. The symptom spectrum was compared with symptoms of a patient group previously assessed for "darkroom disease" (sick building type symptoms). Among the mold-exposed group, persisting asthma-like symptoms and non-specific symptoms were frequent. The researchers concluded that at least a subgroup of mold-exposed persons had long-term respiratory symptoms that cannot be explained on the basis of asthma. Non-specific symptoms attributed to mold exposure appear to represent findings similar to SBS, but are persist despite removal from or remediation of mold exposure (Al-Ahmad et al. 2010).

Some knowledge on long-term health effects is available from intervention studies, which study the effectiveness of remediating buildings damaged by dampness and molds in order to reduce or prevent symptoms. The studies vary with respect to their study designs and have differing outcome measures, and both the persistence and alleviation of symptoms after building repairs have been reported. A Cochrane Collaboration Review Group found very low-quality evidence that repairing moisture-damaged houses and offices decreases asthma-related symptoms and respiratory infections when compared with no intervention among adults, as well as very low-quality evidence that repairing schools did not significantly change the respiratory symptoms among the staff (Sauni et al. 2011).

A study by Rudblad et al. (2002) suggested that nasal hyperreactivity due to moisture damage may persist and only slowly decrease for years. After a 2-year follow-up, nasal mucosal hyper-reactivity to histamine was still higher among teachers in a renovated moisture damage school than among teachers in a control school. The difference between the groups was smaller than at the baseline (Rudblad et al. 2002).

Respiratory symptoms may also persist despite building repairs. One year after remediation among 56 teachers of three moisture-damaged schools, fatigue and headache were significantly reduced but respiratory symptoms did not improve (Patovirta 2004a). In another study by the same authors, a 3-year follow-up after building repairs was conducted

among 27 teachers in a moisture-damaged school and among 12 teachers in a non-damaged control school. No decrease in respiratory symptoms was detected in either school during the follow-up (Patovirta et al. 2004b). With a same type of study design (controlled before–after), Åhman et al. (2000) found a post-intervention disappearance of excess symptoms after 7 months among 44 teachers who were compared with 29 teachers in a control school.

A 3-year follow-up of a 97-person cohort in a water-damaged office building found that substantial remediation did not result in an overall improvement of respiratory health, as reflected by symptom scores, overall medication use, spirometry abnormalities, or sick leave (Iossifova et al. 2011).

Haverinen-Shaughnessy et al. (2008) reported seven case studies of buildings that underwent moisture and mold damage remediation in order to develop methodology for assessing the success of the remediation process. Health effects studies (based on self-reported health status) after 6–12 months of follow-up showed improvement in one case (after moving to another building), partial improvement in two cases, and no improvement in two cases, even though the remediation was considered technically successful. No follow-up was conducted in one case, and in one case, the follow-up failed due to a low response rate. The authors hypothesized that the reason for the persistence of symptoms could be that the remediation was only partially successful and, in one case, that the extended duration of the remediation process could have created additional stress among the occupants and therefore affected perceived health (Haverinen-Shaughnessy et al. 2008).

Jarvis and Morey (2001) did not find improvements in respiratory symptoms 4 months after occupants of a large office building were relocated to a dry building. Four years later, before the re-occupation of the remediated building, the respiratory symptom prevalences had decreased when compared with the prevalences before the relocation, but they were still double when compared with those of the comparison population (Jarvis and Morey 2001).

2.7 Concepts for evaluating health and well-being in this thesis

2.7.1 Illness and disease

By simplifying, patients suffer illnesses while physicians diagnose and treat diseases. Disease is a pathological process or a combination of pathological abnormalities that, at least in theory, is amenable to objective external verification (Coggon 2005). Illness is a subjective state, an absence of well-being. Commonly diseases make a person feel ill. On the other hand, disease may not have an impact on well-being, or a person may feel ill in the absence of any objective evidence of underlying disease (Coggon 2005).

According to a WHO expert committee (1985), work and health interact in many ways. Work often plays a role in promoting both physical and mental health. Physical, chemical, and biological occupational hazards, if they exceed tolerable limits, are recognized causative factors of occupational diseases. There is a direct cause-and-effect relationship between hazard and disease in occupational diseases. The relationship to specific causative factors at work can be established, and the factors concerned can be identified, measured, and eventually controlled (WHO 1985). Occupational diseases differ from one country to another, as they are defined according to national legislation.

The work environment can play a role, together with other risk factors, in the development of diseases with a complex multiple etiology (WHO 1985). Such diseases can be called work-related. In addition to the fact that work-related diseases can be partially caused by work, they may also be aggravated, accelerated, or exacerbated by workplace exposures, and they may impair work capacity. Personal characteristics and other environmental and sociocultural factors usually play a role as risk factors for these diseases. Work-related diseases are much more common than occupational diseases (WHO 1985).

2.7.2 Disability

According to WHO (2001), when an individual experiences a decrement in health, he or she thereby experiences some degree of disability.

The International Classification of Functioning, Disability and Health (ICF) of WHO provides a framework for the description of health and health-related states and disability (WHO 2001). The ICF is based on the biopsychosocial model of disability into which medical and social models of disability have been integrated (WHO 2001). The medical model of disability views disability as a feature of a person, directly caused by disease, trauma, or other health condition, that requires medical or other treatment or the elimination of the pathological cause, to "correct" the problem with the individual. The social model sees disability as a socially created problem and not at all as an attribute of an individual. The perspective of both models is too narrow alone to define the complex phenomenon of disability.

The ICF views disability and functioning as outcomes of interactions between health conditions and contextual (environmental and personal) factors (Figure 5). In the ICF, the term functioning refers to all body functions (physiological, including psychological functions), activities, and participation, while disability is similarly an umbrella term for impairments (problems in body function or structure), activity limitations, and participation restrictions (WHO 2001).

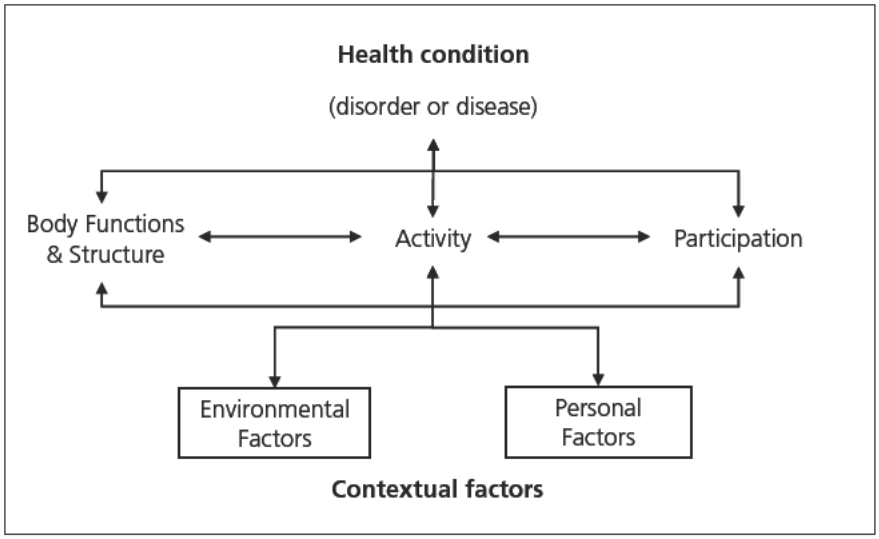


Figure 5. The WHO model of disability (WHO 2001).

According to the ICF, disability involves dysfunctioning in one or more of three domains (impairments, activity limitations, and restricted participation). In clinical terms, impairment in asthma refers to a decrement in lung function below an expected norm, determined through physiological testing. There are multiple approaches to the physiological testing of lung function, both at rest and in exercise, the most conventional of which are spirometry and airway hyper-responsiveness (Bernstein et al. 2006c). The impairment in lung function may have only minor adverse consequences for a person when asthma is controlled with appropriate treatment (GINA 2011). Medication use and symptom severity are clinical measures that provide information for asthma control. Activity limitations in asthma are difficulties in executing such activities as climbing stairs, hurrying, or carrying or moving objects. Participation restrictions are problems a person may experience in involvement in life situations, which, in asthma, could mean restrictions involving household cleaning, hobbies, or visiting friends or restrictions in the performance of work tasks. Disability does not mean a total loss of functioning in any of the three domains, but is a continuum.

Chronic diseases produce symptoms of varying severity and affect patients' assessments of their health status. Traditional methods of assessing health through physiological and clinical practice do not provide insight into a person's well-being. There is evidence showing that correlations between clinical measures and how people are able to function in daily activities are only weak to moderate (Juniper 1999).

2.7.3 Quality of life

Quality of life (QOL) has emerged as an important outcome in health research. It is used to describe the function and well-being of populations with medical conditions (epidemiological perspective) and as an outcome criterion for treatment interventions (clinical perspective) (Heinonen et al. 2004).

The term QOL is intuitively familiar, but it is often vaguely used without conceptual clarity. In the medical literature, investigators frequently use QOL as an interchangeable term for health status (McDowell 2006), although there is criticism that one should not do so because the constructs are distinct (Smith et al. 1999). The term health-related QOL

is often used. It originated to distinguish outcomes relevant to health research from earlier sociological research on subjective well-being and life satisfaction in general populations (Smith et al. 1999). Health-related QOL is meant to capture the experience of health and disease from the viewpoint of the individual (Blanc 2004).

A starting point for defining QOL in health research is the WHO classic definition of health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity" (WHO 1948). Therefore, many of the QOL scales cover at least the physical, emotional, and social dimensions of health. Furthermore, as with the WHO classification of disability and health, the ICF stresses functioning alongside of health (WHO 2001); also components related to functional health status have become apparent in QOL assessment. As a consequence, QOL is generally recognized as a multi-dimensional construct including the following four broad dimensions: physical well-being, functional well-being, mental or emotional well-being, and social well-being (Heinonen et al. 2004).

There is a range of instruments for measuring QOL, as different scales have been developed for different purposes. In health research, QOL measures are divided into two main types, condition or disease-specific, and generic (Juniper 1999).

The specific instruments may be specific for a group of patients (e.g., the elderly), a particular function (e.g., pain, sexual function), or a disease (Juniper 1999). Asthma-specific instruments measure the problems and limitations that patients with asthma experience in their everyday lives (Juniper 1999). Examples of asthma-specific instruments are the Asthma Quality of Life Questionnaire (AQLQ) (Juniper et al. 1993) and the Marks Asthma Quality of Life Questionnaire (Marks et al. 1992).

The strength of generic instruments is their ability to be used for comparing the health status of patients with different conditions. They are also useful for monitoring patients with multiple conditions and for comparing patients with the general population (McDowell 2006). Among the most commonly used and the best validated generic instruments are the Medical Outcomes Survey Short Form 36 (SF-36 or RAND-36) (Ware and Sherbourne 1992; Hays et al. 1993), the Nottingham Health Profile (NHP) (Hunt et al. 1981), and the Sickness Impact Profile (SIP) (Bergner et al. 1981). Shorter versions of some of

these original instruments are available, for example, the Short Form Health Survey-12 Questionnaire (SF-12) (Ware et al. 1996).

In addition, there are QOL instruments that are classified as global (or general) on the basis of a single item. The Visual Analogue Scale (VAS) is an example of a global instrument in which patients indicate their QOL on a line from 0 to 100 while considering an overall view of the QOL (de Boer et al. 2004). A global measure is simple and easy to use, but too rough for certain purposes, for example, for comparing treatments. Therefore, a single-item measure is often accompanied by multi-item questionnaires (de Boer et al. 2004).

Others types of QOL instruments, valuable in health economics, are utility-based measurements allowing cost-utility analyses in health care, often used for estimating quality-adjusted life years (QALYs) (Räsänen et al. 2006).

Finally, QOL is defined by WHO as ”individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (WHO 1995). The WHO definition highlights the view that QOL is subjective, includes both positive and negative facets of life, and is multi-dimensional (WHO 1995).

2.7.4 Work ability and work disability

In the Western world, work disability has become a major public health and economic concern. Work disability is usually defined as time off work, reduced productivity, or working with functional limitations as a result of either traumatic or non-traumatic clinical conditions (Schultz et al. 2007).

The concept work ability concentrates on “something that exists” (Gould et al. 2008), whereas (work) disability is explained as “something that restricts or limits” (Martimo 2010). Work ability is not necessarily dependent on health, although health is considered one of the most important work ability determinants (Gould et al. 2008). According to definitions, work ability can be related to a deterioration in health or to other resources of the worker, to factors related to work and the work-place, or even to the environment outside work (Ilmarinen and Tuomi 2004; van den Berg et al. 2009). Ilmarinen (2006) has illustrated the

dimensions of work ability in the form of a work ability house (Figure 6). The first three floors, the resources of the individual, form the core structures of the house. The fourth floor is that of work. In the immediate surroundings of the work ability house are the family and close community, and the outermost layer is society. The term work ability has often been used in the context of promoting or maintaining work performance. Different indicators of work ability have been developed with the aim of detecting deteriorating work ability as early as possible in order to prevent work disability (Gould et al. 2008). Work ability studies use outcomes like self-rated work ability, work ability index, or early retirement plans.

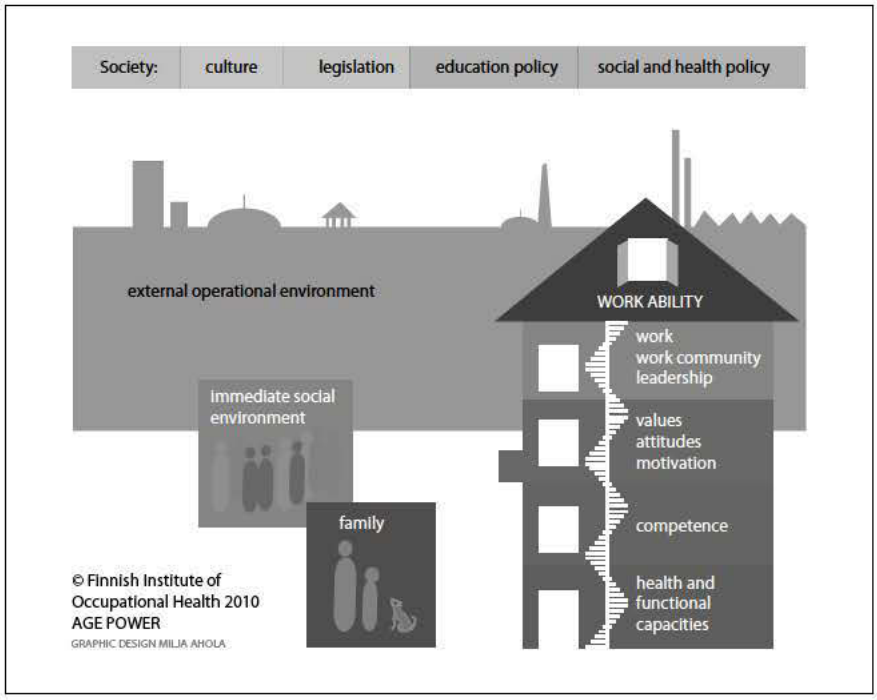


Figure 6. Dimensions of work ability from the point of view of human resources, work, and the environment. The diagram is based on Ilmarinen's (2006) Work Ability House Model (Lundell et al. 2011).

3 AIMS OF THE STUDY

This thesis is based on four studies. The aim of each study below is followed by a rationale that includes the hypothesis that was tested.

1. **To assess and develop methods for the diagnostics of occupational asthma (OA) induced by workplace dampness and mold (study I).**

The hypothesis of the study was that molds, as known sensitizers, induce new-onset adult asthma in people who work in damp and moldy environments. When the study was being planned, there was only limited epidemiological evidence of an association between exposure to indoor dampness and mold and new-onset asthma.

2. **To assess whether prolonged asthma-like symptoms appearing in relation to workplace dampness and mold lead later to the development of asthma (study II).**

The hypothesis of the study was that workers who display prolonged symptoms suggestive of asthma, but whose lung function is normal, may later run an increased risk of developing clinical asthma. And if so, to study whether continued exposure to workplace dampness has an impact on the development of asthma.

3. **To evaluate long-term effects on the quality of life of workers with asthma related to damp indoor work environments (study III).**

Based on clinical experience, the hypothesis was that asthma related to damp and moldy workplaces is persistent, and patients experience substantially deteriorated health and well-being.

4. **To evaluate long-term effects on work ability and related factors of workers with asthma in damp indoor work environments (study IV).**

The hypothesis was that workers with asthma related to damp indoor work environments commonly have long-term work disability, along with persistent symptoms. In particular, the aim was to study whether OA leads to impaired work ability and whether persistent indoor-air symptoms or social factors at work have an impact on work ability.

4 MATERIALS AND METHODS

4.1 Description of the source population

The basis for the studies was the 2200 workers who had been referred to the Finnish Institute of Occupational Health (FIOH) in the period 1995–2004 because of a suspicion of an occupational respiratory disease (Figure 7). All of them had work-related respiratory symptoms appearing in workplaces with suspected moisture and mold damage. The symptoms consisted of upper- or lower-airway symptoms, or both. The workers had been referred to FIOH from all over Finland, mainly by occupational health physicians or pulmonologists.

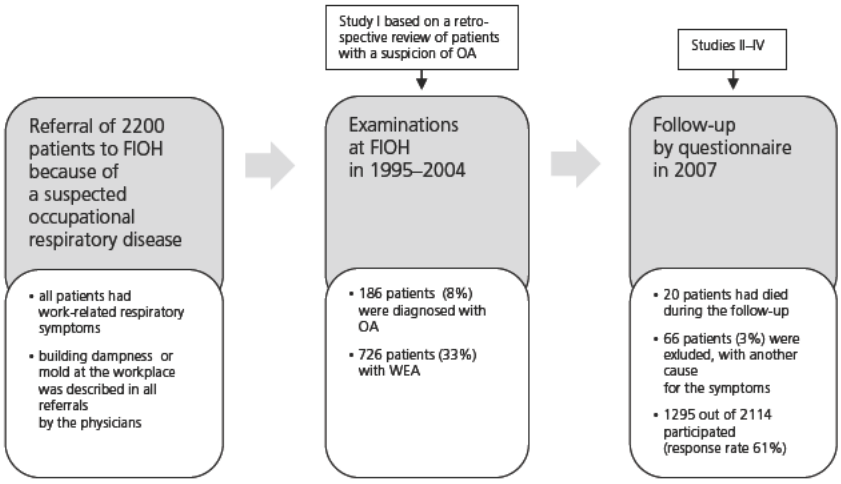


Figure 7. The patient material.

The FIOH examinations had included exposure assessments, detailed occupational and medical histories, and advanced clinical examinations.

For the evaluation of the workplace conditions, reports on technical inspections, quality measurements of the indoor air, and structural measurements of the workplace had been requested from the workplace. In addition, the work environments had been described in the referrals by the physicians, and the information had been corroborated in interviews with the patients.

The medical history of the patients had been taken to assess the symptoms. The work-relatedness of the symptoms had been investigated by asking the patient if the symptoms appeared or worsened at work or improved away from work. The medical records of previous examinations had been acquired.

The patients who had complained of work-related symptoms compatible with asthma (cough, dyspnea, wheezing) had been clinically assessed with respect to possible OA. The investigations had included the assessment of specific sensitization to moisture-damage microbes, lung function tests, histamine challenge tests, serial recordings of peak expiratory flow (PEF), and specific inhalation challenge (SIC) tests with commercially available mold extracts. The possibility for other diseases, like allergies, chronic sinusitis, or chronic obstructive pulmonary disease (COPD), had been assessed.

In the beginning of 2007 (3–12 years after the initial examinations), the patients were followed up with the use of a questionnaire. Those with a definitive other-than-building-related cause for their symptoms (66 patients) were not included in the follow-up. In addition, 20 patients had died during the follow-up. Altogether 1295 of the 2114 persons participated (61%) (Figure 7).

The non-respondent analysis showed that compared with the non-respondents, the participants were older [mean age 54.3 (SD 9.2) years versus 52.0 (SD 9.5) years], more often female (87% versus 84%), and more often diagnosed with OA (10% versus 6%). The frequency of WEA at baseline was similar for the participants and the non-respondents.

4.2 Study population

Retrospective review of the patients (study I). In study I, a retrospective review was conducted of the patients who were suspected of having OA caused by workplace dampness and molds. In the period 1995–2004, SIC was a routine procedure used to demonstrate an association between asthma and indoor molds. Therefore the patients were selected for the analysis from the 694 patients for whom SIC had been carried out. Informed consent to review patient files was obtained from 676 patients. For 425 (63%) of them, acceptable serial PEF records were available.

The 676 patients were placed into three categories according to the probability of OA. The discharge diagnosis given to the patient by FIOH was not considered. Instead, the patient files were reviewed clinical data, and the diagnostic criteria presented in Table 4 were used. The criteria were consistent with the international diagnostic criteria for OA (Fishwick et al. 2008). Thus 156, 45, and 475 patients were categorized as

Table 4. Criteria used for allocating patients into different categories according to the probability of occupational asthma (OA).

	Probable	Possible	Unlikely
Exposure to indoor-air molds at work	Yes	Yes	Yes
Work-related asthma symptoms	Yes	Yes	Yes
Onset of symptoms or asthma temporarily associated with work in a moisture-damaged environment	Yes	Yes	Yes
Asthma diagnosed	Yes	Yes	Yes or asthma-like symptoms only
Serial PEF measurements at and away from work and a specific inhalation challenge (SIC) test	PEF measurements compatible with OA and/or positive SIC	PEF measurements suggestive of OA and negative SIC	PEF measurements inconsistent with OA (or not performed) and negative SIC

having probable, possible, or unlikely mold-induced OA, respectively. The clinical details of the 201 patients with probable or possible OA and those of a sample of patients (57 of 475) unlikely to have OA were reviewed. The sample was randomly selected from those for whom an acceptable serial PEF record was available. In all, particulars of 258 patients were reviewed.

For study I, the patient files concerning the follow-up visit 6 months after the baseline examinations were also reviewed. Of the patients categorized as having probable mold-induced asthma, most (136 of 156) had participated in the follow-up examinations.

Follow-up questionnaire studies (II–IV). Studies II–IV were based on the follow-up questionnaire in 2007, 3–12 years after the baseline examinations (Figure 7). The design of studies II–IV was cross-sectional.

In study II, the study group was comprised of 483 respondents who fulfilled the following inclusion criteria: 1) work-related asthma-like symptoms (cough, dyspnea, wheezing) without objective evidence of asthma in the initial examinations, 2) exposure to indoor dampness or molds or both at work before the initial examinations, 3) absence of indoor dampness at home (as reported by the patients in the initial examinations), and 4) asthma having never been diagnosed earlier. "Work-related symptoms" signified symptoms repeatedly appearing or worsening at work or improving away from work. Patients whose asthma had been diagnosed prior to the investigations at FIOH were likewise excluded. The absence of clinical asthma was ascertained from the medical records of all the patients finally included in the study group.

In studies III and IV, the 28 respondents were first excluded who were diagnosed with alveolitis in the baseline examinations. Thereafter, the study population in study III consisted of 1267 respondents. In study IV, to examine work limitation among the persons of a typical working age, the analyses were restricted to the respondents who were under 65 years of age. Thus the study population in study IV consisted of 1098 respondents.

4.3 Exposure assessment (study I)

In study I, an experienced indoor-air researcher made a retrospective evaluation of each patient's exposure at work by classifying the intensity of microbial exposure on the basis of the available information in the patient case records. The documents usually included reports on damage to the building structure and, in most instances, microbial measurements. The moisture damage and microbial growth had been described by indoor-air researchers with a background in construction engineering and occupational safety or health service personnel. In most cases, material samples had been analyzed for the presence of microbes, which had been identified. In addition, air samples had been taken for the measurement of microbial air concentrations with six-stage impactors. In the assessment of microbial exposure, only winter measurements were considered in the study, as fungal concentrations in outdoor air in the winter are very low in subarctic countries like Finland. The personal exposure was classified into the following four categories of exposure to microbes: low, intermediate, high and not classifiable (Table 5).

The exposure time was calculated on the basis of the first date of employment in a moisture-damaged building, the time the water damage occurred, whenever known, or the date when moisture damage had been first reported. The duration of exposure was estimated as <1 year, 1–5 years, 6–9 years, and ≥10 years.

Table 5. Classification of personal exposure to microbes.

Classification	Definition
Low	An adequate and reliable description of mold damage was available. Single, small mold damage of < 0.5 m^2 was found in the patient's workspace, or limited mold damage (< 1 m^2) was detected in the patient's work environment near the permanent workspace.
Intermediate	An adequate and reliable description was available of the mold damage, the damaged areas were limited in number and size (< 1 m^2), and the total viable concentrations were <100 cfu/m^3 for airborne fungi and <10 cfu/m^3 for actinobacteria. Fungal species requiring high water activity were not dominant in the environmental samples.
High	An adequate and reliable description of the extent of microbial growth (>1 m^2) was reported, or the total viable concentrations of airborne fungi were > 100 cfu/m^3, or the level of airborne actinobacteria was > 10 cfu/m^3, or fungal species requiring high water activity were dominant in the environmental samples. This category usually included extended moisture and mold damage, for example, in the base floor.
Not classifiable	The evidence of exposure to microbes was inadequate or unreliable. Investigations of moisture and mold damage or indoor air measurements had not been undertaken or were not available in the patient files, or the exposure data were not associated with the patient's work area.

4.4 Clinical examinations (study I)

Assessment of sensitization. To assess sensitization to molds, skin prick tests (SPTs) and measurements of specific serum immunoglobulin (Ig) E had been carried out using methods reported previously (Ceska and Lundkvist 1972; EAACI 1989).

The SPTs had been carried out with combinations of 29 different commercially available mold allergens (ALK-Abelló A/S, Copenhagen, Denmark) with histamine hydrochloride (10 mg/mL) as a positive control. A positive reaction indicating sensitization was defined as a weal diameter of ≥3 mm that was equal to or greater than half of that of the histamine reaction. Mold-specific serum IgE antibodies had been determined for the same mold species, if available, using Pharmacia CAP system RAST RIA (Pharmacia, Uppsala, Sweden) until 1996; thereafter the UniCAP system (Pharmacia & Upjohn, Uppsala, Sweden) was introduced and used. Specific IgE values of >0.35 kU/L were defined as positive.

Sensitization to common environmental allergens had been tested by SPT with the following allergens (ALK-Abelló A/S, Copenhagen, Denmark): pollens of birch, alder, timothy, meadow foxtail, mugwort and dandelion; epithelia of horse, dog, cat and cow; dust mites *(Dermatophagoides farinae, Dermatophagoides pteronyssinus)*; and molds *A. alternata* and *Cladosporium herbarum*. Atopy was defined as the patient having had at least one positive SPT reaction.

For the purpose of study I, atopic history was defined as the patient having had infantile eczema, atopic dermatitis, hay fever, non-occupational allergic rhinitis, or allergic asthma.

Lung function measurements. Flow-volume spirometry had been carried out at FIOH with a pneumotachograph spirometer connected to a microcomputer (Medikro 909 or Medikro 904; Medikro Ltd, Kuopio, Finland). Spirometry had been performed according to guidelines of the European Respiratory Society (Quanjer et al. 1993). The bronchodilator test had been carried out with either rimiterol hydrobromide or (from 1997) salbutamol sulfate. An increase of 15% or 200 mL in the forced expiratory volume in 1 s (FEV1) and an increase of 33%, or at least 0.4 L/s, in maximum mid-expiratory flow were regarded as significant. The histamine challenge testing had been performed according to the method

described by Sovijärvi et al. (1993). The provocative dose of inhaled histamine aerosol causing a 15% fall in FEV1 (PD15) was measured. The hyper-responsiveness was graded as strong (PD15 <0.10 mg), moderate (PD15 0.11–0.40 mg), or mild (PD15 0.41–1.6 mg). The single breath diffusion capacity for carbon monoxide and specific diffusion capacity had been measured by a Masterlab Transfer or a Compact Lab Transfer device using Finnish reference values (Viljanen et al. 1982).

Serial PEF monitoring. Serial PEF monitoring at and away from work had been carried out according to Burge (1993). PEF graphs had been drawn, and the diurnal variations had been calculated (the daily maximum minus the daily minimum divided by their mean), the interpretation of the PEF values being based on direct visual analysis and supported by the percentage decreases in PEF. When the patients were allocated into the diagnostic categories of probability, the following principles were adopted: 1) PEF record compatible with OA = ≥20% diurnal variation on at least two workdays and relatively more often on workdays than on non-workdays (Liss and Tarlo 1991; Tarlo et al. 2008); 2) PEF record suggestive of OA = no diurnal variations exceeding 20% but the lowest recordings on workdays, or a ≥20% change longitudinally across workdays with decreasing values towards the end of the work period; 3) PEF record not compatible with OA = <20% diurnal variation with no marked difference between the workdays and non-workdays; 4) PEF record indicating asthma lability = ≥20% diurnal variation both at and away from work.

SIC tests. The challenge tests had been carried out according to international guidelines (Cartier et al. 1989; EAACI 1992). Commercial freeze-dried allergen extracts of *A. fumigatus, Acremonium kiliense*, and *Cladosporium cladosporioides* (for a few tests *C. herbarum*) had been used (ALK-Abelló). They had been the only mold extracts commercially available for bronchial inhalation tests during the study period. The mold species used for the SIC tests had been selected primarily among the species identified in the microbial samples from the workplace. If none of the available species had been identified, the testing had been started with *A. fumigatus* extract. During the 1990s, an increased serum level of IgG antibodies to molds had been used for selecting fungal allergens for the SIC. At the time, IgG antibodies had been considered a proxy

for exposure. Allergen extracts diluted with ALK solvent (ALK-Abelló) had been inhaled with the use of an inspiratory synchronized dosimetric device (Spira Electro 2; Spira Respiratory Care Center Ltd, Hämeenlinna, Finland) with the following settings: driving pressure 0.2 kPa (2 bars), inhalation time 0.8 s, starting volume 50 mL, inspiratory flow 0.5±0.1 L/s, and amount of allergen mixture 0.8–1.0 mL. The used starting allergen dilution had been 1:10 000–1:1000 weight/volume (wt/vol) depending on the severity of the patient's symptoms and the strength of the sensitization. The allergen dose had been increased 5- to 10-fold every 15 minutes if the patient did not react to the previous dose, until the dilution of 1:5 wt/vol had been achieved. The control tests had been carried out with the pure diluent.

After the challenge, the FEV1 and PEF values had been followed using a pocket-size spirometer (One Flow; STI Medical, St Romans, France) for 24 hours according to a protocol described previously (Keskinen et al. 1996). A decrease in FEV1 or PEF of ≥15% from the pre-challenge value during the first hour after the challenge was regarded as a significant immediate reaction. The criterion for a late reaction was a drop of ≥20% after more than 1 h after the challenge. A combination of these reaction types was considered a dual reaction. A prerequisite for a positive test was the absence of a significant reaction (≥10%) to a control SIC test with the pure diluent. The axillary temperature had been routinely followed 1 h and 4 h after the SIC, once in the evening and once the next morning.

4.5 Diagnostic criteria of asthma (studies I and II)

The diagnostic criteria used for asthma were 1) significant improvement (≥15% and at least 200 mL) in the FEV1 or forced vital capacity (FVC) in response to short-acting bronchodilating medication in a bronchodilator test or 2) a repeated daily variation of ≥20% or improvement of ≥15% (and at least 60 L/min) in response to short-acting bronchodilating medication in a 2-week diurnal PEF follow-up.

4.6 Questionnaire (studies II–IV)

Asthma development during the follow-up (study II). The development of new-onset asthma during the follow-up period was established by the question "Have you been diagnosed with asthma by a physician after the examinations at FIOH?"

In order to validate the self-reported asthma diagnoses of the questionnaire study, all those who had reported having received a physician's diagnosis of asthma were contacted. The patients were interviewed by phone and asked for written consent to study their clinical files, which were acquired from respective hospitals and physicians. The same aforementioned diagnostic criteria for asthma (Section 4.5) were used in the assessment of the medical records.

Quality of life (study III). For health-related QOL, the validated Short Form Health Survey-12 Questionnaire (SF-12) (Ware et al. 1996) was used; it consists of 12 items that measure physical and mental dimensions of health. It allows for the calculation of the following two summary scores: a physical component score (comprised of questions on physical functioning, role limitation due to physical health problems, bodily pain, and general health) and a mental component score (questions on vitality, social functioning, role limitation due to emotional health problems, and mental health). The respondents were also asked to evaluate their QOL on a visual analogue scale (VAS) (0—100), which is a single-item instrument with good validity in measuring QOL (de Boer et al. 2004). It is simple to perform and relies on the patient's ability to form an overall judgment of QOL.

Work ability outcomes (study IV). As an indicator of work ability, the participants were asked to estimate their current work ability compared with their lifetime best on a scale from 0 to 10. A score of 0 represented full work disability and a score of 10 indicated work ability at its best. The question is an item included in the Work Ability Index (WAI), which is a validated tool for measuring self-assessed work ability (Tuomi et al. 1998). Those who were on pension were not permitted to answer this question.

Withdrawal from work was used as another, more severe outcome than perceived work ability. The criteria for withdrawal from work were 1) early retirement because of disability (being on disability pension or on a workers' compensation pension), or 2) unemployment. In the

Finnish social security system, a disability pension is paid to a person who is incapable of work due to illness, handicap, or injury. Disability caused by an occupational disease or a work accident entitles workers to a compensation pension.

Exposure continuation (study II). The assessment of continued exposure to workplace dampness was based on a questionnaire inquiry into the measures taken at the workplace and, in cases of relocation, the presence of building-related indoor dampness in the new work environment.

Asthma medication (study III). The current need for asthma medication was inquired about as an estimate of asthma severity. The respondents were asked to name the pharmaceutical products they regularly used to treat asthma. The need for asthma medication was grouped as 1) no need for regular asthma medication, 2) inhaled steroid alone, 3) inhaled steroid combined with a long-acting beta-agonist or leukotriene antagonist, 4) a combination of all of the three medicine groups.

The number of oral steroid bursts needed to control asthma during the past year was also asked. The following four categories of the number of steroid bursts were created: 1) no need during the past year, 2) once a year, 3) twice a year, 4) more often.

Long-term indoor air-symptoms (study IV). Whether or not indoor-air symptoms had been long-lasting was inquired into by the question "How much do the same symptoms that were initiated in the moisture-damaged workplace bother you nowadays?" The respondents were asked to rate the following 14 symptoms on a scale from 1 (not at all) to 5 (very much): eye irritation, hoarseness, nasal congestion, rhinorrhea, sneezing, sinus symptoms, dyspnea, cough, wheezing, fatigue, fever and chills, dermal symptoms, arthralgia or myalgia, and headache. Ratings 1–3 were considered non-significant (= 0) and only ratings 4–5 (much or very much) were taken into consideration (= 1). A symptom sum variable with four categories was constructed as 0 = no significant long-term symptoms, 1–3 symptoms, 4–5 symptoms, or >5 long-term indoor-air symptoms.

Social climate at work (study IV). Social climate at work was measured by three items adapted from the General Nordic Questionnaire (QPSNordic) (Lindström et al. 2000). It is a validated tool measuring psychological and social factors at work. The given question was "What

was the climate like in your workplace with moisture problems?" with the following alternative responses 1) "encouraging and supportive", 2) "relaxed and comfortable", 3) "rigid and rule-based". The scale ranged from 1 (little or not at all) to 5 (very much). The Cronbach's alpha (a measure of the internal consistency) was 0.85. A sum variable was calculated, with the third item reverted. The sum variable was grouped into the following three equal-sized categories: poor, moderate, and good.

Supervisor's cooperation (study IV). With three items, the respondent's experiences with the supervisor's cooperation were inquired about. Non-validated items were used as no established questionnaire for the issue was available. Responses were requested to the following statements on a scale from 1 (disagree totally) to 5 (agree totally): 1) "The supervisor reacted appropriately when I suspected workplace dampness as a cause of my symptoms"; 2) "The supervisor took measures to investigate the damage in a reasonable time"; 3) "The supervisor took measures to remediate the damage in a reasonable time". The Cronbach's alpha was 0.91. A sum variable was calculated, and it was grouped into the three equal-sized categories of low, intermediate, and high.

Anxiety and depression (studies III and IV). For psychological status, the widely used 14-item Hospital Anxiety and Depression Scale was employed (Zigmond and Snaith 1983). This scale is a brief screening instrument. It was selected because its items avoid any reference to physical symptoms. Seven questions relate to anxiety and seven to depression, with total scores for both subscales in the range of 0—21. A value of ≤7 is interpreted as nonclinical, 8—10 indicate possible clinical relevance, and values of ≥11 show important relevance.

Somatization (studies III and IV). Tendencies towards somatization were measured with a 12-item somatization subscale (SCL SOM) from the Hopkins Symptom Checklist (SCL-90) (Derogatis et al. 1973). This subscale is widely used and screens for multiple physical symptoms, focusing on cardiovascular, gastrointestinal, and other systems with autonomic mediation. The Finnish version of the subscale has been validated (Holi et al. 1998).

Hypochondria (study III). To measure the cognitive or emotional dimension of somatization, hypochondriasis, the 7-item version of the Whiteley Index (Whiteley-7) was used (Fink et al. 1999). It reflects the

patient's health anxiety, beliefs, and fears of illness and the attribution of physical sensations to physical illness. The responses for both symptoms and beliefs were rated on a 5-point Likert scale (not at all – very much).

Background variables (studies II–IV). On the basis of job titles, the respondents were classified into the following occupational groups: upper white-collar (e.g., managers and senior officials, teachers, physicians, and other professionals), lower white-collar (e.g., nurses, secretaries, office and customer service clerks, and technicians), and blue-collar (e.g., cleaners, cooks, kitchen helpers, hospital ward assistants, door keepers, repairmen, and machinery mechanics) employees.

Atopic history was defined as a history of infantile eczema or atopic dermatitis, hay fever, or other allergic rhinitis or conjunctivitis.

Current symptoms (studies II and III). The prevalence of current respiratory symptoms was estimated by rating each symptom (cough, dyspnea, and wheezing) on a scale of severity ranging from 1 (not at all) to 5 (very much). In study III, ratings 1–3 were considered non-significant (= 0), and only ratings 4–5 (much or very much) were taken into consideration (= 1).

Co-morbid conditions (studies II–IV). The respondents were asked to mark a list for the presence or absence of their current chronic diseases or injuries diagnosed by a physician. The conditions included accidental injury, musculoskeletal disease, cardiovascular disease, mental disorder, endocrine or metabolic disease, neurological or sensory disease, malignancy, and other disease (Tuomi et al. 1998). Respiratory diseases were excluded. Co-morbidity was classified as 1) no, 2) one, or 3) two or more chronic conditions.

4.7 Statistical analyses

The proportional data in the studies were compared using the chi-square test or Fisher's exact test. In study II, the severity of the symptoms at the follow-up displayed a non-normal distribution. Therefore, when the symptom severities were compared among those still exposed and those unexposed, the Wilcoxon two-sample test was used. The significance level was always set at 0.05.

Logistic regression analysis was used for studying the association between atopy in the SPTs and IgE mold sensitization in study I. Multiple logistic regression analyses were used to determine the risk estimates in the studies in which the outcome variable was dichotomous. The odds ratios (OR) with 95% confidence intervals (95% CI) are presented.

The data in studies III and IV included both categorical and continuous variables. In the preliminary study, there was a need to determine whether the study groups (i.e., those who had OA, WEA, asthma-like symptoms, or upper-respiratory symptoms) differed from each other. When the differences between the groups were compared, chi-square tests for categorical variables and the one-way analysis of variance (ANOVA) for the means of continuous variables were used. However, the main interest was to examine the associations between the determinants and the outcome variables. At first, the associations were studied through the application of cross-tabulations. After these preliminary studies, models were built.

In study III, the physical and mental component scores and the QOL on the VAS scale were used as the outcome variables. All of the outcome variables were considered continuous, and linear regression models were applied. As some explanatory variables were categorical and some continuous, the analysis of covariance (ANCOVA) was applied. The model building strategy was to add independent variables step by step into the model. Only the results of the last models with estimates, standard deviations (SDs), and p-values are presented.

Before the modeling in study IV, the outcome variables were dichotomized. The outcome variable for self-assessed work ability was dichotomized as follows: 0–7 = "poor", 8–10 = "good". The outcome variable "early withdrawal from work" was dichotomized as no/yes. With the use of models, the goal was to estimate the risks for reduced self-assessed work ability and "early withdrawal from work". Logistic regression analyses were used when the associations were examined between the different explanatory factors and the dichotomized outcome variables. The model strategy was as follows: in the beginning, the univariate models were estimated using asthma group, number of long-term indoor-air symptoms, and social climate at work or cooperation of the supervisor as an

explanatory variable. Then, through the addition of potential confounders into the models, multivariate regression models were estimated. The ORs with their 95 % CIs have been presented.

All of the analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

5 RESULTS

5.1 Retrospective review of the patients suspected with occupational asthma (study I)

Patient characteristics and symptoms. The mean age of the study patients was 45.2 (SD 8.4, range 23–61) years. Altogether 90% of the patients were female. Prior to the investigations at FIOH, asthma had been diagnosed and regular medication initiated for 195 (76%) of the patients. In addition to asthma symptoms, the patients had reported symptoms such as eye irritation and hoarseness. General symptoms, including fatigue and a sensation of elevated temperature, had also been reported (Table 6). The mean duration of the respiratory symptoms before the asthma diagnosis was 3.2 (SD 3.0, range 0–17.0) years. Of the patients, 65% were life-long nonsmokers, 12% were ex-smokers, and 23% were current smokers.

Table 6. Prevalence of work-related symptoms and respiratory infections among the patients.

Symptom/disease	All n=258 n (%)	Probable OA n=156 n (%)	Possible OA n=45 n (%)	Unlikely OA n=57 n (%)
Upper-respiratory and ocular symptoms				
Eye irritation	145 (56)	92 (59)	24 (53)	29 (50)
Hoarseness	129 (50)	79 (51)	18 (40)	32 (56)
Nasal congestion	122 (47)	70 (45)	25 (56)	27 (47)
Rhinorrhea	120 (46)	72 (46)	21 (47)	27 (47)
Sneezing	46 (18)	24 (15)	10 (22)	12 (21)
Lower-respiratory symptoms				
Dyspnea	207 (80)	121 (78)	38 (84)	48 (84)
Cough	182 (70)	110 (70)	29 (64)	43 (75)
Wheeze	49 (19)	31 (20)	8 (18)	10 (18)
Asthma symptoms from non-specific irritants	99 (38)	57 (36)	21 (47)	21 (37)
Other symptoms				
Fatigue	109 (42)	68 (44)	16 (36)	25 (44)
Fever and chills	108 (42)	61 (39)	20 (44)	27 (47)
Dermal symptoms	60 (23)	34 (22)	12 (27)	14 (25)
Headache	54 (21)	35 (22)	8 (18)	11 (19)
Arthralgia	48 (19)	31 (20)	10 (22)	7 (12)
Nausea	14 (5)	8 (5)	1 (2)	4 (7)
Myalgia	13 (5)	7 (4)	1 (2)	5 (9)
Vertigo	10 (4)	6 (4)	0	4 (7)
Recurrent respiratory infections	105 (41)	67 (43)	14 (31)	24 (42)

OA=occupational asthma

Exposure. According to their work histories, all of the patients had been exposed to molds. In most instances (66%), the exposure had taken place in schools, hospitals, various office environments, or day-care centers. Correspondingly, most of the patients were teachers, nurses, office workers, or children day-care workers, which explains why most of the workers were female.

In the analysis of the exposure data, the level of exposure was classified as high or intermediate for 79% of the patients. For 15%, the exposure classification was not made due to insufficient data. The duration of exposure exceeded 5 years for 69% of the patients. The level of exposure was significantly higher in the probable OA group than in the unlikely OA group (p=0.049).

Sensitization. Atopy (i.e., sensitization to at least one common environmental allergen in the SPTs) was determined for 33% of the patients. Atopy was equally distributed among the three categories of OA. An elevated level of serum total IgE was significantly more common in the probable and possible OA categories than in the unlikely OA category.

Sensitization to molds, as demonstrated by either SPT or serum IgE, was determined for 15% (39 of 254) of the patients (Table 7). Altogether 26 of these 39 patients (67%) were atopic according to the SPTs. Atopy significantly increased the risk of sensitization to molds (OR 6.5, 95% CI 3.0–14.0). Sensitization to molds occurred the most frequently among the patients in the probable OA group (Table 7). The association between mold sensitization and OA category was statistically significant (p=0.019).

Table 7. Sensitization to molds.

	All n=258	**Probable OA n=156**	**Possible OA n=45**	**Unlikely OA n=57**	
Positive SPT to molds, n/n_t (%) *	36/245 (15)	29/148 (20)	2/45 (4)	5/52 (10)	p=0.022
Elevated serum IgE to molds, n/n_t (%)	22/181 (12)	18/113 (16)	1/30 (3)	3/38 (8)	p=0.114
Either positive SPT or elevated serum IgE to molds, n/n_t (%)	39/254 (15)	31/153 (20)	2/45 (4)	6/56 (11)	p=0.019

OA=occupational asthma; n_t=number of tested patients; SPT=skin prick test; IgE=immunoglobulin E.

* An SPT to molds was performed for 253 patients, but, for 8 of them, the result could not be interpreted because of dermographism.

In the SPTs with mold extracts, *A. fumigatus* induced a positive reaction the most often (25 of 36 patients, 69%), followed by *C. cladosporioides* and *Rhodotorula rubra* (seven positive reactions each), and *A. kiliense* and *Penicillium expansum* (five positive reactions each). One-third of the patients with positive SPTs to molds (13 of 36 patients) displayed a positive reaction to more than one mold.

For the patients with a high, intermediate, or low level of exposure, the IgE sensitization to molds occurred in 9 of 99 (9%), 17 of 97 (18%), and 4 of 15 (27%) patients, respectively.

Lung function. In the baseline examinations at FIOH, most of the patients (89%) showed mild or moderate obstruction in the spirometry. Some degree of hyperresponsiveness was present in 45% of the patients, whereas the bronchial reactivity was normal for 55%.

Serial PEF records of acceptable quality at and away from work were available for 193 (75%) of the 258 patients included in the analyses. According to interpretations of the PEF records, 47 (24%), 77 (40%), and 69 (36%) were compatible, suggestive, or not consistent with OA, respectively.

SIC tests. The SIC test was positive for 133 patients. The positive bronchial reactions were immediate in 35 patients (26%), dual in 35 patients (26%), and late in 63 patients (47%). The decreases in PEF ranged between 15% and 41%, and the FEV1 reductions were between 15% and 49%. Sensitization to molds, demonstrated either by SPT or specific serum IgE, was present for 30 of the 130 patients (23%). [Measurements were not available for 3 of the 133 patients.] Sensitization did not differ in relation to type of reaction (immediate or dual versus late).

The most common mold extract to induce positive reactions in the SIC was *A. fumigatus* (85 positive tests versus 26 with *C. cladosporioides*, 19 with *A. kiliense*, and 3 with *C. herbarum*). Of the mold-sensitized patients, 26 (87%) had a positive SIC reaction to the same mold as shown by the SPT or serum IgE measurement.

During the positive SIC with an active test agent, but not with the control agent, a post-challenge rise of >0.5°C in the axillary body temperature was measured for 11 patients (8%, range of maximum temperature 36.6–38.9). All of these increases occurred after the SIC with mold extract (none after the SIC with a diluent). For 10 of the patients

with an increase in temperature, the pre- and post-challenge diffusing capacity had been measured, but no differences were noted. The type of the bronchial reaction was late for 7 of the 11 patients (immediate for 2 and dual for 2 patients).

Due to the lability of asthma despite optimal treatment, the SIC tests had to be carried out for 40 (16%) of the analyzed patients with ongoing inhaled corticosteroid medication.

Agreement between the serial PEF records and the SIC tests. The agreement between the PEF and SIC tests (i.e., both the SIC and serial PEF monitoring were either positive or negative) was 56%. When the SIC was positive, the serial PEF monitoring was compatible or suggestive of OA for 78% of the patients. In the case of a negative SIC, the proportion of patients with a PEF record compatible with or suggestive of OA was 56% (Table 8).

The comparison between the SIC testing and the proof of specific IgE mold sensitization (SPT or serum IgE measurement) showed a level of agreement of 57%. Type I mold sensitization was more common for the patients with the positive SIC than for the negative SIC (23% versus 7%).

Table 8. Agreement between the serial PEF measurements and SIC tests.*

	SIC positive n=69	SIC negative n=124	
Serial PEF compatible with OA (n=47)	25 (53%)	22 (47%)	p=0.002
Serial PEF suggestive of OA (n=77)	29 (38%)	48 (62%)	
Serial PEF inconsistent with OA (n=69)	15 (22%)	54 (78%)	

OA=occupational asthma; PEF=peak expiratory flow; SIC=specific inhalation challenge.
* Only those included who had both tests available.

Follow-up examinations. A total of 136 of the 156 patients who were classified with probable OA participated in the follow-up examinations 6 months after the diagnosis. Of these persons, only 79 patients (58%) had returned to work, while 53 patients (39%) were not currently working and 4 (3%) were attending vocational training. Altogether 13 patients

were still exposed to the original damp work environment, and 4 reported moisture damage also in their new work environment.

Nearly all of the patients (98%, 133 of 136) used asthma medication regularly: 43% (59 of 136) using inhaled steroids alone, 35% (48 of 136) using inhaled steroids and a long-acting β2-agonist, and 17% (23 of 136) additionally using a leukotriene modifier or theophylline.

For most of the patients (89%), spirometry showed mild or moderate obstruction. The histamine challenge test showed no bronchial hyperresponsiveness for 52% and mild bronchial hyperresponsiveness for 30% of the patients. Asthma medication was continued by all except one patient, asthma lability requiring additive treatment for 23 patients (17%). The symptom status was unchanged for 73 (54%) patients, improved for 60 (44%), and was worse for 3 (2%). None of those still exposed reported improvement in their symptoms.

None of the 11 patients who had reacted with a rise in temperature during a positive SIC reported a deterioration in symptoms in the follow-up examination. The overall symptoms were unchanged for 6 of them (55%) and had improved for 5 (45%).

5.2 Long-term outcomes

5.2.1 From asthma-like symptoms to the development of asthma (study II)

Most of the 483 persons studied were female (88%), the mean age being 45.3 (SD 8.6) years. The mean time from the onset of symptoms to the initial examinations at FIOH was 4.8 (SD 3.3) years. The mean time from the examinations at FIOH to the point of the questionnaire study was 8.3 (SD 2.6) years.

A total of 62 patients (13%) claimed to have developed clinical asthma as diagnosed by a physician during the study period. The mean period from the examinations at FIOH to the asthma diagnosis was 4.8 (SD 3.1) years. During the follow-up, the incidence rate of asthma was 267 per 10 000 person-years. The mean time elapsed from the onset of symptoms to the time of receiving a diagnosis of asthma was 9.2 (SD 5.2) years.

There were no differences in the age or gender distribution between the patients who developed asthma and those who did not. The mean age of the groups was 44.8 (SD 8.8) years and 45.2 (SD 8.6) years, respectively. Most of the patients (78%) worked in office-like surroundings, schools, hospitals, or children's day-care centers.

A variety of work-related symptoms was reported prior to the initial examinations at FIOH. The prevalence of symptoms of the upper-respiratory tract and the eyes had been high. A high prevalence of general symptoms, such as fever or chills, myalgia, arthralgia, headache, and fatigue, had also been reported. The prevalence of none of these irritant or systemic symptoms differed between the persons who developed asthma and those who did not. At the follow-up, the current nasal and eye symptoms were significantly ($p<0.01$) less severe among those no longer exposed to indoor dampness at work than among those still exposed. In addition, the symptom scores for fatigue, fever or chills, myalgia or arthralgia, and headaches were lower for the unexposed patients ($p<0.0004$). Of the three asthma symptoms, the prevalence of dyspnea was higher for those who developed asthma, whereas cough and wheezing did not differ between the groups.

An atopic history, either allergic rhino-conjunctivitis or atopic dermatitis, was a moderate risk factor for asthma (adjusted OR 2.6, 95% CI 1.5—4.6).

Among the patients who were working at the time of the follow-up, a larger proportion of those who developed asthma, than patients who did not, reported that they were still working in the same non-remediated environment (7% versus 2%). A significantly lower proportion of those who had developed asthma had been relocated within the same company or organization than those who had not developed asthma (13% versus 29%). Continued exposure to indoor dampness in the same or new work environment was reported by 19% of the asthmatics and 11% of the non-asthmatics. The proportion of those currently unemployed was higher among those who had developed asthma (48% versus 32%).

Among the currently employed (i.e., working at the time of the questionnaire study) the risk of new-onset asthma in relation to continued workplace exposure was increased more than fourfold (adjusted OR 4.6, 95% CI 1.8–11.6) (Table 9). Continued work in the former, non-remediated work environment was associated with a further increase

in the risk (adjusted OR 6.4, 95% CI 1.5–27.7). Working for a new employer but still exposed to building-related dampness at work was associated with a similarly increased risk (OR 5.7, 95% CI 1.6–20.7).

When stratified by atopic history, the risk of asthma in the continuing exposure situation was only slightly higher among the atopics (OR 5.1, 95% CI 1.4—19.1) than among the non-atopic persons (OR 4.68, 95% CI 1.2—18.6).

Table 9. Risk of asthma development in relation to the continuation of workplace exposure.*

	Development of new asthma		Crude odds ratio		Adjusted odds ratio#	
	Yes n=34†	No n=290§				
	n	n	OR	95% CI	OR	95% CI
Cessation of exposure†† (reference)	12	170	1.00		1.00	
Continuation of exposure						
Working in the same, nonremediated environment	4	10	5.7	1.5–20.8	6.4	1.5–27.7
Relocated in the same organization, moisture damage	3	24	1.8	0.5–6.7	2.9	0.7–12.4
Working for a new employer, moisture damage	5	13	5.4	1.7–17.8	5.7	1.6–20.7
Any of the aforementioned exposure situations	12	47	3.6	1.5–8.6	4.6	1.8–11.6
Working in the same, remediated environment	8	63	1.8	0.7–4.6	2.0	0.7–5.4

OR=odds ratio; CI=confidence interval.
* Only currently employed persons included.
† Information was unavailable for two patients.
§ Information was unavailable for ten patients.
# Adjustment for age, gender, atopic history, and smoking.
†† Relocated in the same organization or working for a new employer, and no moisture damage in the workplace.

Some medical records were obtained for 46 of the 62 patients who reported having developed physician-diagnosed asthma. In 31 cases, the records fulfilled the diagnostic criteria for asthma, which were the same as in the initial examinations, whereas the available clinical records of 15 cases did not. According to the questionnaire study, 48 of the 62 patients were using inhaled steroids regularly. When the excess risk of developing asthma in relation to continued exposure was analyzed for only the 18 persons who had an acceptable physician-diagnosed case of asthma and who were working at the time of the questionnaire study, the statistical significance remained (adjusted OR 4.9, 95% CI 1.3–18.2).

5.2.2 Quality of life (study III)

The study population (n=1295) has been described in Table 1 of article III. The mean time from the initial examinations to the point of follow-up with the questionnaire was 8.0 (SD 2.8, range 3.0–12.0) years. At the time of the follow-up, there were no significant differences in age or smoking habits in comparison with the groups of OA, WEA, asthma-like symptoms, and upper-respiratory symptoms. A total of 60% of the patients had never smoked. The patients with WEA had an atopic history more often than did the patients with OA or those with no asthma. Both asthma groups more often reported coincident chronic diseases or injuries than did the non-asthmatics. Altogether 88% of the respondents were white-collar employees (e.g., teachers, nurses, office workers, or administrators), and 12% were blue-collar employees (e.g., cleaners, kitchen helpers, or doormen).

Of the OA group, a statistically significant proportion was outside worklife at the time of the follow-up. Altogether 41% of the patients with OA received a pension, either because of disability (workers' compensation pension or disability pension) or retirement because of age (63–68 years). In the other groups, pension was not as common (26% of the WEA patients, 23% of the patients with asthma-like symptoms, and 19% of those with upper-respiratory symptoms).

The scores of the generic QOL, depression, anxiety, somatization, and hypochondria indicators are shown in Table 2 of article III. Statistically significant differences were observed between the four groups according to the asthma and symptom status at the baseline. The OA patients had

Table 10. Mean scores for the QOL domains for those currently working or not working, according to the asthma or symptom status at baseline. In all of the QOL domains, a higher value indicates a better QOL.

	OA (n=127)		WEA (n=453)		Asthma-like symptoms (n=483)		Upper-respiratory symptoms (n=204)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
SF-12 physical component score	45.4	29.1	54.7	30.6	62.9	29.7	69.7	28.9	<0.01
Working	55.4	29.1	60.9	29.4	66.9	27.5	76.1	25.1	<0.01
Not working	33.2	24.1	41.7	28.9	54.0	32.3	50.7	31.3	<0.01
SF-12 mental component score	68.9	22.4	69.3	23.2	71.5	21.9	73.4	19.8	0.12
Working	72.2	22.2	72.0	21.4	72.4	20.3	76.7	16.2	0.11
Not working	65.3	22.2	63.7	25.9	69.2	25.2	63.8	25.5	0.23
QOL, VAS	65.0	21.6	69.2	19.8	72.1	18.9	74.0	17.1	<0.01
Working	71.6	19.0	71.7	18.9	73.7	16.7	75.7	15.2	0.11
Not working	57.2	22.3	64.0	20.8	68.2	23.0	69.2	21.2	<0.01

QOL=quality of life; OA=occupational asthma; WEA= work-exacerbated asthma; SF-12=Short Form Health Survey-12 Questionnaire; VAS=visual analogue scale; SD=standard deviation.

the lowest scores, indicating worse QOL, in all of the QOL domains. For the mental component score of the SF-12, the differences between the groups were smaller and not significant. When the asthma groups were combined, 33% of all of the asthmatics had an important or possible clinical relevance for an anxiety disorder versus 37% of the respondents in the non-asthma groups. Correspondingly for depression, 13% of the asthmatics and 11% of the non-asthmatics had an important or possible relevance for an anxiety disorder. Surprisingly, patients with OA seemed to display less anxiety than the other groups. However, this tendency was not statistically significant. The scores of the somatization subscale of the Hopkins Symptom Checklist did not differ significantly between the groups, whereas the Whiteley Index for hypochondria showed statistically significant differences.

Table 10 presents the scores of the QOL domains for those who were working at the time of the follow-up and those who were not. Among those who were not working, the persons with OA had the lowest scores for QOL on the SF-12 physical component scale and the VAS scale.

In a multivariate linear regression analysis, the group status was associated with QOL with respect to the SF-12 physical component score, but not for the SF-12 mental component score. An association could also be shown for the overall QOL measured on the VAS scale. The differences in the QOL scores were compared between each group. For the SF-12 physical component score, the difference between the groups with asthma-like symptoms and upper-respiratory symptoms was not statistically significant ($p=0.411$). Between all of the other groups, the differences were statistically significant ($p<0.001$). For the SF-12 mental component score, there were no statistically significant differences between the groups, whereas, for the VAS scale, the differences were statistically significant when the OA group was compared with each of the other groups ($p<0.05$). Not being employed was a determinant for a poorer QOL in regard to all three QOL dimensions. Adding anxiety, depression, somatization, and hypochondria to the model did not remove the differences between the groups.

The need for regular asthma medication ($p<0.001$) and the need for oral steroid bursts to control asthma ($p<0.001$) was higher for the patients with OA than for those with WEA. A worse QOL (measured by the SF-12 physical component scale or the VAS scale) was associated

with a higher need for asthma medication ($p<0.001$ on both scales) and a more frequent need for oral steroid bursts ($p<0.001$ on both scales). Significant cough and dyspnea were more prevalent among the OA patients than among the WEA patients: 27% versus 17% ($p=0.011$), and 28% versus 17% ($p=0.004$), respectively. For wheezing, the difference was not statistically significant ($p=0.591$).

In a multivariate model including the OA and WEA groups, frequent oral steroid use was a strong determinant for a poorer SF-12 physical component score and the overall QOL on the VAS. When regular asthma medication was included in the model as an explanatory variable, it was found to explain worse QOL with respect to the physical component score (p-value 0.001), but not regarding the other QOL dimensions. Oral steroid use and regular asthma medication could not be added to the same model because of their strong mutual correlation.

5.2.3 Work ability (study IV)

The study population consisted of 1098 persons aged 26–64 years. The characteristics of the study group according to the asthma or symptom group are described in Table 1 of article I. The mean time from the initial examinations at FIOH to the follow-up questionnaire was 7.8 (SD 2.8) years. Most of the patients in the study were female, the vast majority of whom worked in occupations with only light physical demands. Altogether 88% of the respondents were upper or lower white-collar employees (e.g., teachers, health and day-care nurses, other professionals, office workers, or administrators). The initial exposure had most often taken place in office-like workplaces (23%), hospitals and health clinics (22%), schools and colleges (18%), or children's day-care centers (10%).

The OA patients rated their work ability with the lowest scores, 31% of them assessing their work ability as very poor (score 0–5) versus 9% of the respondents in the group with upper-respiratory symptoms. The work ability score for both asthma groups was lower than that of the symptom groups.

At the follow-up, 40% of the OA group was outside worklife. Retirement because of disability or being without a job was also the most frequent (33%) in the OA group, whereas 13% of the WEA patients, 13% of the patients with asthma-like symptoms, and 13% of the patients

with only upper-respiratory symptoms belonged to this category. Of all of those who were retired because of disability or who were without a job, 91 (61%) claimed that the disability or unemployment was a consequence of persisting dampness-related symptoms.

Altogether 128 (12%) of the respondents reported that they had changed occupation. In addition, 136 (13%) reported having changed employer because of dampness-related symptoms.

The distributions of both of the work ability outcomes are presented in Table 2 of article IV, according to the determinants and other explanatory variables.

The OA patients had a markedly increased risk of poor work ability. When adjusted for individual variables (age, gender, occupational group, smoking, atopic history and co-morbidity), the OR was 2.6 (95% CI 1.4–4.7) (Table 11). In addition, the WEA patients had an increased risk for poor work ability (OR 1.8, 95% CI 1.2–2.8). OA had a strong association with withdrawal from work due to early retirement or unemployment (adjusted OR 5.7, 95% CI 2.8–11.9) (Table 11). For the WEA and asthma-like symptoms groups, the associations with early withdrawal from work were not statistically significant. When depression and somatization were added to the model, the risks remained statistically significant.

Multiple long-term indoor-air symptoms at the follow-up increased the risk of poor self-assessed work ability. When adjusted for individual factors, the OR was 2.7 (95% CI 1.9–3.8) for those with 1–3 symptoms, increasing to 9.7 (95% CI 5.7–16.5) for those with >5 symptoms (Table 11). After adjustment for depression and somatization, the risks remained significantly elevated. Multiple long-term symptoms were not associated with early withdrawal from work.

A poor social climate at the workplace and poor experiences with supervisor's cooperation were associated with both poor self-assessed work ability and early withdrawal from work, when adjusted for the individual variables (Table 11). When depression and somatization were added to the models, the associations remained for early withdrawal from work, but not for self-assessed work ability (Table 11).

Table 11. Results of the univariate and multivariate logistic models for the risks of poor self-assessed work ability and early withdrawal from work.

	Poor self-assessed work ability			Early withdrawal from work		
	Univariate models	Adjusted for individual variables*	Adjusted for individual variables*, depression and somatization	Univariate models	Adjusted for individual variables*	Adjusted for individual variables*, depression and somatization
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Asthma or symptom status at baseline						
Upper-respiratory symptoms†	1.0	1.0	1.0	1.0	1.0	1.0
Asthma-like symptoms	1.3 (0.9–1.9)	1.2 (0.8–1.7)	1.0 (0.6–.5)	1.8 (1.0–3.5)	1.6 (0.8–3.1)	1.3 (0.7–2.6)
WEA	1.9 (1.3–2.8)	1.8 (1.2–2.8)	1.8 (1.1–3.0)	1.7 (0.9–3.3)	1.6 (0.8–3.1)	1.4 (0.7–2.7)
OA	2.5 (1.4–4.4)	2.6 (1.4–4.7)	2.5 (1.3–4.9)	6.4 (3.2–12.7)	5.7 (2.8–11.9)	4.6 (2.2–9.8)
Number of long-term, indoor air symptoms						
0	1.0	1.0	1.0	1.0	1.0	1.0
1–3	2.8 (2.0–3.8)	2.7 (1.9–3.8)	2.0 (1.4–3.0)	1.6 (1.1–2.4)	1.2 (0.8–1.9)	1.0 (0.6–1.5)
4–5	4.4 (2.8–6.9)	4.4 (2.7–7.1)	2.7 (1.6–4.7)	1.2 (0.7–2.2)	0.9 (0.4–1.7)	0.6 (0.3–1.3)
>5	10.9 (6.6–18.2)	9.7 (5.7–16.5)	6.1 (3.4–11.2)	1.5 (0.9–2.7)	1.1 (0.6–2.0)	0.6 (0.3–1.3)
Social climate at work						
Good	1.0	1.0	1.0	1.0	1.0	1.0
Moderate	1.1 (0.8–1.5)	1.1 (0.7–1.6)	0.9 (0.6–1.4)	1.4 (0.8–2.4)	1.4 (0.8–2.4)	1.3 (0.7–2.4)
Poor	1.6 (1.2–2.3)	1.5 (1.1–2.2)	1.2 (0.8–1.8)	2.4 (1.5–3.9)	2.3 (1.4–3.8)	2.1 (1.2–3.6)
Experiences with supervisor's co-operation						
Good	1.0	1.0	1.0	1.0	1.0	1.0
Moderate	1.5 (1.1–2.1)	1.5 (1.0–2.1)	1.3 (0.9–1.9)	1.1 (0.7–1.9)	1.1 (0.7–2.0)	1.3 (0.7–2.2)
Poor	1.9 (1.4–2.6)	1.7 (1.2–2.5)	1.4 (0.9–2.1)	2.7 (1.7–4.2)	2.4 (1.5–4.0)	2.5 (1.5–4.1)

* The individual variables included age, gender, occupational group, smoking, atopic history, and co-morbidity.

† Neither asthma nor asthma-like symptoms, but upper-respiratory symptoms in the initial examinations.

WEA=work-exacerbated asthma; OA=occupational asthma.

6 DISCUSSION

6.1 Diagnostics of occupational asthma

6.1.1 Exposure assessment

Demonstrating the exposure (i.e., identifying an occupational agent at a workplace that is a potential cause of OA) is a prerequisite for making a diagnosis of OA. With respect to indoor dampness and related factors, the issue is not straightforward. When this study was being planned, there were no accurate guidelines for the exposure assessment, and inconsistent practices were used. In Finland in the 1990s, IgG antibodies were considered a proxy for exposure. Their value in clinical diagnostics was contradicted already in 1998 in the so-called Majvik recommendation (Majvik 1998), which included guidelines by an expert group for the diagnostics of diseases induced by building moisture and mold. The review of scientific evidence by IOM in 2004 concluded that there is a lack of valid quantitative methods for assessing exposure (IOM 2004). The current knowledge is the same. There are still no health-based limits for harmful or safe mold exposure. According to the latest literature review (Mendell et al. 2011), conventional quantitative measurements of fungi or other microbiological exposures, such as counts of culturable airborne fungi, have shown less consistent associations with health effects than have qualitative assessments, such as visible dampness and mold or mold odor.

A major obstacle to demonstrating a building-related factor as a cause of an occupational disease is the difficulty of identifying a specific causative agent among a multitude of candidates. As several mold species have been reported to specifically trigger allergic asthma, much

research has focused on fungal spores as the main offending agent (Portnoy et al. 2008; Sahakian et al. 2008). Most studies that demonstrate an association between asthma development and damp indoor spaces are based on the presence of visible mold or mold odor (WHO 2009; Mendell et al. 2011). Apart from indoor allergens (e.g., from pets) other hazardous factors in indoor air have not been shown to be risk factors for asthma development. For example, several studies have found associations between VOCs and asthma symptoms, but literature reviews have found no consistent evidence for an association between the commonly measured indoor VOC exposures and the onset of new asthma (Nielsen 2007).

Molds are ubiquitous in our environment, indoors as well as outdoors. If there is excess mold growth in the work environment, exposure to molds is however not restricted to the workplace. As Finland is a subarctic country, the outdoor concentrations of airborne fungi are very low in the winter (Reponen et al. 1992). In indoor air, winter concentrations are usually below 100 cfu/m^3 in home environments (Reponen et al. 1992), and even lower, <50 cfu/m^3, in office environments (Salonen et al. 2007) and school environments (Meklin et al. 2003). These limits signify the probability to identify abnormal microbial sources indoors, and many contributing factors must be considered when the concentrations of the spores are interpreted. Distinguishing harmful occupational exposures is therefore challenging.

For study I, a three-level classification was established for the intensity of microbial exposure. The exposure of each patient case was classified on the basis of the data in patient files. In most of the cases, a characterization of moisture damage, as well as microbial growth, had been undertaken. Exposure to molds could be retrospectively verified from technical and microbial reports. Therefore, a rough grading according to the extent and location of the damage was usable. The assessment was semi-quantitative. For 85% of the cases, reliable data were available in the patient files and confirmed the exposure to dampness and molds. "The high-level category" of exposure showed a statistically significant association with the probable OA category. This finding suggests that the exposure assessment that was used had some validity.

There are no valid methods for quantitative exposure assessment. Mold growth in relation to moisture damage can be regarded as an indicator of the total exposure to all dampness-related factors (like spores and hyphal fragments of fungi, spores and cells of bacteria, toxins, chemical degradation products of building materials) (WHO 2009). Inflammatory responses have been found to many microbiological agents related to dampness, and this finding supports the biological plausibility of a potential causal association between dampness-related factors and asthma (see Section 2.3.9). No single causative agent has been identified relevant to asthma or other health effects; instead, the mechanisms are likely to be complex and multifactorial (WHO 2009). Mold growth is always considered to be the result of excess dampness, and excess dampness is invariably accompanied by mold before long (Fisk et al. 2007). The results of study I support the existing literature that the demonstration of excess mold growth in association with workplace moisture damage is a relevant criterion for the assessment of exposure. In OA diagnostics, an individual exposure assessment is needed, and it can be based on descriptions of the extent and location of the moisture and mold damage in the building structures, as well as on microbial measurements as described in study I.

6.1.2 Specific inhalation challenge tests

In the diagnostics of OA, the SIC test is generally considered to be as close as possible to a gold standard (Newman Taylor et al. 2004; Nicholson et al. 2012). It represents an important tool for confirming a diagnosis of OA, for identifying the agent responsible for asthma when there are multiple possible agents in the workplace, and for identifying new agents responsible for asthma (Vandenplas et al. 2006). When SIC tests are available in a specialized center, they have been recommended to be preferred to other means in the confirmation of WRA (Vandenplas et al. 2006). According to current guidelines, for people with suspected sensitizer-induced OA, using SIC test is suggested when the diagnosis or causative agent remains equivocal (Tarlo et al. 2008). As FIOH is a national reference institute, SIC is a routine method for ascertaining causality in the diagnostics of OA.

From the 1990s on, asthma induced by indoor molds has been compensated as OA in Finland. As molds are generally known as sensitizers, SIC testing was adopted for the OA diagnostics of building-related asthma. Although the epidemiological evidence was limited with respect to an association between dampness and mold and asthma, positive reactions to mold extracts in SIC testing were considered to demonstrate a relationship with mold exposure and asthma. Therefore, for study I, there were results available for routinely performed SIC tests that could be used in the retrospective review.

For the SIC testing, there had been access to three commercial test extracts (*A. fumigatus, A. kiliense, and C. cladosporioides*). The extracts were not standardized. SIC test agents contain a small amount of proteins and carbohydrates (Esch 2004). The *A. fumigatus* extract elicited most of the positive reactions in the study patients and, therefore, reflects the fact that most tests were performed with *A. fumigatus*. The rationale for using *A. fumigatus* as the primary test extract had been that *Aspergillus* species represent dominant genuses in mold-damaged buildings (Simon-Nobbe et al. 2008), and *Aspergillus* species are also known to cross-react and share epitopes with other mold species (e.g., *Cladosporium*) (Horner et al. 1995; Vojdani 2004; Simon-Nobbe et al. 2008).

Sensitization to molds was found in 23% of the SIC positive cases. In a previous study on rhinitis patients with positive nasal provocation tests with microbial extracts, specific IgE had been determined similarly for a small proportion of patients only (Karvala et al. 2008). The mechanisms behind the positive SIC reactions remain unknown.

The usefulness of the SIC test is however modest with respect to dampness and molds at workplaces. The exposure situation at work includes a multitude of other components as well (e.g., spores, metabolic products of microbes, toxins, and chemicals emitted from construction and interior materials). Thus the choice of one or several microbes identified on a single sampling occasion may be totally wrong. A broad spectrum of microbial genera and species can be found on building materials and in indoor air, and species and concentrations fluctuate over time. Sampling microbes on single occasions does not necessarily reveal the relevant species. On the other hand, as the mechanisms and causative factors of dampness-related asthma are unknown, and the SIC is a method with which to identify sensitizer-induced OA, SIC with fungal

allergens may not serve as an ideal test. Thus a negative SIC contributes little, if any, information.

6.1.3 Serial PEF monitoring

In study I, serial PEF monitoring could be compared to the SIC results. The overall agreement between the serial PEF monitoring and the SIC testing (both being either positive or negative) was 56%. For the patients with a positive SIC test, the agreement with the serial PEF monitoring was 78%. Considering the flaws of the SIC, this figure is fairly high (figures 80%–100% could be regarded as high).

In the diagnostics of OA, serial PEF recordings have a high sensitivity and specificity when tested against SIC tests, averaging 80% and 90% respectively (Newman Taylor et al. 2004). Acceptable serial PEF records are possible to obtain for about two-thirds of those for whom OA is being considered (Newman Taylor et al. 2004). The percentage in the material (study I) was only slightly lower (63%). If occupational health services fail to initiate serial PEF monitoring in association with damp buildings, this opportunity is often lost. As there is generally a time lag of 1–3 years before a patient arrives for examinations at FIOH, the moisture damage has often already been repaired – sometimes the entire building has been demolished, the work contract has ended, or the patient simply refuses to go back to the workplace. In addition, deficiencies have been reported in the quality of serial PEF measurements performed in health care units before referral to FIOH (Sauni et al. 2009).

By comparison, serial PEF records are superior to SIC testing in reflecting the entire complex exposure situation at the workplace. Thus serial PEF recording is the principal and most reliable diagnostic tool available. It is however, essential that serial PEF monitoring be carried out correctly. It should be initiated without delay, preferably before the initiation of any anti-inflammatory medication. The reliability of serial PEF monitoring using ordinary peak flow meters has been questioned (Malo et al. 1995, Quirce et al. 1995). It may be advisable to use a computerized peak flow meter in order to improve both quality and reliability. Increases in bronchial hyper-reactivity (Nicholson et al. 2005) or exhaled nitric oxide (Lemiere 2007) over an exposure period may be a way to improve the reliability of PEF recording. While serial PEF

records do demonstrate the association with work, the major weakness is that they do not accurately differentiate between WEA and OA (Chiry et al. 2007). For the diagnosing of OA, other aspects, like the exposure, disease history, and immunological assessment, have to be included.

6.1.4 Differentiation between OA and WEA

Differentiating OA (which is asthma caused by workplace exposures) from WEA (which is asthma exacerbated by workplace exposures) is the main difficulty in establishing the diagnosis of OA. There are several reasons for a possible diagnostic misclassification concerning asthma related to building dampness and mold. In study I, the category of unlikely asthma represented WEA. This group may well have included cases of OA. As a negative SIC test does not exclude the possibility that some other microbe or agent was the cause of asthma, the uncertainty of the diagnoses was probably greatest in this category, especially if serial PEF recordings were not available. Thus not all cases of OA are recognized, and, on the other hand, serial PEF measurements are not specific to OA (Chiry et al. 2007). However, all of the patients had been exposed to a damp environment and had suffered from work-related exacerbations and deterioration of their asthma. Therefore, from the point of view of secondary prevention, the distinction between WEA and OA is less important (Wagner and Wegman 1998). The need for proper asthma treatment, building repairs, or relocation is the same regardless of the type of diagnosis.

An accurate separation between the two types of WRA is not always possible. For compensation purposes, the diagnostic practice in Finland has been to determine OA cases. Inequality experiences are yet in many cases unavoidable so that, with similar symptoms, which even worsen in similar work environments, one person gets a diagnosis of OA and another person does not. For a patient, it is difficult to understand the difference between causality and exacerbation. Remaining without an OA diagnosis may be a disappointment because of lost benefits, but also because of experienced injustice. This situation has often led to prolonged appeal processes among patients with building-related asthma.

6.2 Long-term outcomes

6.2.1 Asthma development

The results of study II suggest that asthma-like symptoms in relation to exposure to a damp and moldy work environment are associated with an increase in the risk of developing asthma later. The study population had been exposed to indoor dampness and molds at their workplaces. A significant proportion of the patients reported having developed asthma during the follow-up period (mean 8.3 years). The incidence of new-onset asthma in this group was high, 267 per 10 000 person-years. By comparison, the incidence of asthma in a Finnish birth cohort born in 1966 was 18.5 per 10 000 person-years (Kujala et al. 2005) and that of a population cohort in Helsinki was 37 per 10 000 person-years (Pallasaho et al. 2011). Study II was based on a clinical patient series, and therefore direct comparisons cannot be made.

The finding that asthma-like symptoms may increase the risk of developing asthma is supported by the results of some earlier studies, but such a relationship has not earlier been shown for occupational environments. The findings may apply to other occupational environments with irritant and sensitizing exposures as well. A follow-up study (mean time 4.4 years) on adults suffering from chronic cough without having clinical asthma revealed that 16% (29 of 182 patients) were diagnosed with asthma (Puolijoki and Lahdensuo 1987). In another Finnish study on children aged 7–12 years, who had lower-airway symptoms but did not fulfill the criteria for asthma, one-third (11 of 33 children) developed asthma during a 2-year follow-up period (Remes et al. 1998). In study II, the proportion of those who developed asthma was lower (13%). However, the 62 patients who had developed asthma by the time of the questionnaire study had developed asthma slowly. They reported having suffered from work-related asthma-like symptoms for a mean of 4.8 years earlier and a further mean of 4.8 years after the examinations at FIOH before the diagnosis of asthma was established. The percentage would probably have been higher if the study had had a prospective study design in which also those with a shorter symptomatic period prior to developing asthma would have been included.

Impact of exposure continuation on asthma development

The most important risk factor for developing clinical asthma in study II was continuing exposure to indoor dampness in the work environment. The results suggest a clear association between factors related to indoor dampness and the development of asthma. The continuation of any exposure to dampness was associated with a more than fourfold increase in the risk of asthma (OR 4.6, 95% CI 1.8–11.6). Continued work in the former, non-remediated work environment was associated with a further increase in the risk (OR 6.4, 95% CI 1.5–27.7). When the results are interpreted, the limitations of self-reported data should be considered (discussed in more detail in Section 6.4.2).

Working in a remediated work environment was associated with a decrease in the risk of developing asthma, although the excess risk remained statistically non-significant (OR 2.0, 95% CI 0.7–5.4). The statistical non-significance was likely due to the small number of workers in this category. The remaining excess risk for repaired work environments found in the study may indicate that the remediation of the buildings had been insufficient. In a report of seven case studies of buildings that underwent remediation for different degrees of moisture and mold damage, the results showed that successful remediation is difficult (Haverinen-Shaughnessy et al. 2008). Only in one of seven cases was the remediation completely successful (Haverinen-Shaughnessy et al. 2008).

The findings of study II agree with the results of some recent studies showing that the successful remediation of moldy buildings has significantly reduced asthma morbidity (Jarvis and Morey 2001; Patovirta et al. 2004b). In the intervention study of Jarvis and Morey (2001), a high rate of asthma was found for the 488 occupants of a mold-contaminated office building. After thorough repairs, no excess building-related illness occurred in the 5-year follow-up. In another study, a cluster of asthma cases was identified in a school with indoor dampness and molds, and after building repairs no new cases of asthma appeared among the 31 teachers in a 3-year follow-up (Patovirta et al. 2004b). Similarly, a well-designed intervention study by Kercsmar et al. (2006) showed that the removal of sources of dampness and molds was followed by a significant decrease in the exacerbation of asthma among children. However,

intervention studies on the effect of the remediation of moisture- and mold-damaged buildings are sparse, and the study designs and outcome measures have varied.

A Cochrane Collaboration Review Group conducted a systematic review of the effects of repairing buildings damaged by dampness and mold on respiratory health (Sauni et al. 2011). The group found only moderate to very low-quality evidence that repairing mold-damaged houses and offices decreases asthma-related symptoms and respiratory infections when compared with no intervention among adults (Sauni et al. 2011). The group demanded better quality studies to determine the most effective way to carry out the remediation of damp and mold-damaged buildings to minimize respiratory health hazards (Sauni et al. 2011). Thus it seems important that further studies on this topic be conducted to corroborate the associations that were found in study II.

The results of study II suggest that preventive measures to avoid further exposure are relevant to prevent asthma development. In practice, this finding means that the remediation of moisture and mold damage or the relocation of workers with asthma-like symptoms to a non-moisture-damaged environment is necessary. This conclusion agrees with the WHO recommendation that, in order to avoid adverse health effects, persistent building dampness and microbial growth on interior surfaces should be prevented or minimized. This effort requires well-designed, well-constructed, and well-maintained buildings with proper control of ventilation and temperatures (WHO 2009).

6.2.2 Quality of life and work ability

One clinical impression is that some of the patients whose symptoms initiated in moisture-damaged workplaces suffer from prolonged symptoms that deteriorate their well-being. Some patients report symptoms that they attribute to mold odor or low-level exposures to environmental chemicals, even if there is no major moisture damage or microbial growth in the present environment. However, the subject has not been widely studied. For example, a recent Swedish literature review on the association between adult asthma and dampness and mold stated that the prognosis of symptoms induced by damp and moldy environments is unclear (Torén et al. 2010).

Study III showed that a high proportion of patients with OA caused by indoor-air dampness and molds had impaired QOL 3–12 years after their initial diagnosis when they were compared with patients with WEA and patients with no asthma but with symptoms related to the exposure. In a multivariate model adjusted for age, gender, smoking, atopic history, co-morbidity, and psychological factors, the differences between the groups remained for the physical component of the QOL but not for the mental component. One of the first articles on QOL and OA was a study by Malo et al. (1993), in which the authors investigated persons with OA after their removal from exposure for two or more years. In comparison with persons with non-OA, the OA group showed greater impairment in QOL; this finding corresponds to the results of study III.

Not being employed was a strong determinant of deteriorated QOL in all of its dimensions. The finding that those who were employed had the best QOL scores has earlier been shown for workers diagnosed with OA induced by Western red cedar (Dimich-Ward et al. 2007).

In the follow-up (study IV) among workers previously examined because of a suspicion of an occupational disease related to respiratory symptoms in damp and moldy workplaces, OA and WEA were found to be associated with impaired self-assessed work ability. The diagnosis of OA was associated with a strong, nearly sixfold risk for withdrawal from work due to unemployment or retirement because of disability, in a comparison with a reference group with upper-respiratory symptoms only.

The participants rated their work ability as being worse than in an earlier population-based study from Finland (Gould et al. 2008). Altogether 44% of the entire study population, and even 57% of the OA group, assessed their work ability as 7 or lower (on a scale of 0–10) compared with the lifetime best versus 19% of women aged 45–54 years in the Finnish general population (Gould et al. 2008). Self-assessed work ability has been proven to be a good predictor of retirement due to work disability (Ilmarinen and Tuomi 2004).

In the OA group of study IV, the major reason (31%) for work cessation was retirement because of disability. In comparison, 7% of the Finnish general population aged 16–64 years was on a disability pension in 2007, as was 20% of the age group of 55–64 years (ETK 2008). The proportion of employed persons appears to be surprisingly low, as most of the patients with OA were in occupations with no high physical demands

(i.e., teachers, nurses, office-workers, etc.). They should not become disabled to work when adequately medicated and removed from exposure to moist and moldy environments. In previous studies, OA has been found to be associated with significant socioeconomic impacts (Ameille et al. 1997; Larbanois et al. 2002; Vandenplas et al. 2003; Vandenplas et al. 2011) related to the need of leaving a job, changing occupation, and finding alternative work. To avoid exposure, there is no need for patients with building-related asthma to change occupation, unlike for OA induced by more traditional work sensitizers. Instead, building repairs or a change of workplace is required. In OA studies, removing the worker from the workplace has been linked to better medical outcomes, but invariably to worse socioeconomic outcomes (Henneberger et al. 2011; Vandenplas et al. 2011).

In general, the results of studies III and IV corroborate the clinical impression that a large proportion of patients with OA in relation to exposure to moisture and mold-damaged workplaces has long-standing limitations in everyday life and remains symptomatic and unable to work. The studies may have a wider relevance, as a considerable number of asthma cases has been considered attributable to building dampness and mold (Mudarri and Fisk 2007), even though not generally recognized as OA in many countries.

The results may reflect the fact that the remediation of a building may be time-consuming and not always successful (Haverinen-Shaughnessy et al. 2008; Iossifova et al. 2011), and arrangements for relocation are not always easy to achieve. These factors may, at least at an early stage of symptoms, lengthen sickness absences and delay return to work, which in turn may lead to permanent disability. Several studies have shown evidence indicating that lengthy periods of sickness absence are associated with an increased risk of disability pension (Lund et al. 2008; Wallman et al. 2009).

6.2.3 Why did the outcomes differ between OA and WEA patients

Compensation benefits

It could have been expected that the OA patients would be better off than the other groups due to a liberal compensation system for occupational diseases. In Finland, OA is compensated through the statutory accident compensation system, whereas WEA is not. Compensation covers, for example, medical expenses, income replacement, and vocational rehabilitation. Benefits due to occupational diseases are better than those due to non-occupational diseases, which are covered by general social insurance. Despite compensation benefits, the OA patients clearly had a lower QOL than all of the other groups of patients, they rated their work ability as being lower, and they more often withdrew from work.

Asthma severity

It is unclear whether asthma severity explained the differences between the asthma groups in studies III and IV. As estimated by the use of asthma medication, the asthma symptoms of the OA patients were more persistent, as well as more severe, than those of the WEA patients in study III. A large proportion of the OA patients were using heavy medication still 3–12 years after the diagnosis. Only 11% of the OA patients did not use inhaled steroids, and the need for oral steroid bursts was clearly greater. Both parameters correlated well with QOL—the more medication taken, the worse the QOL. This finding tallies well with the results of a study by Miedinger et al. (2011), in which objectively measured disease activity seemed to be the principal determinant of QOL among 73 patients with OA 2 years after the diagnosis.

According to a systemic review of cohort studies, asthma severity has been found to have a weak positive relation to work disability. One study found a positive relation, while another study found no such relation (Detaille et al. 2009). In a study conducted among OA patients, the severity of asthma was not an important determinant of work status (Ameille et al. 1997). Asthma in general has been shown to be associated with an increased risk of long-term all-cause disability (Hakola et al. 2011).

There may be various reasons for the persistence and severity of the disease, both individual and environmental. To avoid exposure, the options are building remediation or a change to an alternative work environment. Moisture and mold damage in buildings has been excessively common in Finland (Salonen et al. 2007), and often other deficiencies worsening the quality of indoor air, like poor ventilation, occur in connection with moisture problems. Successful repairs are not always easy to achieve. The success estimate of the remediation is dependent on the expectations and the type of measure used (technical criteria, concentration of microbes, or the level of discomfort of the occupants) (Haverinen-Shaughnessy et al. 2008). In some buildings, the inhabitants may exhibit persisting symptoms despite multiple environmental improvements, and even if the remediation is considered technically successful (Haverinen-Shaughnessy et al. 2008; Norbäck 2009). A 3-year follow-up of a 97-person cohort in a water-damaged building found that substantial remediation did not result in an improvement in respiratory health, as reflected by symptom scores, overall medication use, spirometry abnormalities, or sick leave (Iossifova et al. 2011).

To objectively investigate differences in asthma severity between OA and WEA, clinical follow-up studies are needed. If the difference exists, it is possible that originally the more severe cases of asthma have been diagnosed as OA or that mold-induced asthma has a worse prognosis. With a longitudinal study design, uncertainties about the direction of the cause and effect can be minimized.

Mental disorders

After adjustment for depression and anxiety, the differences in QOL between the groups remained. For the patients in study III, the rates of anxiety and depression were lower than shown by Björnsson et al. (1998), who reported positive associations between building-related symptoms and anxiety and depression, as measured by the Hospital Anxiety and Depression Scale. In addition, compared with the results of previous studies on asthmatics, psychological distress was lower than expected among our patients (Lavoie et al. 2006; Kullowatz et al. 2007; Yacoub et al. 2007; Malo et al. 2009). Yacoub et al. (2007) reported significant rates of depression and anxiety, close to 50%, 2 years after the cessation

of exposure among persons with sensitizer-induced OA. In a study by Malo et al. (2009), the rates were up to 40% 3–22 years after the diagnosis of acute irritant-induced asthma. The rates seem to be higher for OA than for non-OA, as Lavoie et al. (2006) observed rates of 23% for anxiety disorders and 20% for depressive disorders in a study on tertiary care patients with asthma.

Neither somatization nor hypochondria explained the differences in QOL between the groups. Earlier, a tendency towards somatization was shown to be associated with symptoms related to the SBS (Berglund and Gidlöf Gunnarsson 2000), which is the reason somatization was included in the present study. The mean scores of the somatization subscale of the Hopkins Symptom Checklist for a community sample of the Finnish population in a study by Holi et al. (1998) were clearly lower than those of our patients, and in an outpatient sample of psychiatric Finnish patients the scores were higher. Higher somatization scores (Mattila et al. 2008), as well as higher hypochondria scores (Rief et al. 2001), have been shown to be associated with female gender, and females were overrepresented in the material of the present study. Similarly, there is an association with somatic diagnoses (Mattila et al. 2008), as all of the symptoms on the somatization subscale may be reflections of a physical illness. In study III, the results did not point to any greater degree of somatization among OA patients than among the other groups. The hypochondriac features measured by a self-rating scale, the Whiteley Index, did not seem to be high in any group; yet a somewhat lower value was scored by the upper-respiratory symptoms group.

In study IV, the models were adjusted for depression and somatization. The adjustment did not markedly modify the risks of poor self-rated work ability and early withdrawal from work among the OA patients. In conclusion, mental disorders did not explain the differences in QOL and work ability outcomes between the OA and WEA patients.

The stressful nature of an OA diagnosis

A recent report has argued that the sudden onset of OA in a previously healthy person may have a psychological impact (Figure 8) (Lavoie et al. 2009). The stressful nature of an OA diagnosis could have been true especially for the patients in the present study, many of whom had seri-

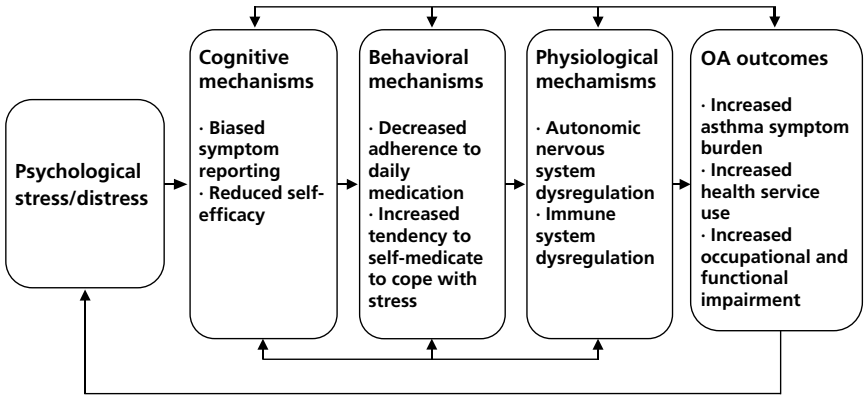


Figure 8. Potential mechanisms linking psychological distress to worse OA outcomes (Lavoie et al. 2009). OA=occupational asthma.

ous health concerns. This possibility may at least partly explain the worse outcomes in the OA group when it was compared with the WEA group.

Although mental disorders (anxiety, depression, somatization, or hypochondria) did not explain the differences in outcome between the OA and WEA patients, the lack of difference does not rule out distress related to an OA diagnosis as a contributing factor. In general, several psychosocial factors, which are not mental disorders, have been recognized as risk factors for disability, such as attitudes or beliefs, emotional reactions such as fear or distress, or relational factors such as conflict or lack of support (Sullivan et al. 2005).

6.2.4 Impact of the symptom picture on work ability

Those with multiple persistent indoor-air symptoms considerably more often perceived their current work ability to be poor when compared with that of those with less significant symptoms. After adjustment for individual variables (e.g., co-morbidity, depression, and somatization), the association between multiple persistent symptoms and impaired self-assessed work ability remained. In a previous study, long-lasting symptoms were shown to be common in some persons with earlier exposure to building dampness and mold (Al-Ahmad et al. 2010), but

the association with impaired work ability that was found in the present study is a new finding. Multiple persistent symptoms were not found to be associated with early withdrawal from work, and this finding may reflect the heterogeneity of the groups. Along with leaving work, the symptoms become alleviated or not. The findings of Al-Ahmad et al. (2010) suggest that mold-exposed persons whose symptoms could initially be attributed to asthma or other allergic responses have long-term respiratory symptoms that cannot be explained on the basis of asthma and that overlap with sick building symptoms. In the present study, the patients in both asthma groups had a non-specific symptom complex similar to that of the SBS, which was common for all of the groups at the baseline (study I). It seems that asthma amplifies the effect of non-specific symptoms with respect to work disability.

In study I, the study population consisted of workers with asthma symptoms who also experienced a variety of non-specific symptoms, like fatigue, fever and chills, dermal symptoms, headache, and arthralgia (Table 4 in article I). The findings concerning the symptom spectrum are in accordance with that of several previous reports (Reijula and Sundman-Digert 2004; Brightman et al. 2008; Wolff et al. 2009; Al-Ahmad et al. 2010). According to the literature, asthma symptoms may also overlap with asthma-like symptoms caused by, for example, vocal cord dysfunction or other disorders (Morris and Christopher 2010; GINA 2011). In other words, people with asthma may also perceive asthma-like symptoms that cannot be explained on the basis of asthma, and this phenomenon is worth noting in the management and control of asthma.

The results of Al-Ahmad et al. (2010) suggest that the non-specific symptom complex related to indoor dampness and mold (described in study I) has similarities to MCS. The researchers studied some features associated with MCS (e.g., sensitivity to detergents, new carpets, and chemical taste) among the patients with earlier exposure to building dampness and mold. The MCS follow-up scores of the mold-exposed group were similar to those of the sick building group and showed marked differences from the normal control group, the finding suggesting a possible degree of overlap for the mold-exposed group with MCS (Al-Ahmad et al. 2010). Overlapping with SBS and MCS has been previously reported (Kipen and Fiedler 2002), and asthma has been recognized as a risk factor for MCS (Kreutzer et al. 1999).

6.2.5 Impact of workplace psychosocial factors on work ability

Perceived poor social climate at work and poor experiences with a supervisor's cooperation at an early stage of the symptoms were determinants for impaired self-assessed work ability and early withdrawal from work. The findings agree with those of previous studies showing a correlation between the psychosocial work environment and indoor-air symptoms (Mendelson et al. 2000; Lahtinen et al. 2004; Runeson et al. 2006; Bakke et al. 2007). Low social support has been found to be associated with indoor-air complaints and symptoms (Mendelson et al. 2000; Runeson et al. 2006). In a Finnish study, Lahtinen et al. (2002) found problems with cooperation for 71% of the workplaces with moisture and mold damage, the employees being more dissatisfied with the cooperation than the superiors. The employees generally felt that the problems they experienced were being downplayed by the management, and they also felt mistrust towards the implemented measures (Lahtinen et al. 2002). According to study IV, it appears that those who perceive their psychosocial work environment more negatively were at an increased risk of long-term adverse work outcomes.

The results are in accordance with the widely recognized fact that causes of disability are multifactorial and not associated with medical conditions alone.

6.3 Limitations of the risk paradigm

Occupational medicine first emerged as a specialist discipline in response to chemical, physical, and biological hazards at work that caused serious and often fatal disease (Coggon 2005). Considerable progress has been made to reduce and eliminate many serious occupational hazards, particularly in developed countries (Blair 2005). Diseases, such as lead poisoning, chemical-induced cancers, and pneumoconiosis had identifiable causes and so proved readily preventable (Baxter et al. 2010). However, the understanding of occupational exposures in the development of chronic diseases and conditions is far from complete (Blair 2005). Not all hazards are under control; the continuing high incidence of disorders

such as WRA is evidence of this problem (Coggon 2005). According to epidemiological studies, occupational causes are not a minor contributor to the disease burden of the population, and there is still potential for prevention.

Simultaneously, there are disorders, including a relationship with work, that cannot be wholly explained by their assumed occupational causes (Baxter et al. 2010). The focus of occupational medicine in developed countries has shifted to these work-related disorders that cause substantial disability and that do not always arise from detectable organic pathology, but rather are responses to triggering exposures that are conditioned by individual characteristics and cultural circumstances (Coggon 2005). Examples of such work-related disorders are low-back pain, occupational stress, and also MCS and SBS. The classical approach to risk management – that a noxious agent or activity produces an injury that can be prevented by eliminating or reducing exposure – has served well in the past, but it may not work for these conditions due to a lack of knowledge and the complexity of the interaction (Räsänen 1998; Coggon 2005). This situation has important implications for the way in which such illnesses can be managed and prevented (Coggon 2005).

It is probable that multiple mechanisms combine to contribute to these expressions of illness. Environmental exposures may have direct health effects, or they may act as symptom triggers, but the mechanisms may be very complex where susceptibility factors (e.g., immunological responses regulated by genetic factors) and modifying factors (e.g., knowledge, beliefs, emotions, and social support) interact (Figure 9) (Kipen and Fiedler 2002). Control of exposures may not always be effective or is not effective enough to reduce the occurrence of illness or disability. The recognition that many kinds of factors may be involved enhances preventive opportunities because control over illnesses can be achieved by the effective management of different dimensions.

As disability is not merely a single disease, simple medicalization of indoor-air problems has not resulted in the successful management of disability. The situation is not only unsatisfactory to the patient, but also to physicians who have been educated to search for precise medical diagnoses. Regarding non-specific low-back pain, which constitutes 95% of low-back pain, it has been recognized that the term non-specific fails to meet the expectations of a "proper" diagnosis and leaves some uncertainty about its

treatment and prognosis, and may lead to a failure of communication and a lack of confidence (Waddell 2005). Another approach is to demedicalize the problem by seeing disability in a larger, biopsychosocial context and to search for disability determinants and focus on disability prevention.

It seems that asthma in damp indoor work environments occurs as a part of a larger disorder. Asthma as a specific disease is relatively easy to diagnose and, in most cases, easy to treat. When asthma is amplified by the non-specific symptom complex, the person suffers from an illness

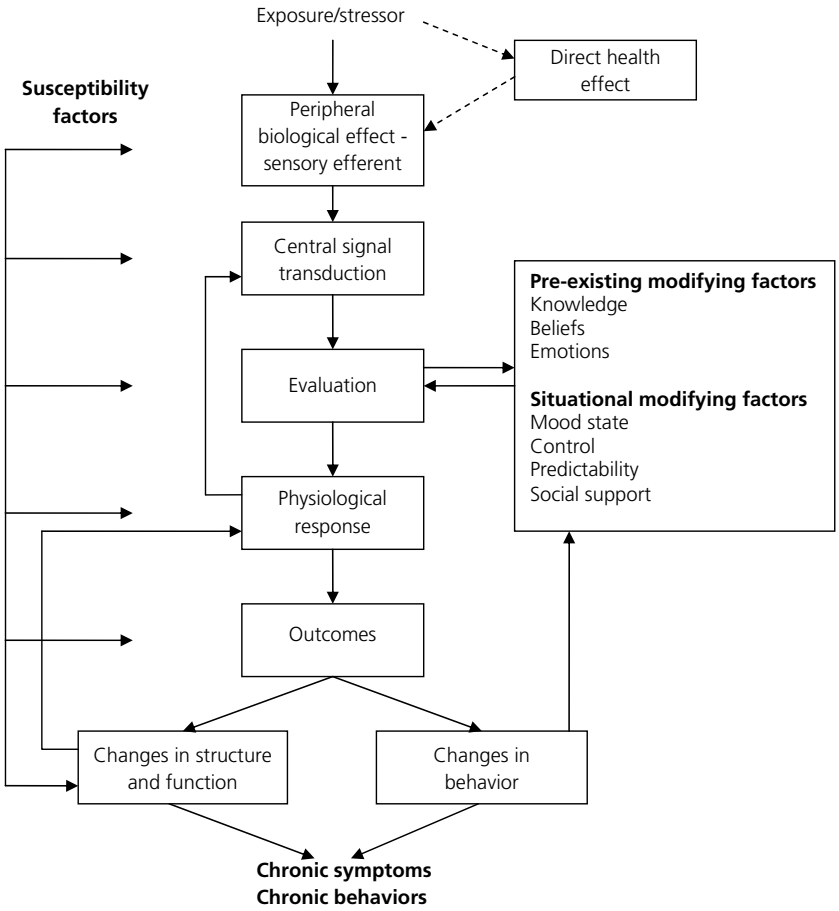


Figure 9. Model of the interrelationships between exposures, susceptibility, modifying factors, and symptoms (Kipen and Fiedler 2002).

that may cause substantial disability. At one end of the continuum are asthmatics whose symptoms improve after building repairs or relocation away from damp environments, and at the other end are persons who, despite these efforts, remain symptomatic.

At the individual level, multifactorial illnesses do not agree with the definition of an occupational disease, which requires that a specific factor inducing the disease be identified and a causal relationship to the factor at work be established. It can be discussed whether OA diagnostics rather harm than benefit individuals, as the accurate separation between OA and WEA induced by indoor dampness and mold is not possible. For medico-legal reasons, the prevailing practice in Finland has been to diagnose asthma induced by workplace dampness and mold as an occupational disease. As with traditional sensitizer-induced OA, defining the exposure and establishing a causal relationship between the exposure and asthma is not possible with the same accuracy. Therefore, clear clinical guidelines for the diagnostics are required to minimize discrepancies.

6.4 Work disability prevention

Regarding building-related conditions or asthma, there has been little research on work disability prevention. Most of the literature on work disability prevention involves low-back pain, which is the most common reason for long-term absence and work disability in industrialized countries (Loisel et al. 2005). Recently, there has been increased interest in the prevention of work disability regardless of the underlying health condition. Studies have identified some consistent results about the risk factors of work disability and interventions, which, according to front line researchers on the subject, appear to be generalizable across different conditions (Pransky et al. 2011). Therefore, it is interesting to glance through the literature concerning musculoskeletal disorders and the prevention of work disability.

Early investigators of low-back pain noted that persons with similar clinical conditions and severity often had very different work outcomes (Pransky et al. 2011). Back schools teaching correct ergonomic techniques or workplace modifications did not succeed in preventing musculoskeletal disability. A biomedical model, based on anatomy and biomechanics

began to evolve into a biopsychosocial model, in which disability is considered a result of human functioning influenced by biomedical, psychological, workplace, health care and compensation system factors (Feuerstein 1991; Loisel et al. 2005). Several significant psychosocial risk factors in the vast literature have been identified, such as those that exist primarily within the individual (e.g., inappropriate fears and beliefs, catastrophizing, disability perceptions, little hope of healing, loss of self efficacy, depressed mood, and anxiety), but also those that are workplace or system-related (e.g., job stress, work dissatisfaction, and lack of social support at work) (Sullivan et al. 2005). Epidemiological evidence suggests that personal circumstances, pain beliefs, and other non-medical factors are more important in the perpetuation of chronic pain and disability (Shaw et al. 2009). The researchers point out that psychosocial risk factors are not mental disorders nor would they necessarily be considered indices of mental dysfunction (Sullivan et al. 2005). They further claim that fear of pain is associated with avoidance behavior, which accentuates anxiety and the long-term negative functional impact (Dupeyron et al. 2011). Patients develop a negative interpretation – catastrophizing – in which physical activity supposedly causes damage and exacerbates pain (Dupeyron et al. 2011).

The researchers dealing with disability due to low-back pain have recognized the difficulties concerning how to implement the knowledge in practice and how to use it in clinical decision making (Lambeek 2009). Work disability prevention should focus on the psychosocial and environmental factors that impede return to work and self-management approaches, together with both clinical and occupational interventions (Waddell and Burton 2005; Costa-Black et al. 2010). For example, therapeutic patient education appears to be critical in order to help patients to better understand their condition and reduce the negative consequences of fear-avoidance behavior (Dupeyron et al. 2011). The education not only includes traditional biomedical information and advice, but also information and organized activities, all of which are designed to overcome fear-avoidance beliefs and promote self-responsibility and self-care (Waddell and Burton 2001; Dupeyron et al. 2011). Patients must be able to understand and manage low-back pain to stay active and improve their QOL (Dupeyron et al. 2011). Workplace interventions, like changes in work design, work conditions

or the work environment, have been shown to reduce sickness absence among workers with musculoskeletal disorders when compared with usual care (van Oostrom et al. 2009). In these interventions, the worker, the supervisor or employer, and a professional in occupational health are involved in formulating a return-to-work plan, but stakeholders from outside the workplace are frequently not, as reviewed a Cochrane Collaboration review group. The authors reported that return to work seems to be influenced by a worker's ability to function and adapt to pain and symptoms rather than to a complete disappearance of pain and other symptoms (van Oostrom et al. 2009).

6.5 Validity issues

6.5.1 The patient series

The large number of persons included in a study is one of its strengths. FIOH acts as a reference institute in the diagnostics of occupational diseases in Finland, and therefore a large material of patient cases was accumulated nationwide. Thus the study participants were derived from the same source population. In addition, in an international comparison, the experience of FIOH in the diagnostics of occupational diseases related to workplace dampness and molds is large. Due to the thorough diagnostic procedures used, the study material can be considered well-characterized. The patients were carefully examined according to diagnostic practices of the time period.

Still, the possibility of diagnostic misclassification is inevitably a weakness of the study. As discussed in Section 6.1.4, a differentiation between OA and WEA caused by building dampness and molds is difficult to achieve. In the 10-year period during which the patient material was collected, SIC tests with mold extracts were routinely used at FIOH in the diagnostics of OA. Thus the diagnostic practices were homogeneous throughout the study period, although some differences between clinicians cannot be ruled out. In addition, the accessibility to test extracts varied throughout the years. Therefore, in study I, the discharge diagnoses given to the patient by FIOH were not used. Instead, the patients were retrospectively classified into groups of probable, possible, and unlikely

OA according to clinical information and test results gathered from the patient files, and also using internationally recommended diagnostic criteria. As the information on SIC tests was available, the utility of PEF monitoring at and away from work as compared with the use of SICs could be assessed.

Exposure was also retrospectively assessed by an experienced indoor-air researcher to insure that the exposure was verified as objectively as possible by homogeneous principles. The evaluation of exposure was based on objective data from the technical reports on building structure damage and analyses on microbial sampling from the workplace. The workplace investigations had not necessarily been performed with aim of proving an occupational disease for the worker in question, but, instead, for solving the indoor-air problem of the workplace. Thus inadequate documents on exposure could mean unreliably performed investigations specifically from the patient's work area. The limitations in defining exposure and assessing causality belong to the nature of the problem and the lack of knowledge concerning exposure, dose–response relationships, causal relations, and, consequently, a paucity of diagnostic tools to prove causal relations.

6.5.2 The questionnaire

The response rate, 61%, for the questionnaire can be regarded as adequate when the long follow-up time is considered. The analysis of non-respondents showed that the OA patients had been more likely to participate in the study. There is, however, little reason to believe that the OA patients with a poor QOL or poor work ability would have been more prone to respond than those with a good value. Even if there would have been a difference in the response rates in relation to the outcome, it would apply to the participants in each group, and, therefore, this potential for bias is limited. A large proportion of those initially referred for investigations did have upper-respiratory symptoms only, the work-relatedness was probably never substantiated, and many never did receive any diagnosis at all. All these people would presumably have lost their interest in participating in a study specifically concerned with work-related respiratory disorders. Similarly it can be assumed that patients still suffering from symptoms were more interested in participat-

ing than those totally symptomless. It may be a source of bias, but it is unlikely to be a major one.

Although studies II–IV were based on a follow-up of the patient series, the study design of all of them was cross-sectional, limiting the interpretation of the results. The outcome variables and the determinants were measured at the same time; hence conclusions about causal relationships cannot be drawn. For example, the assessments of social climate at work were measured at the same time as the outcomes; therefore temporal order could not be demonstrated. If a person attributes disability to workplace conditions, he or she may be more inclined to criticize factors at work when these variables are measured simultaneously. Likewise, in study II, the study design did not allow for the establishment of a causal relation between exposure continuation and asthma development. The results of the studies are instead associations.

The follow-up was based on self-reported data, which is one of the limitations of the study. In the interpretation of the results, limiting the data collection to a questionnaire must be taken into account. Because of the large size of the study population, a clinical re-examination of the patients was unfeasible. The same was true for a thorough investigation of home and workplace conditions at the time of the follow-up. In study II, the information on exposure conditions at the time of the follow-up was based on self-reported data. The information may have been influenced by the participants' awareness of the exposure of interest (i.e., indoor dampness at their workplaces). The persistence of symptoms at work and a physician's diagnosis of asthma at follow-up may have made them more inclined to observe and report dampness at work as compared with those whose symptoms had ceased or attenuated. However, the highest risk of asthma was associated with continued work in the same non-remediated environment. The information on the measures used to repair these workplaces should be reliable.

In addition, the outcome of study II (the development of asthma) was established using questionnaire information on physician-diagnosed asthma. The question is widely used in epidemiological investigations and has been considered to be highly specific (99%) with respect to asthma (Torén et al. 1993). The sensitivity is moderate (Torén et al. 1993) and selective for the severity of disease (Torén et al. 2006). The high specificity makes the question suitable for comparisons of risk

estimates, whereas the moderate sensitivity would lead to an underestimation of incidence, especially for mild disease (Torén et al. 1993; Torén et al. 2006). Although the question concerning a physician's diagnosis of asthma has been shown to be remarkably reliable, the possibility of diagnostic misclassification was considered, and a retrospective assessment of the validity of the patients' allegations was attempted. All those who had reported having received a physician's diagnosis of asthma were contacted. As there was a proportion of cases that could not be reached and 15 cases that did not fulfill the diagnostic criteria, a certain degree of misclassification could not be ruled out. The extent of this bias is difficult to assess. However, the analysis of the 18 verified cases who were still working (an association with an over fourfold risk remained between continued exposure and asthma development) strongly supported the finding of an association between exposure and the risk of developing asthma. In summary, it is unlikely that information bias would explain the associations found between continued exposure to indoor dampness and the development of asthma.

In study IV, two outcomes were used to avoid being dependent solely on self-rating. The two outcomes supplement each other in that self-rated work ability is a good predictor of disability and the second outcome, early withdrawal from work, is a more objective measure of disability, even though dependent on the social context.

Some selection bias, especially in studies II–IV, cannot be ruled out. A series of patients who had been referred to FIOH because of a suspicion of an occupational disease was followed up, and the practices of the referral physicians may have varied. With regard to studies III–IV, the patient series included a representative sample of patients with dampness-related asthma, as most of the OA cases in the country were diagnosed at the FIOH clinic, with known expertise in occupational diseases. For the same reason, the reference group (with upper-respiratory symptoms without asthma) may have had a more severe condition than all of the symptomatic, exposed persons in general, and this possibility may have diluted the effect.

It can be debated whether or not a comparison group of OA or WEA due to conventional, specific asthmagens should have been used in studies III and IV. Such a study design could have introduced other uncertainties and comparison biases, for instance, which exposures causing OA

would have been the most suitable for comparison. Most conventional OA cases have professions with higher physical demands and represent social groups other than the employees in studies III and IV. However, adjustment was practicable for most of the factors that, based on the literature and prior knowledge, are related to indoor-air symptoms (Norbäck 2009) or work disability among asthmatics, for example, gender and occupation type (blue- versus white-collar) (Detaille et al. 2009).

7 CONCLUSIONS

This thesis aimed at answering the study questions by testing the hypotheses of the four studies related to asthma and workplace dampness and molds.

1. The review of the clinically examined patients in study I supports the epidemiological evidence that indoor dampness and mold are associated with new-onset adult asthma. For the primary and secondary prevention of asthma, the current evidence is sufficient to recommend remediation of workplace moisture and mold damage.

   In the OA diagnostics, the presence of excess mold growth can be used as an indicator of exposure. Although there are no valid, quantitative methods for assessing exposure to dampness-related factors, qualitative exposure assessment is sufficient for OA diagnostics. It can be based on descriptions of the extent and location of the moisture and mold damage in the building structures and on microbial measurements. The agreement between the two diagnostic tests, SIC testing with mold extracts and serial PEF monitoring, proved to be acceptably high, in order to regard serial PEF monitoring as an applicable method in the clinical evaluation of OA induced by indoor dampness and molds. This in particular considering the flaws of the SIC, for example due to the complex exposure situation.

   Specific IgE-mediated sensitization to molds occurs, but in a small proportion of cases only. The mechanisms

of asthma induced by indoor dampness and mold remain largely unknown.

2. The results suggest that, for workers with work-related asthma-like symptoms occurring in relation to indoor dampness and molds at work, continuing to work in such environments creates a risk for developing asthma. The association appeared strongest if the worker continued in his or her former unremediated workplace or in any work with continued exposure to indoor dampness. The avoidance of further exposure seemed to decrease the risk significantly. Continued work in the former, but remediated workplace was associated with a reduced risk. Preventive measures to avoid further exposure seem to be relevant in order to prevent asthma development. In practice, such measures would involve remediation of moisture and mold damage or relocation of the worker with asthma-like symptoms to a non-moisture-damaged environment. Follow-up by occupational health services is recommended for patients with respiratory symptoms related to workplace dampness.

3. The results corroborate the clinical impression that a proportion of patients with asthma in relation to exposure to moisture- and mold-damaged workplaces has long-standing limitations in everyday life and remains symptomatic and unable to work.

   Patients diagnosed with OA had worse outcomes than did those with WEA or only respiratory symptoms without asthma. They had a lower QOL and poorer work ability, and they were more often withdrawn from work. Mental disorders did not explain the impact of OA, QOL, or work ability. As estimated by the use of asthma medication, OA seemed to be more severe than WEA. Greater use of asthma medication was a determinant for a worse QOL physical component. Clinical follow-up studies investigating the severity of asthma objectively could add to the knowledge

on the nature of indoor dampness-induced asthma. The acknowledgement of and compensation for dampness-induced asthma as an occupational disease does not seem to be beneficial in preventing disability. More apt measures, like early support and workplace management practices concerning work ability are required.

4. Persons who evaluated their social work environment more negatively and those with multiple, persisting indoor-air symptoms appeared to have an increased risk for poor work ability outcomes. This finding agrees with the widely recognized fact that causes of disability are multifactorial and not associated with medical conditions alone. Some still unknown factors may contribute to an impaired QOL and work ability.

8 POLICY IMPLICATIONS AND RECOMMENDATIONS

On the basis of the findings of this thesis and prior scientific literature, the following recommendations can be made:

1. In the diagnostics of OA induced by workplace dampness and molds, serial PEF monitoring is the principal diagnostic tool available for demonstrating an association between workplace exposure and asthma. SIC testing, which is generally regarded to be the most reliable method for identifying an agent causing OA, is not suitable for diagnosing OA induced by dampness and mold. Unlike SIC testing, serial PEF measurements reflect the entire complex exposure situation at the workplace. The major weakness is that they do not accurately differentiate between WEA and OA.

   Serial PEF monitoring should be initiated without delay once the patient reveals that his or her lower-respiratory symptoms worsen at work or improve away from work. Guidelines for clinicians with respect to the diagnostics of OA induced by workplace dampness and mold are presented as algorithms in Appendices 2 and 3. Appendix 2 explains how to investigate asthma symptoms in occupational health services, and Appendix 3 considers how to proceed in investigations in special health care.

2. Clinical follow-up in occupational health care is recommended for patients with respiratory symptoms related to workplace dampness. The follow-up, the frequency of which depends on the symptoms, includes monitoring symptoms and repeating lung function tests for the early detection and management of asthma. Occupational health professionals have a role in encouraging the workplace to remediate moisture and mold damage from the health point of view. Relocation of the worker to non-moisture damaged work environments is an option.

3. Asthma related to damp indoor work environments is associated with long-term disability. This is a novel health problem, for which it is not wholly clear whether traditional risk management works well. Together with eliminating or reducing exposure to workplace dampness and dampness-related factors, an approach using a biopsychosocial model is needed for disability prevention.

4. An action model for use in occupational health services for the disability prevention of workers with asthma related to workplace dampness is presented in Appendix 4. Together with occupational health services, the worker and the workplace should be involved in planning and processing work retention and return-to-work.

5. Research is required for the causes of disability and the effectiveness of preventive measures (e.g., building repairs, relocation of workers, or other interventions aimed at disability prevention).

9 REFERENCES

Åhman M, Lundin A, Musabasic V, Söderman E (2000). Improved health after intervention in a school with moisture problems. Indoor Air **10**(1): 57–62.

Al-Ahmad M, Manno M, Ng V, Ribeiro M, Liss GM, Tarlo SM (2010). Symptoms after mould exposure including Stachybotrys chartarum, and comparison with darkroom disease. Allergy **65**(2): 245–55.

Ameille J, Pairon JC, Bayeux MC, Brochard P, Choudat D, Conso F, Devienne A, Garnier R, Iwatsubo Y (1997). Consequences of occupational asthma on employment and financial status: a follow-up study. Eur Respir J **10**(1): 55–8.

Ameille J, Pauli G, Calastreng-Crinquand A, Vervloet D, Iwatsubo Y, Popin E, Bayeux-Dunglas MC, Kopferschmitt-Kubler MC (2003). Reported incidence of occupational asthma in France, 1996-99: the ONAP programme. Occup Environ Med **60**(2): 136–41.

Ammattitautiasetus (1988). [The Occupational Diseases Ordinance] 29.12.1988/1347. Available from: http://www.finlex.fi. Finnish.

Ammattitautilaki (1988). [The Occupational Diseases Act] 29.12.1988/1343. Available from: http://www.finlex.fi. Finnish.

Andersson K (2008). Examining building-related symptoms in clinical practice. Scand J Work Environ Health **34**(Suppl 4): 50–53.

Ando M, Suga M, Nishiura Y, Miyajima M (1995). Summer-type hypersensitivity pneumonitis. Intern Med **34**(8): 707–12.

Antova T, Pattenden S, Brunekreef B, Heinrich J, Rudnai P, Forastiere F, Luttmann-Gibson H, Grize L, Katsnelson B, Moshammer H, Nikiforov B, Slachtova H, Slotova K, Zlotkowska R, Fletcher T (2008). Exposure to indoor mould and children's respiratory health in the PATY study. J Epidemiol Community Health **62**(8): 708–14.

Apostolakos MJ, Rossmoore H, Beckett WS (2001). Hypersensitivity pneumonitis from ordinary residential exposures. Environ Health Perspect **109**(9): 979–81.

Arif AA, Whitehead LW, Delclos GL, Tortolero SR, Lee ES (2002). Prevalence and risk factors of work related asthma by industry among United States workers: data from the third national health and nutrition examination survey (1988-94). Occup Environ Med **59**(8): 505–11.

Bakke JV, Moen BE, Wieslander G, Norback D (2007). Gender and the physical and psychosocial work environments are related to indoor air symptoms. J Occup Environ Med **49**(6): 641–50.

Bakke JV, Norback D, Wieslander G, Hollund BE, Florvaag E, Haugen EN, Moen BE (2008). Symptoms, complaints, ocular and nasal physiological signs in university staff in relation to indoor environment - temperature and gender interactions. Indoor Air **18**(2): 131–43.

Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, Maestrelli P, Rooyackers J, Schlunssen V, Vandenplas O, Wilken D (2012). Guidelines for the management of work-related asthma. Eur Respir J **39**(3): 529–45.

Baxter P, Tar-Ching A, Cockcroft A, Durrington P, Harrington J (2010). The changing face of occupational diseases. In: Baxter PJ, Aw TC, Cockcroft A, Durrington P, Harrington JM, eds. Hunter's Diseases of Occupations. 10th edition. London: Hodder Arnold; **p.** 24–9.

Berglund B, Gidlöf Gunnarsson A (2000). Relationships between occupant personality and the sick building syndrome explored. Indoor Air **10**(3): 152–69.

Bergner M, Bobbitt RA, Carter WB, Gilson BS (1981). The Sickness Impact Profile: development and final revision of a health status measure. Med Care **19**(8): 787–805.

Bernstein D, Campo P, Baur X (2006b). Clinical assessment and management of occupational asthma. In: Bernstein IL, Chang-Yeung M, Malo J-L, Bernstein DI, eds. Asthma in the workplace. 3rd ed. New York: Taylor & Francis Group; **p.** 161–78.

Bernstein IL, Bernstein DI, Chan-Yeung M, Malo J-L (2006a). Definition and classification of asthma in the workplace. In: Bernstein IL, Chang-Yeung M, Malo J-L, Bernstein DI, eds. Asthma in the workplace. 3rd ed. New York: Taylor & Francis Group; **p**. 1–8.

Bernstein IL, Keskinen H, Blanc PD, Chan-Yeung M, Malo J-L (2006c). Medicolegal aspects, compensation aspects, and evaluation of impairment/disability. In: Bernstein IL, Chang-Yeung M, Malo J-L, Bernstein DI, eds. Asthma in the workplace. 3rd ed. New York: Taylor & Francis Group; **p.** 319–51.

Bernstein JA, Alexis N, Bacchus H, Bernstein IL, Fritz P, Horner E, Li N, Mason S, Nel A, Oullette J, Reijula K, Reponen T, Seltzer J, Smith A, Tarlo SM (2008). The health effects of non-industrial indoor air pollution. J Allergy Clin Immunol **121**(3): 585–91.

Bjerg A, Ekerljung L, Middelveld R, Dahlen SE, Forsberg B, Franklin K, Larsson K, Lotvall J, Olafsdottir IS, Torén K, Lundback B, Janson C (2011). Increased prevalence of symptoms of rhinitis but not of asthma between 1990 and 2008 in Swedish adults: comparisons of the ECRHS and GA(2)LEN surveys. PLoS One **6**(2): e16082.

Björnsson E, Janson C, Norbäck D, Boman G (1998). Symptoms related to the sick building syndrome in a general population sample: associations with atopy, bronchial hyperresponsiveness and anxiety. Int J Tuberc Lung Dis **2**(12): 1023–8.

Blair A (2005). Occupational medicine: at a turning point or an expansion. Occup Environ Med **62**(5): 285; discussion 287.

Blanc PD (2004). Why quality of life should matter to occupational health researchers. Occup Environ Med 61(7): 571.

Bornehag CG, Blomquist G, Gyntelberg F, Jarvholm B, Malmberg P, Nordvall L, Nielsen A, Pershagen G, Sundell J (2001). Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects (NORDDAMP). Indoor Air **11**(2): 72–86.

Bornehag CG, Sundell J, Bonini S, Custovic A, Malmberg P, Skerfving S, Sigsgaard T, Verhoeff A (2004). Dampness in buildings as a risk factor for health effects, EUROEXPO: a multidisciplinary review of the literature (1998-2000) on dampness and mite exposure in buildings and health effects. Indoor Air **14**(4): 243–57.

Bornehag CG, Sundell J, Hagerhed-Engman L, Sigsgaard T (2005). Association between ventilation rates in 390 Swedish homes and allergic symptoms in children. Indoor air **15**(4): 275–80.

Bourke SJ, Dalphin JC, Boyd G, McSharry C, Baldwin CI, Calvert JE (2001). Hypersensitivity pneumonitis: current concepts. Eur Respir J **18**(Suppl 32): 81s–92s.

Brasche S, Bullinger M, Morfeld M, Gebhardt HJ, Bischof W (2001). Why do women suffer from sick building syndrome more often than men? –subjective higher sensitivity versus objective causes. Indoor Air **11**(4): 217–22.

Brasel TL, Martin JM, Carriker CG, Wilson SC, Straus DC (2005). Detection of airborne Stachybotrys chartarum macrocyclic trichothecene mycotoxins in the indoor environment. Appl Environ Microbiol **71**(11): 7376–88.

Brauer C, Mikkelsen S (2010). The influence of individual and contextual psychosocial work factors on the perception of the indoor environment at work: a multilevel analysis. Int Arch Occup Environ Health **83**(6): 639–51.

Brightman HS, Milton DK, Wypij D, Burge HA, Spengler JD (2008). Evaluating building-related symptoms using the US EPA BASE study results. Indoor Air **18**(4): 335–45.

Burge PS (1993). Use of serial measurements of peak flow in the diagnosis of occupational asthma. Occup Med **8**(2): 279–94.

Burge PS (2004). Sick building syndrome. Occup Environ Med **61**(2): 185–90.

Bush RK, Portnoy JM, Saxon A, Terr AI, Wood RA (2006). The medical effects of mold exposure. J Allergy Clin Immunol **117**(2): 326–33.

Cartier A, Bernstein IL, Burge PS, Cohn JR, Fabbri LM, Hargreave FE, Malo JL, McKay RT, Salvaggio JE (1989). Guidelines for bronchoprovocation on the investigation of occupational asthma. Report of the Subcommittee on Bronchoprovocation for Occupational Asthma. J Allergy Clin Immunol **84**(5 Pt 2): 823–9.

Ceska M, Lundkvist U (1972). A new and simple radioimmunoassay method for the determination of IgE. Immunochemistry **9**(10): 1021–30.

Chiry S, Boulet LP, Lepage J, Forget A, Begin D, Chaboillez S, Malo JL, Gerin M, Lemiere C (2009). Frequency of work-related respiratory symptoms in workers without asthma. Am J Ind Med **52**(6): 447–54.

Chiry S, Cartier A, Malo JL, Tarlo SM, Lemiere C (2007). Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. Chest **132**(2): 483–8.

Coggon D (2005). Occupational medicine at a turning point. Occup Environ Med 62(5): 281–3.

Costa-Black KM, Loisel P, Anema JR, Pransky G (2010). Back pain and work. Best Pract Res Clin Rheumatol **24**(2): 227–40.

Cox-Ganser JM, Rao CY, Park JH, Schumpert JC, Kreiss K (2009). Asthma and respiratory symptoms in hospital workers related to dampness and biological contaminants. Indoor Air **19**(4): 280–90.

Cox-Ganser JM, White SK, Jones R, Hilsbos K, Storey E, Enright PL, Rao CY, Kreiss K (2005). Respiratory morbidity in office workers in a water-damaged building. Environ Health Perspect **113**(4): 485–90.

Crook B, Burton N (2010). Indoor moulds, sick building syndrome and building related illness. Fungal Biol Rev **24**(3-4): 106–13.

Dalton PH, Jaen C (2010). Responses to odors in occupational environments. Curr Opin Allergy Clin Immunol **10**(2): 127–32.

de Boer AG, van Lanschot JJ, Stalmeier PF, van Sandick JW, Hulscher JB, de Haes JC, Sprangers MA (2004). Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res **13**(2): 311–20.

de Groene GJ, Pal TM, Beach J, Tarlo SM, Spreeuwers D, Frings-Dresen MH, Mattioli S, Verbeek JH (2011). Workplace interventions for treatment of occupational asthma. Cochrane Database Syst Rev(5): CD006308.

Derogatis LR, Lipman RS, Covi L (1973). SCL-90: an outpatient psychiatric rating scale–preliminary report. Psychopharmacol Bull **9**(1): 13–28.

Detaille SI, Heerkens YF, Engels JA, van der Gulden JW, van Dijk FJ (2009). Common prognostic factors of work disability among employees with a chronic somatic disease: a systematic review of cohort studies. Scand J Work Environ Health **35**(4): 261–81.

Dicpinigaitis PV (2006). Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. Chest **129**(1 Suppl): 75S–79S.

Dimich-Ward H, Taliadouros V, Teschke K, Chow Y, Abboud R, Chan-Yeung M (2007). Quality of life and employment status of workers with Western red cedar asthma. J Occup Environ Med **49**(9): 1040–5.

Douwes J (2005). (1–>3)-Beta-D-glucans and respiratory health: a review of the scientific evidence. Indoor Air **15**(3): 160–9.

Dupeyron A, Ribinik P, Gelis A, Genty M, Claus D, Herisson C, Coudeyre E (2011). Education in the management of low back pain: literature review and recall of key recommendations for practice. Ann Phys Rehabil Med **54**(5): 319–35.

EAACI (1989). Skin tests used in type I allergy testing Position paper. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. Allergy **44**(Suppl 10): 1–59.

EAACI (1992). Guidelines for the diagnosis of occupational asthma. Subcommittee on 'Occupational Allergy' of the European Academy of Allergology and Clinical Immunology. Clin Exp Allergy **22**(1): 103–8.

Edvardsson B, Stenberg B, Bergdahl J, Eriksson N, Linden G, Widman L (2008). Medical and social prognoses of non-specific building-related symptoms (Sick Building Syndrome): a follow-up study of patients previously referred to hospital. Int Arch Occup Environ Health **81**(7): 805–12.

Enriquez-Matas A, Quirce S, Hernandez E, Vereda A, Carnes J, Sastre J (2007). Hypersensitivity pneumonitis caused by domestic exposure to molds. J Investig Allergol Clin Immunol **17**(2): 126–7.

Esch RE (2004). Manufacturing and standardizing fungal allergen products. J Allergy Clin Immunol **113**(2): 210–5.

ETK (2008). Statistical Yearbook of Pensioners in Finland 2007. Official Statistics of Finland, Social Protection 2008. Helsinki: Finnish Centre for Pensions and The Social Insurance Institution of Finland. Available from: http://www.etk.fi/en/service/home/770/publications. Finnish, Swedish, English.

Eurostat (2011) [Internet]. Health and safety at work; Data. Luxembourg: European Commission, Eurostat (the statistical office of the European Union) [updated 2011 April 15; cited 2012 March 23]. Available from: http://epp.eurostat.ec.europa.eu/portal/page/portal/health/health_safety_work/data

Feuerstein M (1991). A multidisciplinary approach to the prevention, evaluation, and management of work disability. J Occup Rehabil **1**(1): 5–12.

Fiedler N, Kelly-McNeil K, Ohman-Strickland P, Zhang J, Ottenweller J, Kipen HM (2008). Negative affect and chemical intolerance as risk factors for building-related symptoms: a controlled exposure study. Psychosom Med **70**(2): 254–62.

Fink P, Ewald H, Jensen J, Sorensen L, Engberg M, Holm M, Munk-Jorgensen P (1999). Screening for somatization and hypochondriasis in primary care and neurological in-patients: a seven-item scale for hypochondriasis and somatization. J Psychosom Res **46**(3): 261–73.

Fishwick D, Barber CM, Bradshaw LM, Harris-Roberts J, Francis M, Naylor S, Ayres J, Burge PS, Corne JM, Cullinan P, Frank TL, Hendrick D, Hoyle J, Jaakkola M, Newman-Taylor A, Nicholson P, Niven R, Pickering A, Rawbone R, Stenton C, Warburton CJ, Curran AD (2008). Standards of care for occupational asthma. Thorax **63**(3): 240–50.

Fishwick D, Bradshaw L, Davies J, Henson M, Stenton C, Burge S, Niven R, Warburton CJ, Hendrick D, Rogers T, Rawbone R, Curran AD (2007). Are we failing workers with symptoms suggestive of occupational asthma? Prim Care Respir J **16**(5): 304–10.

Fisk WJ, Eliseeva EA, Mendell MJ (2010). Association of residential dampness and mold with respiratory tract infections and bronchitis: a meta-analysis. Environ Health **9**: 72.

Fisk WJ, Lei-Gomez Q, Mendell MJ (2007). Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. Indoor Air **17**(4): 284–96.

Fletcher AM, London MA, Gelberg KH, Grey AJ (2006). Characteristics of patients with work-related asthma seen in the New York State Occupational Health Clinics. J Occup Environ Med **48**(11): 1203–11.

Gibson PR, Lindberg A (2011). Physicians' perceptions and practices regarding patient reports of multiple chemical sensitivity. ISRN Nurs **2011**: 838930.

GINA (2011) [Internet]. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) [updated 2011 Dec; cited 2012 March 15]. Available from: http://www.ginasthma.org/.

Gomzi M, Bobic J, Radosevic-Vidacek B, Macan J, Varnai VM, Milkovic-Kraus S, Kanceljak-Macan B (2007). Sick building syndrome: psychological, somatic, and environmental determinants. Arch Environ Occup Health **62**(3): 147–55.

Gould R, Ilmarinen J, Järvisalo J, Koskinen S, eds (2008). Dimensions of work ability. Results of the Health 2000 Survey. Helsinki: Finnish Centre for Pensions, The Social Insurance Institution, National Public Health Institution, Finnish Institute of Occupational Health. Available from: http://www.etk.fi/en/service/home/770/publications

Gunnbjörnsdottir MI, Franklin KA, Norbäck D, Björnsson E, Gislason D, Lindberg E, Svanes C, Omenaas E, Norrman E, Jogi R, Jensen EJ, Dahlman-Höglund A, Janson C, RHINE Study Group (2006). Prevalence and incidence of respiratory symptoms in relation to indoor dampness: the RHINE Study. Thorax **61**(3): 221-5.

Haahtela T (1999). Early treatment of asthma. Allergy **54**(Suppl 49): 74–81.

Hakola R, Kauppi P, Leino T, Ojajarvi A, Pentti J, Oksanen T, Haahtela T, Kivimaki M, Vahtera J (2011). Persistent asthma, comorbid conditions and the risk of work disability: a prospective cohort study. Allergy **66**(12): 1598–603.

Haverinen U (2002). Modeling moisture damage observations and their association with health symptoms. Doctoral Dissertation. Kuopio: National Public Health Institute, Department of Environmental Health.

Haverinen-Shaughnessy U (2012). Prevalence of dampness and mold in European housing stock. J Expo Sci Environ Epidemiol **22**(5): 461–7.

Haverinen-Shaughnessy U, Hyvarinen A, Putus T, Nevalainen A (2008). Monitoring success of remediation: seven case studies of moisture and mold damaged buildings. Sci Total Environ **399**(1-3): 19–27.

Haverinen U, Husman T, Vahteristo M, Koskinen O, Moschandreas D, Nevalainen A, Pekkanen J (2001). Comparison of two-level and three-level classifications of moisture-damaged dwellings in relation to health effects. Indoor Air **11**(3): 192–9.

Hays RD, Sherbourne CD, Mazel RM (1993). The RAND 36-Item Health Survey 1.0. Health Econ **2**(3): 217–27.

Heinonen H, Aro AR, Aalto AM, Uutela A (2004). Is the evaluation of the global quality of life determined by emotional status? Qual Life Res **13**(8): 1347–56.

Hellgren U-M, Palomäki E, Lahtinen M, Riuttala H, Reijula K (2008). Complaints and symptoms among hospital staff in relation to indoor air and the condition and need for repairs in hospital buildings. Scand J Work Environ Health **34**(Suppl 4): 58–63.

Hellgren UM, Hyvärinen M, Holopainen R, Reijula K (2011). Perceived indoor air quality, air-related symptoms and ventilation in Finnish hospitals. Int J Occup Med Environ Health **24**(1): 48–56.

Henneberger PK, Redlich CA, Callahan DB, Harber P, Lemiere C, Martin J, Tarlo SM, Vandenplas O, Torén K (2011). An official american thoracic society statement: work-exacerbated asthma. Am J Respir Crit Care Med **184**(3): 368–78.

Hodgson M (2002). Indoor environmental exposures and symptoms. Environ Health Perspect **110**(Suppl 4): 663–7.

Holi MM, Sammallahti PR, Aalberg VA (1998). A Finnish validation study of the SCL-90. Acta Psychiatr Scand **97**(1): 42–6.

Hope AP, Simon RA (2007). Excess dampness and mold growth in homes: an evidence-based review of the aeroirritant effect and its potential causes. Allergy Asthma Proc **28**(3): 262–70.

Horner WE, Helbling A, Salvaggio JE, Lehrer SB (1995). Fungal allergens. Clin Microbiol Rev **8**(2): 161–79.

Hoy R (2012). Work-related laryngeal syndromes. Curr Opin Allergy Clin Immunol **12**(2): 95–101.

Hoy RF, Ribeiro M, Anderson J, Tarlo SM (2010). Work-associated irritable larynx syndrome. Occup Med (Lond) **60**(7): 546–51.

Hunt SM, McKenna SP, McEwen J, Williams J, Papp E (1981). The Nottingham Health Profile: subjective health status and medical consultations. Soc Sci Med A **15**(3 Pt 1): 221–9.

Hyvärinen A, Sebastian A, Pekkanen J, Larsson L, Korppi M, Putus T, Nevalainen A (2006). Characterizing microbial exposure with ergosterol, 3-hydroxy fatty acids, and viable microbes in house dust: determinants and association with childhood asthma. Arch Environ Occup Health **61**(4): 149–57.

IARC (1993). IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 56: Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins - summary of data reported and evaluation. Lyon: International Agency for Research on Cancer.

IARC (2002). IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 82: Some traditional herbal medicines, some mycotoxins, naphtalene and styrene - summary of data reported and evaluation. Lyon: International Agency for Reasearch on Cancer.

Ilmarinen J (2006). Towards a longer worklife. Helsinki: Finnish Institute of Occupational Health.

Ilmarinen J, Tuomi K (2004). Past, present and future of work ability. People and Work Research Reports **65**: 1–25.

Immonen J, Meklin T, Taskinen T, Nevalainen A, Korppi M (2001). Skin-prick test findings in students from moisture- and mould-damaged schools: a 3-year follow-up study. Pediatr Allergy Immunol **12**(2): 87–94.

IOM (2004). Damp Indoor Spaces and Health, Institute of Medicine. Washington, DC: The National Academies Press.

Iossifova YY, Cox-Ganser JM, Park JH, White SK, Kreiss K (2011). Lack of respiratory improvement following remediation of a water-damaged office building. Am J Ind Med **54**(4): 269–77.

Iossifova YY, Reponen T, Ryan PH, Levin L, Bernstein DI, Lockey JE, Hershey GK, Villareal M, LeMasters G (2009). Mold exposure during infancy as a predictor of potential asthma development. Ann Allergy Asthma Immunol **102**(2): 131–7.

Iversen M (2002). Toxic pneumonitis: "Organic" agents. In: Hendrick DJ, Burge PS, Beckett WS, Churg A, eds. Occupational Disorders of the Lung. Edinburgh: WB Saunders; **p.** 221–7.

Jaakkola JJ, Hwang BF, Jaakkola N (2005). Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. Environ Health Perspect **113**(3): 357–61.

Jaakkola JJ, Ieromnimon A, Jaakkola MS (2006a). Interior surface materials and asthma in adults: a population-based incident case-control study. Am J Epidemiol **164**(8): 742–9.

Jaakkola JJ, Knight TL (2008). The role of exposure to phthalates from polyvinyl chloride products in the development of asthma and allergies: a systematic review and meta-analysis. Environ Health Perspect **116**(7): 845–53.

Jaakkola JJK, Jaakkola MS (2010). Health effects related to non-industrial workplace indoor environments. In: Baxter PJ, Aw TC, Cockcroft A, Durrington P, Harrington JM, eds. Hunter's Diseases of Occupations. 10th edition. London: Hodder Arnold; **p.** 921–38.

Jaakkola MS, Ieromnimon A, Jaakkola JJ (2006b). Are atopy and specific IgE to mites and molds important for adult asthma? J Allergy Clin Immunol **117**(3): 642–8.

Jaakkola MS, Jaakkola JJ (2012). Assessment of public health impact of work-related asthma. BMC Med Res Methodol **12**(1): 22.

Jaakkola MS, Nordman H, Piipari R, Uitti J, Laitinen J, Karjalainen A, Hahtola P, Jaakkola JJ (2002). Indoor dampness and molds and development of adult-onset asthma: a population-based incident case-control study. Environ Health Perspect **110**(5): 543–7.

Jarvis JQ, Morey PR (2001). Allergic respiratory disease and fungal remediation in a building in a subtropical climate. Appl Occup Environ Hyg **16**(3): 380–8.

Juniper EF (1999). Health-related quality of life in asthma. Curr Opin Pulm Med **5**(2): 105-10.

Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE (1993). Measuring quality of life in asthma. Am Rev Respir Dis **147**(4): 832–8.

Kankkunen P, Rintahaka J, Aalto A, Leino M, Majuri ML, Alenius H, Wolff H, Matikainen S (2009). Trichothecene mycotoxins activate inflammatory response in human macrophages. J Immunol **182**(10): 6418–25.

Karjalainen A, Kurppa K, Martikainen R, Karjalainen J, Klaukka T (2002). Exploration of asthma risk by occupation–extended analysis of an incidence study of the Finnish population. Scand J Work Environ Health **28**(1): 49–57.

Karjalainen A, Kurppa K, Martikainen R, Klaukka T, Karjalainen J (2001). Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. Am J Respir Crit Care Med **164**(4): 565–8.

Karjalainen A, Kurppa K, Virtanen S, Keskinen H, Nordman H (2000). Incidence of occupational asthma by occupation and industry in Finland. Am J Ind Med **37**(5): 451–8.

Karjalainen A, Niederlaender E (2004). Occupational Diseases in Europe in 2001. Luxembourg: European Communities, Eurostat. Available from: http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-NK-04-015/EN/KS-NK-04-015-EN.PDF.

Karvala K, Nordman H, Luukkonen R, Nykyri E, Lappalainen S, Hannu T, Toskala E (2008). Occupational rhinitis in damp and moldy workplaces. Am J Rhinol **22**(5): 457–62.

Katayama N, Fujimura M, Yasui M, Ogawa H, Nakao S (2008). Hypersensitivity pneumonitis and bronchial asthma attacks caused by environmental fungi. Allergol Int **57**(3): 277–80.

Kercsmar CM, Dearborn DG, Schluchter M, Xue L, Kirchner HL, Sobolewski J, Greenberg SJ, Vesper SJ, Allan T (2006). Reduction in asthma morbidity in children as a result of home remediation aimed at moisture sources. Environ Health Perspect **114(**10): 1574–80.

Keskinen H, Piirilä P, Nordman H, Nurminen M (1996). Pocket-sized spirometer for monitoring bronchial challenge procedures. Clin Physiol **16**(6): 633–43.

Kipen HM, Fiedler N (2002). Environmental factors in medically unexplained symptoms and related syndromes: the evidence and the challenge. Environ Health Perspect **110**(Suppl 4): 597–9.

Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, Greenberger PA, Kariuki B, Kita H, Kurup VP, Moss RB, Niven RM, Pashley CH, Slavin RG, Vijay HM, Wardlaw AJ (2012). Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol **129**(2): 280–91; quiz 292–3.

Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, Radon K, Torén K, Alliksoo A, Benke G, Blanc PD, Dahlman-Hoglund A, D'Errico A, Hery M, Kennedy S, Kunzli N, Leynaert B, Mirabelli MC, Muniozguren N, Norback D, Olivieri M, Payo F, Villani S, van Sprundel M, Urrutia I, Wieslander G, Sunyer J, Anto JM (2007). Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). Lancet **370**(9584): 336–41.

Kolmodin-Hedman B, Blomquist G, Sikstrom E (1986). Mould exposure in museum personnel. Int Arch Occup Environ Health **57**(4): 321–3.

Kotimaa MH, Terho EO, Husman K (1987). Airborne moulds and actinomycetes in work environment of farmers. Eur J Respir Dis Suppl **152**: 91–100.

Kreutzer R, Neutra RR, Lashuay N (1999). Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol **150**(1): 1–12.

Kujala V, Remes J, Latvala J, Jarvelin MR (2005). Incidence of asthma in twelve thousand Finnish adults born in 1966. Int J Occup Med Environ Health **18**(3): 255–8.

Kullowatz A, Kanniess F, Dahme B, Magnussen H, Ritz T (2007). Association of depression and anxiety with health care use and quality of life in asthma patients. Respir Med **101**(3): 638–44.

Lahtinen M, Huuhtanen P, Kahkonen E, Reijula K (2002). Psychosocial dimensions of solving an indoor air problem. Indoor Air **12**(1): 33–46.

Lahtinen M, Huuhtanen P, Reijula K (1998). Sick building syndrome and psychosocial factors - a literature review. Indoor Air **8**(S4): 71–80.

Lahtinen M, Lappalainen S, Reijula K (2008). Multiprofessional teams resolving indoor-air problems - emphasis on the psychosocial perspective. Scand J Work Environ Health **34**(Suppl 4): 30–4.

Lahtinen M, Salonen H, Lappalainen S, Huttunen J, Reijula K (2009). Renovation of a "sick building": the challenge of attaining the confidence of occupants. Am J Ind Med **52**(5): 438–45.

Lahtinen M, Sundman-Digert C, Reijula K (2004). Psychosocial work environment and indoor air problems: a questionnaire as a means of problem diagnosis. Occup Environ Med **61**(2): 143–9.

Lambeek LC, van Mechelen W, Buijs PC, Loisel P, Anema JR (2009). An integrated care program to prevent work disability due to chronic low back pain: a process evaluation within a randomized controlled trial. BMC Musculoskelet Rehabil **10**: 147.

Laney AS, Cragin LA, Blevins LZ, Sumner AD, Cox-Ganser JM, Kreiss K, Moffatt SG, Lohff CJ (2009). Sarcoidosis, asthma, and asthma-like symptoms among occupants of a historically water-damaged office building. Indoor Air **19**(1): 83–90.

Larbanois A, Jamart J, Delwiche JP, Vandenplas O (2002). Socioeconomic outcome of subjects experiencing asthma symptoms at work. Eur Respir J **19**(6): 1107–13.

Lavoie KL, Bacon SL, Barone S, Cartier A, Ditto B, Labrecque M (2006). What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? Chest **130**(4): 1039–47.

Lavoie KL, Joseph M, Bacon SL (2009). Psychological distress and occupational asthma. Curr Opin Allergy Clin Immunol **9**(2): 103–9.

Lehtinen A, Rahkonen E (2004). Tapaturma- ja liikennevakuutuksen täyskustannusvastuu. Suomen Lääkäril **59**(17): 1825–7. Finnish.

Leino M (2006). Damp building moulds: Assessment of sensitization in patients and studies into mechanisms of airway inflammation using experimental models. Thesis. Helsinki: University of Helsinki, Faculty of Medicine.

Leino MS, Alenius HT, Fyhrquist-Vanni N, Wolff HJ, Reijula KE, Hintikka EL, Salkinoja-Salonen MS, Haahtela T, Makela MJ (2006). Intranasal exposure to Stachybotrys chartarum enhances airway inflammation in allergic mice. Am J Respir Crit Care Med **173**(5): 512–8.

Leino M, Makela M, Reijula K, Haahtela T, Mussalo-Rauhamaa H, Tuomi T, Hintikka EL, Alenius H (2003). Intranasal exposure to a damp building mould, Stachybotrys chartarum, induces lung inflammation in mice by satratoxin-independent mechanisms. Clin Exp Allergy **33**(11): 1603–10.

Leira HL, Bratt U, Slastad S (2005). Notified cases of occupational asthma in Norway: exposure and consequences for health and income. Am J Ind Med **48**(5): 359–64.

Lemiere C (2007). Induced sputum and exhaled nitric oxide as noninvasive markers of airway inflammation from work exposures. Curr Opin Allergy Clin Immunol **7**(2): 133–7.

Lignell U, Meklin T, Rintala H, Hyvärinen A, Vepsälainen A, Pekkanen J, Nevalainen A (2008). Evaluation of quantitative PCR and culture methods for detection of house dust fungi and streptomycetes in relation to moisture damage of the house. Lett Appl Microbiol **47**(4): 303–8.

Lindström K, Elo A-L, Skogstad A, Dallner M, Gamberale F, Hottinen V, Knardahl S, Örhede E (2000). User's Guide for the QPSNordic: General Nordic Questionnaire for Psychological and Social Factors at Work. Copenhagen: Nordic Council of Ministers.

Liss GM, Tarlo SM (1991). Peak expiratory flow rates in possible occupational asthma. Chest **100**(5): 1480.

Loisel P, Buchbinder R, Hazard R, Keller R, Scheel I, van Tulder M, Webster B (2005). Prevention of work disability due to musculoskeletal disorders: the challenge of implementing evidence. J Occup Rehabil **15**(4): 507–24.

Lorenz W, Sigrist G, Shakibaei M, Mobasheri A, Trautmann C (2006). A hypothesis for the origin and pathogenesis of rheumatoid diseases. Rheumatol Int **26**(7): 641–54.

Lund T, Kivimaki M, Labriola M, Villadsen E, Christensen KB (2008). Using administrative sickness absence data as a marker of future disability pension: the prospective DREAM study of Danish private sector employees. Occup Environ Med **65**(1): 28–31.

Lundell S, Tuominen E, Hussi T, Klemola S, Lehto E, Mäkinen E, Oldenbourg R, Saarelma-Thiel T, Ilmarinen J (2011). Ikävoimaa työhön. Helsinki: Työterveyslaitos. Finnish.

Luosujärvi RA, Husman TM, Seuri M, Pietikäinen MA, Pollari P, Pelkonen J, Hujakka HT, Kaipiainen-Seppänen OA, Aho K (2003). Joint symptoms and diseases associated with moisture damage in a health center. Clin Rheumatol **22**(6): 381–5.

Maier WC, Arrighi HM, Morray B, Llewellyn C, Redding GJ (1997). Indoor risk factors for asthma and wheezing among Seattle school children. Environ Health Perspect **105**(2): 208–14.

Majvik (1998). Majvikin suositus: Kosteusvauriomikrobien aiheuttamien oireiden selvittely. Suomen Lääkäril **53**(18-19): 2149. Finnish.

Majvik (2007). Majvik II -suositus: Kosteusvauriomikrobeihin liittyvien oireiden selvittely. Suomen Lääkäril **62**(7): 655–64. Finnish.

Malmberg P, Rask-Andersen A, Rosenhall L (1993). Exposure to microorganisms associated with allergic alveolitis and febrile reactions to mold dust in farmers. Chest **103**(4): 1202–9.

Malo JL, Boulet LP, Dewitte JD, Cartier A, L'Archeveque J, Cote J, Bedard G, Boucher S, Champagne F, Tessier G, et al. (1993). Quality of life of subjects with occupational asthma. J Allergy Clin Immunol **91**(6): 1121–7.

Malo JL, Trudeau C, Ghezzo H, L'Archeveque J, Cartier A. Do subjects investigated for occupational asthma through serial peak expiratory flow measurements falsify their results? J Allergy Clin Immunol **96**(5 Pt 1): 601-7.

Malo JL, Chan-Yeung M (2009). Agents causing occupational asthma. J Allergy Clin Immunol **123**(3): 545–50.

Malo JL, L'Archeveque J, Castellanos L, Lavoie K, Ghezzo H, Maghni K (2009). Long-term outcomes of acute irritant-induced asthma. Am J Respir Crit Care Med **179**(10): 923–8.

Marabini A, Siracusa A, Stopponi R, Tacconi C, Abbritti G (2003). Outcome of occupational asthma in patients with continuous exposure: a 3-year longitudinal study during pharmacologic treatment. Chest **124**(6): 2372–6.

Marks GB, Dunn SM, Woolcock AJ (1992). A scale for the measurement of quality of life in adults with asthma. J Clin Epidemiol **45**(5): 461–72.

Marmot AF, Eley J, Stafford M, Stansfeld SA, Warwick E, Marmot MG (2006). Building health: an epidemiological study of "sick building syndrome" in the Whitehall II study. Occup Environ Med **63**(4): 283–9.

Martimo KP (2010). Musculoskeletal disorders, disability and work. Doctoral Dissertation. Kuopio: Institute of Public Health and Clinical Nutrition, University of Eastern Finland.

Matheson MC, Abramson MJ, Dharmage SC, Forbes AB, Raven JM, Thien CK, Walters EH (2005). Changes in indoor allergen and fungal levels predict changes in asthma activity among young adults. Clin Exp Allergy **35**(7): 907-13.

Matte TD, Hoffman RE, Rosenman KD, Stanbury M (1990). Surveillance of occupational asthma under the SENSOR model. Chest **98**(Suppl 5): 173S–8S.

Mattila AK, Kronholm E, Jula A, Salminen JK, Koivisto AM, Mielonen RL, Joukamaa M (2008). Alexithymia and somatization in general population. Psychosom Med **70**(6): 716–22.

Maynard RL (2010). Risks and hazards in occupational and environmental exposures. In: Baxter PJ, Aw TC, Cockcroft A, Durrington P, Harrington JM, eds. Hunter's Diseases of Occupations. 10th edition. London: Hodder Arnold; **p.** 141–7.

Mazurek JM, Filios M, Willis R, Rosenman KD, Reilly MJ, McGreevy K, Schill DP, Valiante D, Pechter E, Davis L, Flattery J, Harrison R (2008). Work-related asthma in the educational services industry: California, Massachusetts, Michigan, and New Jersey, 1993-2000. Am J Ind Med **51**(1): 47–59.

McDonald JC, Chen Y, Zekveld C, Cherry NM (2005). Incidence by occupation and industry of acute work related respiratory diseases in the UK, 1992–2001. Occup Environ Med **62**(12): 836–42.

McDowell I (2006). General health status and quality of life. In: Measuring Health. A guide to rating scales and questionnaires. 3rd edition. New York: Oxford University Press; p. 520-703.

Meklin T, Hyvarinen A, Toivola M, Reponen T, Koponen V, Husman T, Taskinen T, Korppi M, Nevalainen A (2003). Effect of building frame and moisture damage on microbiological indoor air quality in school buildings. AIHA J (Fairfax, Va) **64**(1): 108–16.

Meklin T, Putus T, Hyvärinen A, Haverinen-Shaughnessy U, Lignell U, Nevalainen A (2007). Koulurakennusten kosteus- ja homevauriot. Opas ongelmien selvittämiseen. Kansanterveyslaitoksen julkaisuja C 9/2007. Helsinki: Kansanterveyslaitos. Finnish.

Mendell MJ (2003). Indices for IEQ and building-related symptoms. Indoor Air **13**(4): 364-8; author reply 373–4.

Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J (2011). Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. Environ Health Perspect **119**(6): 748–56.

Mendelson M, Catano V, Kelloway K (2000). The role of stress and social support in Sick Building Syndrome. Work & Stress **14**(2): 137–55.

Miedinger D, Lavoie KL, L'Archeveque J, Ghezzo H, Zunzunuegui MV, Malo JL (2011). Quality-of-Life, Psychological, and Cost Outcomes 2 Years After Diagnosis of Occupational Asthma. J Occup Environ Med **53**(3): 231–8.

Millqvist E (2011). The airway sensory hyperreactivity syndrome. Pulm Pharmacol Ther **24**(3): 263–6.

Moore VC, Jaakkola MS, Burge PS (2010). A systematic review of serial peak expiratory flow measurements in the diagnosis of occupational asthma. Ann Respir Med **1**: 31–44.

Morris MJ, Christopher KL (2010). Diagnostic criteria for the classification of vocal cord dysfunction. Chest **138**(5): 1213–23.

Mudarri D, Fisk WJ (2007). Public health and economic impact of dampness and mold. Indoor Air **17**(3): 226–35.

Myllykangas-Luosujärvi R, Seuri M, Husman T, Korhonen R, Pakkala K, Aho K (2002). A cluster of inflammatory rheumatic diseases in a moisture-damaged office. Clin Exp Rheumatol **20**(6): 833–6.

Nafstad P, Oie L, Mehl R, Gaarder PI, Lodrup-Carlsen KC, Botten G, Magnus P, Jaakkola JJK (1998). Residential dampness problems and symptoms and signs of bronchial obstruction in young Norwegian children. Am J Respir Crit Care **157**(2): 410–4.

Nagayoshi M, Tada Y, West J, Ochiai E, Watanabe A, Toyotome T, Tanabe N, Takiguchi Y, Shigeta A, Yasuda T, Shibuya K, Kamei K, Tatsumi K (2011). Inhalation of Stachybotrys chartarum evokes pulmonary arterial remodeling in mice, attenuated by Rho-kinase inhibitor. Mycopathologia **172**(1): 5–15.

Nevalainen A, Partanen P, Jääskeläinen E, Hyvärinen A, Koskinen O, Meklin T, Vahteristo M, Koivisto J, T H (1998). Prevalence of moisture problems in Finnish houses. Indoor Air **8**(Suppl 4): 45–49.

Newman Taylor A, Nicholson P, Cullinan P, Boyle C, Burge P (2004). Guidelines for the prevention, identification & management of occupational asthma: evidence review & recommendations. London: British Occupational Health Research Foundation.

Nicholson PJ, Cullinan P, Burge S (2012). Concise guidance: diagnosis, management and prevention of occupational asthma. Clin Med **12**(2): 156–9.

Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C (2005). Evidence based guidelines for the prevention, identification, and management of occupational asthma. Occup Environ Med **62**(5): 290–9.

NICNAS, OCS (2008). Australian Government Department of Health and Ageing and Office of Chemical safety. A scientific review of multiple chemical sensitivity: identifying key research needs. Working Draft Report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and the Office of Chemical Safety (OCS). Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/63D8BC270AC92502CA2574F8001BCDF9/$File/MCSdrafReport.pdf

Nielsen GD, Larsen ST, Olsen O, Lovik M, Poulsen LK, Glue C, Wolkoff P (2007). Do indoor chemicals promote development of airway allergy? Indoor Air **17**(3): 236–55.

Niemelä R, Seppänen O, Korhonen P, Reijula K (2006). Prevalence of building-related symptoms as an indicator of health and productivity. Am J Ind Med **49**(10): 819–25.

Norbäck D (2009). An update on sick building syndrome. Curr Opin Allergy Clin Immunol **9**(1): 55–9.

Nordman H, Karjalainen A, Keskinen H (1999). Incidence of occupational asthma: A comparison by reporting systems. Am J Ind Med **36**(Suppl 1): 130–3.

Oie L, Nafstad P, Botten G, Magnus P, Jaakkola JK (1999). Ventilation in homes and bronchial obstruction in young children. Epidemiology **10**(3): 294-9.

Oksa P, Palo L, Saalo A, Jolanki R, Mäkinen I, Kauppinen T, eds (2010). Ammattitaudit ja ammattitautiepäilyt 2008. Työperäisten sairauksien rekisteriin kirjatut uudet tapaukset. Helsinki: Työterveyslaitos. Finnish.

Oksa P, Palo L, Saalo A, Jolanki R, Mäkinen I, Kauppinen T, eds (2011). Ammattitaudit ja ammattitautiepäilyt 2009. Työperäisten sairauksien rekisteriin kirjatut uudet tapaukset. Helsinki: Työterveyslaitos. Finnish.

Oksa P, Palo L, Saalo A, Jolanki R, Mäkinen I, Kauppinen T, eds (2012). Ammattitaudit ja ammattitautiepäilyt 2010. Työperäisten sairauksien rekisteriin kirjatut uudet tapaukset. Helsinki: Työterveyslaitos. Finnish.

Orriols R, Costa R, Albanell M, Alberti C, Castejon J, Monso E, Panades R, Rubira N, Zock JP (2006). Reported occupational respiratory diseases in Catalonia. Occup Environ Med **63**(4): 255–60.

Pallasaho P, Juusela M, Lindqvist A, Sovijarvi A, Lundback B, Ronmark E (2011). Allergic rhinoconjunctivitis doubles the risk for incident asthma–results from a population study in Helsinki, Finland. Respir Med **105**(10): 1449–56.

Paris C, Ngatchou-Wandji J, Luc A, McNamee R, Bensefa-Colas L, Larabi L, Telle-Lamberton M, Herin F, Bergeret A, Bonneterre V, Brochard P, Choudat D, Dupas D, Garnier R, Pairon JC, Agius RM, Ameille J (2012). Work-related asthma in France: recent trends for the period 2001-2009. Occup Environ Med **69**(6): 391–7.

Park JH, Cox-Ganser JM (2011). Mold exposure and respiratory health in damp indoor environments. Front Biosci (Elite Ed) **3**: 757–71.

Park JH, Cox-Ganser JM, Kreiss K, White SK, Rao CY (2008). Hydrophilic fungi and ergosterol associated with respiratory illness in a water-damaged building. Environ Health Perspect **116**(1): 45–50.

Patovirta RL, Meklin T, Nevalainen A, Husman T (2004a). Effects of mould remediation on school teachers' health. Int J Environ Health Res **14**(6): 415–27.

Patovirta RL, Husman T, Haverinen U, Vahteristo M, Uitti JA, Tukiainen H, Nevalainen A (2004b). The remediation of mold damaged school–a three-year follow-up study on teachers' health. Cent Eur J Public Health **12**(1): 36–42.

Pavord ID, Chung KF (2008). Management of chronic cough. Lancet **371**(9621): 1375–84.

Pekkanen J, Hyvärinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A (2007). Moisture damage and childhood asthma: a population-based incident case-control study. Eur Respir J **29**(3): 509–15.

Peltola J, Andersson MA, Haahtela T, Mussalo-Rauhamaa H, Rainey FA, Kroppenstedt RM, Samson RA, Salkinoja-Salonen MS (2001). Toxic-metabolite-producing bacteria and fungus in an indoor environment. Appl Environ Microbiol **67**(7): 3269–74.

Pennanen S, Mussalo-Rauhamaa H, Harju A, Pippuri M, Liesivuori J, Elg P, Hakala K, Haahtela T (2007). Exposure to mites, sensitisation and allergy to mites in moisture damaged buildings. Indoor and Built Environment **16**(1): 19–27.

Piipari R, Keskinen H (2005). Agents causing occupational asthma in Finland in 1986-2002: cow epithelium bypassed by moulds from moisture-damaged buildings. Clin Exp Allergy **35**(12): 1632–7.

Portnoy JM, Barnes CS, Kennedy K (2008). Importance of mold allergy in asthma. Curr Allergy Asthma Rep **8**(1): 71–8.

Pransky GS, Loisel P, Anema JR (2011). Work disability prevention research: current and future prospects. J Occup Rehabil **21**(3): 287–92.

Puolijoki H, Lahdensuo A (1987). Chronic cough as a risk indicator of broncho-pulmonary disease. Eur J Respir Dis **71**(2): 77–85.

Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC (1993). Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J **5**(Suppl 16): 5–40.

Quirce S, Contreras G, Dybuncio A, Chan-Yeung M (1995). Peak expiratory flow monitoring is not a reliable method for establishing the diagnosis of occupational asthma. Am J Respir Crit Care Med **152**(3): 1100–2.

Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman Taylor A, Cullinan P (2007). Outcome of occupational asthma after cessation of exposure: a systematic review. Thorax **62**(2): 147–52.

Räsänen K (1998). Illness-related care within occupational health services. Relationship with general primary care, work-related illness and workplace health promotion in Finland. Doctoral dissertation. Kuopio: Department of Public Health and General Practice, University of Kuopio.

Räsänen P, Roine E, Sintonen H, Semberg-Konttinen V, Ryynänen OP, Roine R (2006). Use of quality-adjusted life years for the estimation of effectiveness of health care: A systematic literature review. Int J Technol Assess Health Care **22**(2): 235–41.

Redlich CA, Sparer J, Cullen MR (1997). Sick-building syndrome. Lancet **349(**9057): 1013–6.

Reijula K (2010). Sisäilmasto. In: Kauppinen T, Hanhela R, Kandolin I, Karjalainen A, Kasvio A, Perkiö-Mäkelä M, Priha E, Toikkanen J, Viluksela M, eds. Työ ja terveys Suomessa 2009. Helsinki: Työterveyslaitos; **p.** 59–63. Finnish.

Reijula K, Leino M, Mussalo-Rauhamaa H, Nikulin M, Alenius H, Mikkola J, Elg P, Kari O, Mäkinen-Kiljunen S, Haahtela T (2003). IgE-mediated allergy to fungal allergens in Finland with special reference to Alternaria alternata and Cladosporium herbarum. Ann Allergy Asthma Immunol **91**(3): 280–7.

Reijula K, Sundman-Digert C (2004). Assessment of indoor air problems at work with a questionnaire. Occup Environ Med **61**(1): 33–8.

Remes ST, Korppi M, Remes K (1998). Outcome of children with respiratory symptoms without objective evidence of asthma: a two-year, prospective, follow-up study. Acta Paediatr **87**(2): 165–8.

Reponen T, Nevalainen A, Jantunen M, Pellikka M, Kalliokoski P (1992). Normal range criteria for indoor air bacteria and fungal spores in subarctic climate. Indoor Air **2**(1): 26–31.

Rief W, Hessel A, Braehler E (2001). Somatization symptoms and hypochondriacal features in the general population. Psychosom Med **63**(4): 595–602.

Rioux JP, Malo JL, L'Archeveque J, Rabhi K, Labrecque M (2008). Workplace-specific challenges as a contribution to the diagnosis of occupational asthma. Eur Respir J **32**(4): 997–1003.

Rönmark E, Perzanowski M, Platts-Mills T, Lundbäck B (2002). Incidence rates and risk factors for asthma among school children: a 2-year follow-up report from the obstructive lung disease in Northern Sweden (OLIN) studies. Respir Med **96**(12): 1006–13.

Rudblad S, Andersson K, Stridh G, Bodin L, Juto JE (2002). Slowly decreasing mucosal hyperreactivity years after working in a school with moisture problems. Indoor Air **12**(2): 138–44.

Runeson R, Norbäck D (2005). Associations among sick building syndrome, psychosocial factors, and personality traits. Percept Mot Skills **100**(3 Pt 1): 747–59.

Runeson R, Norbäck D, Klinteberg B, Edling C (2004). The influence of personality, measured by the Karolinska Scales of Personality (KSP), on symptoms among subjects in suspected sick buildings. Indoor Air **14**(6): 394–404.

Runeson R, Norbäck D, Stattin H (2003). Symptoms and sense of coherence–a follow-up study of personnel from workplace buildings with indoor air problems. Int Arch Occup Environ Health **76**(1): 29–38.

Runeson R, Wahlstedt K, Norbäck D (2007). Projective drawings for assessing stress among subjects with medical symptoms compatible with sick building syndrome, and validation of a modified version of the Stress Load Index from the Drawing Personality Profile: a pilot study. Percept Mot Skills **104**(1): 111–22.

Runeson R, Wahlstedt K, Wieslander G, Norbäck D (2006). Personal and psychosocial factors and symptoms compatible with sick building syndrome in the Swedish workforce. Indoor Air **16**(6): 445–53.

Rytilä P, Ghaly L, Varghese S, Chung W, Selroos O, Haahtela T (2008). Treatment with inhaled steroids in patients with symptoms suggestive of asthma but with normal lung function. Eur Respir J **32**(4): 989–96.

Saarinen K, Karjalainen A, Martikainen R, Uitti J, Tammilehto L, Klaukka T, Kurppa K (2003). Prevalence of work-aggravated symptoms in clinically established asthma. Eur Respir J **22**(2): 305–9.

Sahakian NM, Park JH, Cox-Ganser JM (2008). Dampness and mold in the indoor environment: implications for asthma. Immunol Allergy Clin North Am **28**(3): 485–505, vii.

Salonen H (2009). Indoor air contaminants in office buildings. Doctoral Dissertation. Kuopio: Department of Environmental Science, University of Kuopio.

Salonen H, Lappalainen S, Lindroos O, Harju R, Reijula K (2007). Fungi and bacteria in mould-damaged and non-damaged office environments in a subarctic climate. Atmospheric environment **41**(32): 6797–6807.

Salonen H, Pasanen AL, Lappalainen S, Riuttala H, Tuomi T, Pasanen P, Bäck B, Reijula K (2009a). Volatile organic compounds and formaldehyde as explaining factors for sensory irritation in office environments. J Occup Environ Hyg **6**(4): 239–47.

Salonen HJ, Lappalainen SK, Riuttala HM, Tossavainen AP, Pasanen PO, Reijula KE (2009b). Man-made vitreous fibers in office buildings in the Helsinki area. Journal of occupational and environmental hygiene **6**(10): 624–31.

Sauni R, Kauppi P, Helaskoski E, Virtema P, Verbeek J (2009). Audit of quality of diagnostic procedures for occupational asthma. Occup Med (Lond) **59**(4): 230–6.

Sauni R, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T, Verbeek J (2011). Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD007897.

SCHER (2007). Opinion on risk assessment on indoor air quality. Scientific Committee on Health and Environmental Risks. Brussels: European Commission. Available from http://ec.europa.eu/health/ph_risk_en.htm

Schneider T (2008a). Dust and fibers as a cause of indoor environment problems. Scand J Work Environ Health **34**(Suppl 4): 10–7.

Schneider T (2008b). Resolving indoor air problems. Scand J Work Environ Health **34**(Suppl 4): 25–9.

Schultz IZ, Stowell AW, Feuerstein M, Gatchel RJ (2007). Models of return to work for musculoskeletal disorders. J Occup Rehabil **17**(2): 327–52.

Seppänen OA, Fisk WJ (2004). Summary of human responses to ventilation. Indoor Air **14**(Suppl 7): 102–18.

Seuri M, Husman K, Kinnunen H, Reiman M, Kreus R, Kuronen P, Lehtomaki K, Paananen M (2000). An outbreak of respiratory diseases among workers at a water-damaged building–a case report. Indoor Air **10**(3): 138–45.

Shaw WS, van der Windt DA, Main CJ, Loisel P, Linton SJ (2009). Early patient screening and intervention to address individual-level occupational factors ("blue flags") in back disability. J Occup Rehabil **19**(1): 64–80.

Simon-Nobbe B, Denk U, Poll V, Rid R, Breitenbach M (2008). The spectrum of fungal allergy. Int Arch Allergy Immunol **145**(1): 58–86.

Slezak JA, Persky VW, Kviz FJ, Ramakrishnan V, Byers C (1998). Asthma prevalence and risk factors in selected Head Start sites in Chicago. J Asthma **35**(2): 203–12.

Smith KW, Avis NE, Assmann SF (1999). Distinguishing between quality of life and health status in quality of life research: a meta-analysis. Qual Life Res **8**(5): 447–59.

Sovijarvi AR, Malmberg LP, Reinikainen K, Rytila P, Poppius H (1993). A rapid dosimetric method with controlled tidal breathing for histamine challenge. Repeatability and distribution of bronchial reactivity in a clinical material. Chest **104**(1): 164–70.

Stenberg B, Wall S (1995). Why do women report 'sick building symptoms' more often than men? Soc Sci Med **40**(4): 491–502.

STM (2003). Asumisterveysohje. Asuntojen ja muiden oleskelutilojen fysikaaliset, kemialliset ja mikrobiologiset tekijät. Sosiaali- ja terveysministeriön oppaita 2003:1 [Instructions regarding physical, chemical and biological factors in housing and other living premises]. Helsinki: Ministry of Social Affairs and Health. Finnish.

STM (2009). Kosteusvauriot työpaikoilla. Kosteusvauriotyöryhmän muistio. Sosiaali- ja terveysministeriön selvityksiä 2009:18 [Moisture damages in workplaces. Memo of the working group on moisture damages]. Helsinki: Ministry of Social Affairs and Health. Finnish.

Storey E, Dangman KH, Schenk P, DeBernando RL, Yang CS, Bracker A, Hodgson MJ (2004). Guidance for Clinicians on the Recognition and Management of Health Effects Related to Mold Exposure and Moisture Indoors. Farmington, CT: University of Connecticut Health Center.

Sullivan MJ, Feuerstein M, Gatchel R, Linton SJ, Pransky G (2005). Integrating psychosocial and behavioral interventions to achieve optimal rehabilitation outcomes. J Occup Rehabil **15**(4): 475–89.

Sundell J, Levin H, Nazaroff WW, Cain WS, Fisk WJ, Grimsrud DT, Gyntelberg F, Li Y, Persily AK, Pickering AC, Samet JM, Spengler JD, Taylor ST, Weschler CJ (2011). Ventilation rates and health: multidisciplinary review of the scientific literature. Indoor Air **21**(3): 191–204.

Tarlo SM, Balmes J, Balkissoon R, Beach J, Beckett W, Bernstein D, Blanc PD, Brooks SM, Cowl CT, Daroowalla F, Harber P, Lemiere C, Liss GM, Pacheco KA, Redlich CA, Rowe B, Heitzer J (2008). Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest **134**(3 Suppl): 1S–41S.

Täubel M, Sulyok M, Vishwanath V, Bloom E, Turunen M, Järvi K, Kauhanen E, Krska R, Hyvärinen A, Larsson L, Nevalainen A (2011). Co-occurrence of toxic bacterial and fungal secondary metabolites in moisture-damaged indoor environments. Indoor Air **21**(5): 368–75.

Thörn Å (1999). The emergence and preservation of sick building syndrome: research challenges of a modern age disease. Doctoral dissertation. Stockholm: Karolinska Institutet. Available from: http://publications.ki.se/jspui/bitstream/10616/38099/1/thesis.pdf

Thorn J, Brisman J, Torén K (2001). Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. Allergy **56**(4): 287–92.

Tola S (2004). Lakisääteinen tapaturmavakuutus. In: Aro T, Huunan-Seppälä A, Kivekäs J, Tola S, Torstila I, eds. Vakuutuslääketiede. 2nd ed. Helsinki: Kustannus Oy Duodecim; **p.** 251–256. Finnish.

Torén K, Albin M, Järvholm B (2010). Systematiska kunskapsöversikter; 1. Betydelsen av fukt och mögel i inomhusmiljö för astma hos vuxna. Arbete och Hälsa Nr 2010;44(8). Göteborg: Göteborgs Universitet. Swedish.

Torén K, Blanc PD (2009). Asthma caused by occupational exposures is common - a systematic analysis of estimates of the population-attributable fraction. BMC Pulm Med **9**: 7.

Torén K, Brisman J, Jarvholm B (1993). Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. Chest **104**(2): 600–8.

Torén K, Palmqvist M, Lowhagen O, Balder B, Tunsater A (2006). Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. J Clin Epidemiol **59**(1): 90–3.

Trout D, Bernstein J, Martinez K, Biagini R, Wallingford K (2001). Bioaerosol lung damage in a worker with repeated exposure to fungi in a water-damaged building. Environ Health Perspect **109**(6): 641–4.

Tuomainen A, Seuri M, Sieppi A (2004). Indoor air quality and health problems associated with damp floor coverings. Int Arch Occup Environ Health **77**(3): 222–6.

Tuomi K, Ilmarinen J, Jahkola A, Katajarinne L, Tulkki A (1998). Work ability index. Helsinki: Finnish Institute of Occupational Health.

Tuomi T, Reijula K, Johnsson T, Hemminki K, Hintikka EL, Lindroos O, Kalso S, Koukila-Kahkola P, Mussalo-Rauhamaa H, Haahtela T (2000). Mycotoxins in crude building materials from water-damaged buildings. Appl Environ Microbiol **66**(5): 1899–904.

TVL (2011) [Internet]. Lakisääteinen tapaturmavakuutus = Finnish Statutory Accident Insurance System. Helsinki: Tapaturmavakuutuslaitosten liitto (TVL) = Federation of Accident Insurance Institutions (FAII). [updated in Finnish 2011 Feb 4; updated in English 2005 Oct 18; cited 2012 March 23]. Available from: http://www.tvl.fi/www/page/tvl_www_2097. Finnish, English.

van den Berg TI, Elders LA, de Zwart BC, Burdorf A (2009). The effects of work-related and individual factors on the Work Ability Index: a systematic review. Occup Environ Med **66**(4): 211–20.

van Oostrom SH, Driessen MT, de Vet HC, Franche RL, Schonstein E, Loisel P, van Mechelen W, Anema JR (2009). Workplace interventions for preventing work disability. Cochrane Database Syst Rev(2): CD006955.

van Strien RT, Gehring U, Belanger K, Triche E, Gent J, Bracken MB, Leaderer BP (2004). The influence of air conditioning, humidity, temperature and other household characteristics on mite allergen concentrations in the northeastern United States. Allergy **59**(6): 645–52.

Vandenplas O (2011). Occupational asthma: etiologies and risk factors. Allergy Asthma Immunol Res **3**(3): 157–67.

Vandenplas O, Cartier A, Malo J-L (2006). Occupational challenge tests. In: Bernstein IL, Chang-Yeung M, Malo J-L, Bernstein DI, eds. Asthma in the workplace. 3rd ed. New York: Taylor & Francis Group; **p.** 227–252.

Vandenplas O, Dressel H, Wilken D, Jamart J, Heederik D, Maestrelli P, Sigsgaard T, Henneberger P, Baur X (2011). Management of occupational asthma: cessation or reduction of exposure? A systematic review of available evidence. Eur Respir J **38**(4): 804–11.

Vandenplas O, Henneberger PK (2007). Socioeconomic outcomes in work-exacerbated asthma. Curr Opin Allergy Clin Immunol **7**(3): 236–41.

Vandenplas O, Larbanois A, Bugli C, Kempeneers E, Nemery B (2005). Épidémiologie de l'asthme professionnel en Belgique. [The epidemiology of occupational asthma in Belgium]. Rev Mal Respir **22**(3): 421–30. French.

Vandenplas O, Torén K, Blanc PD (2003). Health and socioeconomic impact of work-related asthma. Eur Respir J **22**(4): 689–97.

Viljanen AA, Viljanen BC, Halttunen PK, Kreus KE (1982). Pulmonary diffusing capacity and volumes in healthy adults measured with the single breath technique. Scand J Clin Lab Invest **42**(Suppl 159): 21–34.

Vojdani A (2004). Cross-reactivity of Aspergillus, Penicillium, and Stachybotrys antigens using affinity-purified antibodies and immunoassay. Arch Environ Health **59**(5): 256–65.

von Hertzen LC, Haahtela T (2004). Asthma and atopy - the price of affluence? Allergy **59**(2): 124–37.

Waddell G (2005). Subgroups within "nonspecific" low back pain. J Rheumatol **32**(3): 395–6.

Waddell G, Burton AK (2001). Occupational health guidelines for the management of low back pain at work: evidence review. Occup Med (Lond) **51**(2): 124–35.

Waddell G, Burton AK (2005). Concepts of rehabilitation for the management of low back pain. Best Pract Res Clin Rheumatol **19**(4): 655–70.

Wagner GR, Wegman DH (1998). Occupational asthma: prevention by definition. Am J Ind Med **33**(5): 427–9.

Wallman T, Wedel H, Palmer E, Rosengren A, Johansson S, Eriksson H, Svardsudd K (2009). Sick-leave track record and other potential predictors of a disability pension. A population based study of 8,218 men and women followed for 16 years. BMC Public Health **9**: 104.

Ware J, Jr., Kosinski M, Keller SD (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care **34**(3): 220–33.

Ware JE, Jr., Sherbourne CD (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care **30**(6): 473–83.

WHO (1948) [Internet]. WHO definition of health [cited 2012 May 26]. Available from: http://www.who.int/about/definition/en/print.html

WHO (1983). Indoor Air Pollutants: exposure and health effects. EURO Reports and Studies 78. Copenhagen: WHO Regional Office for Europe.

WHO (1985). Identification and control of work-related diseases. Report of a WHO expert committee. Technical Report Series 714. Geneva: World Health Organization.

WHO (1995). The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med **41**(10): 1403–9.

WHO (2001). The international classification of functioning, disability and health. Geneva: World Health Organization.

WHO (2009). WHO guidelines for indoor air quality: dampness and mould. Copenhagen: WHO Regional Office for Europe. Available from: http://www.euro.who.int/document/E92645.pdf

Wieslander G, Kumlin A, Norbäck D (2010). Dampness and 2-ethyl-1-hexanol in floor construction of rehabilitation centre: Health effects in staff. Arch Environ Occup Health **65**(1): 3-11.

Wolff CH (2011). Innate immunity and the pathogenicity of inhaled microbial particles. Int J Biol Sci **7**(3): 261–8.

Wolff H, Mussalo-Rauhamaa H, Raitio H, Elg P, Orpana A, Piilonen A, Haahtela T (2009). Patients referred to an indoor air health clinic: exposure to water-damaged buildings causes an increase of lymphocytes in bronchoalveolar lavage and a decrease of CD19 leucocytes in peripheral blood. Scand J Clin Lab Invest **69**(5): 537–44.

Wolkoff P, Wilkins CK, Clausen PA, Nielsen GD (2006). Organic compounds in office environments - sensory irritation, odor, measurements and the role of reactive chemistry. Indoor Air **16**(1): 7–19.

Yacoub MR, Lavoie K, Lacoste G, Daigle S, L'Archeveque J, Ghezzo H, Lemiere C, Malo JL (2007). Assessment of impairment/disability due to occupational asthma through a multidimensional approach. Eur Respir J **29**(5): 889–96.

Yang CY, Tien YC, Hsieh HJ, Kao WY, Lin MC (1998). Indoor environmental risk factors and childhood asthma: a case-control study in a subtropical area. Pediatr Pulmonol **26**(2): 120–4.

Yike I, Dearborn D (2011). Guest editorial–novel insights into the pathology of Stachybotrys chartarum. Mycopathologia **172**(1): 1–3.

Yike I, Distler AM, Ziady AG, Dearborn DG (2006). Mycotoxin adducts on human serum albumin: biomarkers of exposure to Stachybotrys chartarum. Environ Health Perspect **114**(8): 1221-6.

Yli-Pirilä T, Kusnetsov J, Haatainen S, Hänninen M, Jalava P, Reiman M, Seuri M, Hirvonen MR, Nevalainen A (2004). Amoebae and other protozoa in material samples from moisture-damaged buildings. Environ Res **96**(3): 250–6.

Zigmond AS, Snaith RP (1983). The hospital anxiety and depression scale. Acta Psychiatr Scand **67**(6): 361–70.

APPENDICES

Appendix 1.

Studies on associations between asthma development and dampness, mold, or agents associated with dampness in children

Appendix 2.

Flow chart for the investigation of suspected OA related to workplace dampness, for use by occupational health services

Appendix 3.

Flow chart for the investigation of suspected OA related to workplace dampness, for use by special health care

Appendix 4.

A suggestion for an individual-level practical approach to disability prevention for workers with asthma related to workplace dampness, for use by occupational health services. The suggestion is based on current literature.

Appendix 1.

Studies on associations between asthma development and dampness, mold, or agents associated with dampness among children (adapted from IOM 2004 and Mendell et al. 2011). Risk estimates presented as odds ratios with 95% confidence intervals, unless indicated otherwise.

Reference	Subjects	Outcome	Dampness or mold measure	Exposure self-reported (S)/ observed (O)	Risk estimate
Nested and incident case–control studies					
Infante-Rivard 1993	457 newly diagnosed infant cases and 457 controls, aged 3–4 years, in Montreal, Canada	Asthma diagnosis	Parent-reported humidifier use (not an indication of indoor dampness)	S	1.89 (1.30–2.74)
Yang et al. 1998	86 cases with a first-time diagnosis of asthma and 86 controls, age 3–15 years in Kaohsiung, Taiwan	Asthma diagnosis	Parent-reported home dampness	S	1.77 (1.24–2.53)
Nafstad et al. 1998	251 children <2 years old with bronchial obstruction and 251 matched controls from population-based sample of 3754 newborns in Oslo, Norway	Diagnosis of bronchial obstruction	Parent-reported dampness Inspector-observed dampness	S O	2.5 (1.1–5.5) 3.8 (2.0–7.2)
Oie et al. 1999	172 children <2 years old with bronchial obstruction; 172 matched controls from population-based sample of 3754 newborns (same population as Nafstad)	Bronchial obstruction	Surveyor-verified dampness	O	2.4 (1.25–4.44)
Cohort studies					
Maier et al. 1997	925 children aged 5–9 years in Seattle, United States	Parent-reported physician-diagnosed asthma (ever)	Water damage Other wetness/no water damage	S S	1.7 (1.0–2.8) 1.1 (0.6–1.8)
Slezak et al. 1998	1085 children aged 3–5 years in Head Start programs in Chicago, United States	Parental-reported physician-diagnosed asthma (ever)	Parental-reported dampness or mold in prior 12 months	S	1.94 (1.23–3.04)

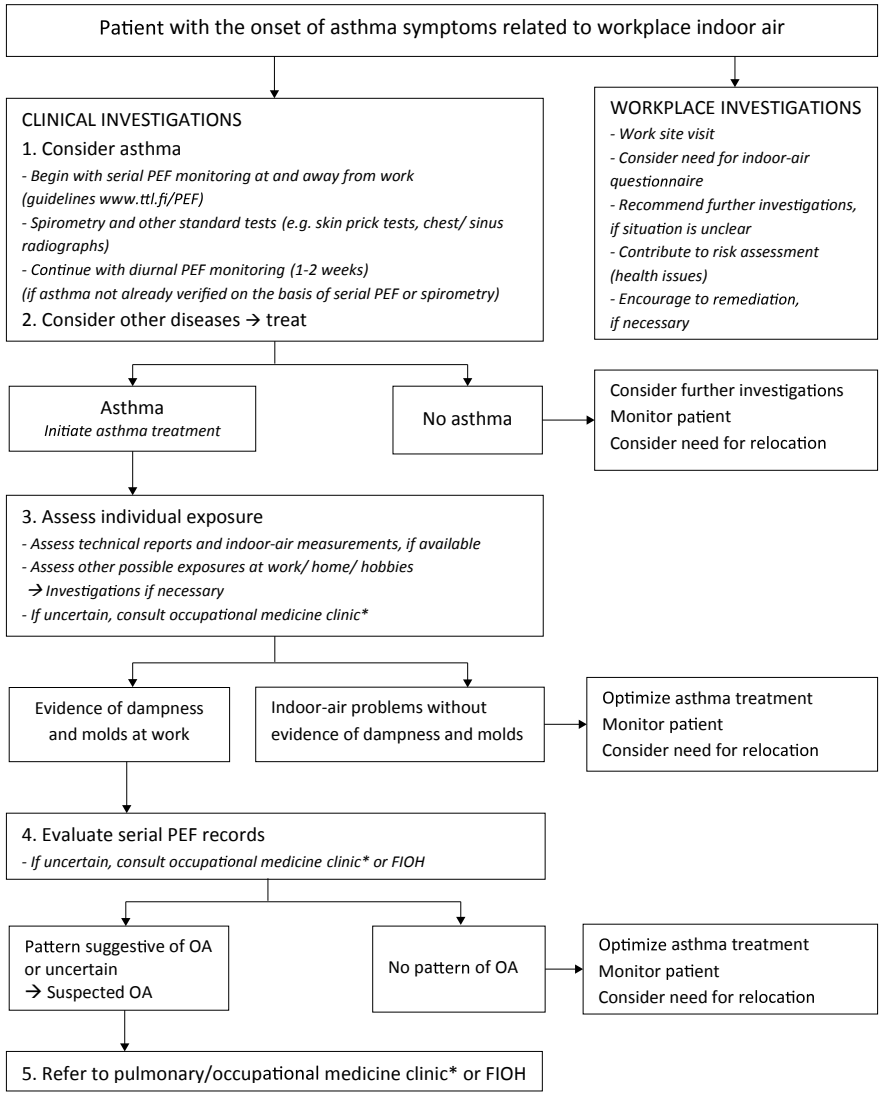
Prospective studies					
Rönmark et al. 2002	3431 children aged 7–8 years in northern Sweden	Ever asthma, incident in prior 12 months	Parent-reported dampness at home	S	1.13 (0.63–2.03)
Jaakkola et al. 2005	1916 children aged 1–7 years in Espoo, Finland	Asthma development	Mold odor	S	IRR 2.44 (1.07–5.60)
			Visible mold	S	IRR 0.65 (0.24–1.72)
			Moisture in the surfaces	S	IRR 0.92 (0.54–1.54)
			Water damage	S	IRR 1.01 (0.45–2.26)
Iossifova et al. 2009	483 children, age 3 years, born to atopic parent from Cincinnati, US	Recurrent wheezing in children with atopy at age 3	Low mold/water damage = Moldy odor or visible mold or water damage area <0.2 m^2, from home inspection at age 8 months	O	1.86 (0.86–4.00)
			High mold/water damage = Visible mold or water damage area ≥0.2 m^2, from home inspection at age 8 months	O	6.16 (1.38–27.44)
			(1– >3)-β-D-glucan quartile, µg/g (in settled dust at age 8 months):		
			I: 0.35–22.0	O	1.91 (0.18–20.56)
			II: 22.1–60.0	O	0.97 (0.72–1.31)
			III:60.1–133.0	O	0.80 (0.54–1.18)
			IV: 133.1–960.0	O	0.47 (0.13–1.71)
			Endotoxin in dust, interquartile range	O	1.37 (0.86–2.19)
		Asthma predictive index at age 3	Low mold/water damage	O	1.68 (0.96–2.94)
			High mold/water damage	O	7.08 (2.22–12.60)
			(1– >3)-β-D-glucan quartile, µg/g (in settled dust at age 8 months):		
			I: 0.35–22.0	O	3.44 (0.50–23.52)
			II: 22.1–60.0	O	1.14 (0.87–1.50)
			III:60.1–133.0	O	0.91 (0.70–1.17)
			IV: 133.1–960.0	O	0.61 (0.24–1.59)
			Endotoxin in dust, interquartile range	O	1.37 (0.96–1.96)
Retrospective studies					
Pekkanen et al. 2007	362 children with asthma, age 12–84 months, in Kuopio region, Finland	New asthma diagnosis	Any suspected moisture damage in whole home	O	0.63 (0.28–1.45)
			Area of water damage in whole home	O	1.01 (0.98–1.05)
			Visible mold in whole home	O	1.24 (0.73–2.11)
			Some mold odor in whole home	O	1.35 (0.42–4.36)
			Clear mold odor in whole home	O	4.12 (0.65–26.01)
			Minor or major moisture damage, main living area	O	2.24 (1.25–4.01)
			Minor moisture damage, main living area	O	2.11 (1.06–4.21)
			Major moisture damage, main living area	O	2.46 (1.09–5.55)
			Maximum severity (1–2) moisture damage, main living area	O	2.75 (1.40–5.40)
			Maximum severity (2+) moisture damage, main living area	O	4.04 (1.60–10.20)
			Area of damage m^2	O	1.36 (0.91–2.03)

Appendix 1 continues

Reference	Subjects	Outcome	Dampness or mold measure	Exposure self-reported (S)/ observed (O)	Risk estimate
			Mold growth, mold spots, main living area	O	4.01 (1.12–14.32)
			Mold growth, visible mold, main living area	O	1.95 (0.69–5.47)
			Visible mold, main living area	O	2.59 (1.15–5.85)
			Mold odor, main living area	O	2.96 (0.62–14.19)
			Minor or major moisture damage, kitchen	O	1.41 (0.80–2.47)
			Visible mold, kitchen	O	1.13 (0.63–2.04)
			Minor or major moisture damage, bathroom	O	0.70 (0.39–1.25)
			Visible mold, bathroom	O	0.81 (0.44–1.49)
			Minor or major moisture damage, other interior spaces	O	0.77 (0.40–1.46)
			Visible mold, other interior spaces	O	0.86 (0.37–2.00)
			Moisture damage in child's bedroom	O	1.97 (1.00–3.90)
Cross-sectional studies					
Hyvärinen et al. 2006	36 children with new asthma and 36 control children, age 12–84 months	Newly diagnosed asthma or at least 2 attacks of wheezing per day	LPS in home floor dust, per 0.01 nmol/mg	O	0.75 (0.40–1.42)
			3-OH fatty acids in home floor dust (C-10), per 0.01 nmol/mg	O	0.81 (0.50–1.33)
			3-OH fatty acids in home floor dust (C-12), per 0.01 nmol/mg	O	0.72 (0.42–1.24)
			3-OH fatty acids in home floor dust (C-14), per 0.01 nmol/mg	O	0.93 (0.51–1.69)
			3-OH fatty acids in home floor dust (C-16), per 0.01 nmol/mg	O	0.98 (0.59–1.64)
			Culturable mesophilic bacteria in home floor dust, per 10E5 cfu/g	O	1.01 (0.99–1.03)
			Culturable mesophilic actinomycetes in home floor dust, per 10E3 cfu/g	O	1.18 (0.99–1.42)
			Ergosterol in home floor dust, per 10E3 pg/mg	O	1.12 (0.97–1.30)
			Culturable mesophilic fungi in home floor dust, per 10E5 cfu/g	O	1.08 (0.95–1.23)
			Culturable xerophilic fungi in home floor dust, per 10E5 cfu/g	O	1.11 (0.94–1.31)

Appendix 2.

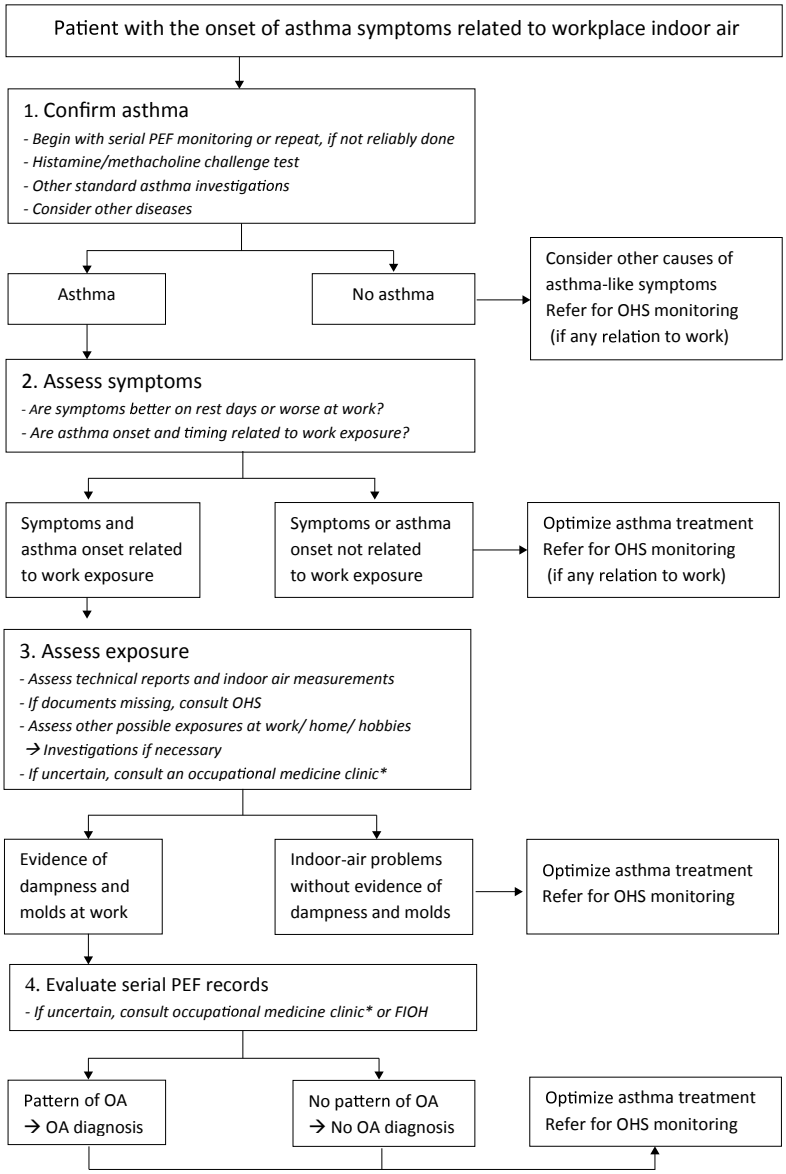
Flow chart for the investigation of suspected OA related to workplace dampness, for use by occupational health services



***at a central hospital; OA=occupational asthma; PEF=peak expiratory flow; FIOH=Finnish Institute of Occupational Health**

Appendix 3.

Flow chart for the investigation of suspected OA related to workplace dampness, for use by special health care



***at a central hospital; OA=occupational asthma; PEF=peak expiratory flow; OHS=occupational health services; FIOH=Finnish Institute of Occupational Health**

Appendix 4.

A suggestion for an individual-level practical approach to disability prevention for workers with asthma related to workplace dampness, for use by occupational health services. The suggestion is based on current literature.

Investigate according to best clinical practices	• Symptoms may refer to a variety of conditions, and are not specific to indoor-air pollutants
Aim to achieve and maintain clinical control of asthma (GINA 2011, Baur et al. 2012)	• Regular medication • Asthma education and guided self-management • Weight loss for the obese • Smokers: counseling and offering smoking cessation programs • Regular follow-up
Recognize and treat co-existing diseases (GINA 2011)	• Rhinitis, chronic sinusitis, nasal polyps • Gastroesophageal reflux disease • Obstructive sleep apnea • Psychiatric disorders
Assess occupational and environmental factors that trigger symptoms (SCHER 2007, Tarlo et al. 2008, STM 2009, Henneberger et al. 2011, GINA 2011)	• Good risk management at the workplace, including risk communication, is needed: • Abnormal sources of indoor-air pollutants are identified and the risks are assessed, followed by necessary actions (remediation, repairs and evaluation of their success) • Viral infections, common allergens and irritants
Guidance for symptom management (NICNAS and OCS 2008, GINA 2011)	• As total avoidance of low-level irritants and odors generally proves impossible, advise ways to minimize contact with perceived triggers
Provide the patient with information about the nature of the symptoms (NICNAS and OCS 2008, GINA 2011)	• Asthma is usually a persistent disease • Symptoms run a varying course • Cautiously reassure the patient that grave medical diagnoses have been ruled out or that he or she does not have a progressive disease • Sometimes the symptoms are persistent; in that case the focus is on improving functional status rather than on eradicating symptoms
Encourage to remain at work (NICNAS and OCS 2008; Costa-Black et al. 2010)	• Involvement of the worker, the employer, and OHS in planning work retention and return-to-work • Favor temporary work modifications (e.g., relocation, remote work) instead of long sickness absences • Identify obstacles to (return to) work and provide support to overcome them
Encourage to maintain normal activity levels (NICNAS and OCS 2008; Costa-Black et al. 2010, GINA 2011)	• Encourage to resume activities, (e.g., gently graduated exercise program) • Counsel to avoid avoidance behavior
Involve the patient actively in the treatment process (NICNAS and OCS 2008)	• Encourage self-management • Set realistic goals • Focus on coping, not on sick role
Provide an empathic relationship to offer understanding and support (NICNAS and OCS 2008)	• Accept that the person feels ill and is disabled by the illness • Encourage the person to try to come to terms with his or her disability • Maintain a long-term positive approach • Develop a positive attitude toward the future