Do Indoor Molds in Nonindustrial Environments Threaten Workers’ Health? A Review of the Epidemiologic Evidence

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Abbreviations: CFU, colony-forming units; CI, confidence interval.

INTRODUCTION

Since the early 1980s, mucosal, skin, and respiratory symptoms, in addition to general symptoms such as fatigue and headache, have been related to the indoor climate of nonindustrial workplaces. Mold growth has been suggested as a causal factor because the health complaints frequently have been related to indicators of microbial contamination: visible signs of mold growth, moisture, and water damage (1).

Molds refer to growing colonies of different species of fungi. Fungi are nonphotosynthetic plant bodies that are ubiquitous in nature and decompose organic material. The species differ in size, but most are about 10 µm in diameter. Fungi are able to grow at a relative humidity of between 75 percent and 95 percent at normal room temperature. Fungi reproduce by spores that spread by air, depending on climatic factors, activity in the surrounding environment, and physiologic properties of the individual species (2, 3). Growing fungi may produce metabolites to protect a nutrient source from bacteria. Mycotoxins are metabolites that are able to initiate a toxic response in vertebrates when ingested, inhaled, or otherwise absorbed.

Mold antigens may induce an immunoglobulin E–mediated response (4, 5). β-(1,3)-D-glucan is a polyglucose structure of mold cell walls that can induce inflammatory reactions through a specific receptor (6, 7). Ergosterol is the primary membrane sterol of filamentous fungi, and extracellular polysaccharides are stable carbohydrates secreted during fungal growth. At present, there is no evidence for a pathogenic role of ergosterol or extracellular polysaccharides in allergic or inflammatory reactions to fungal components (8).

High-level exposure to airborne mold spores may cause allergic alveolitis (e.g., farmer’s lung) (9). Aerosols from air humidifiers heavily contaminated by bacteria, algae, or molds may cause inhalation fever (humidifier fever) (10). Single cases of occupational asthma have been attributed to mold exposure (11, 12), and asthma severity has been associated with outdoor mold spore levels in children and adolescents (13). Mold-contaminated food and feed have been held responsible for serious cases of poisoning in humans and livestock (14). It was discussed recently whether mycotoxins may be responsible for cases of acute idiopathic pulmonary hemorrhage in infants (15, 16).

Among employees of nonindustrial workplaces with visible signs of mold growth, moisture, or water damage, there has been an increasing concern about possible health effects. This review evaluates this concern based on present epidemiologic literature. Recently, the topic was partly reviewed by Husman, Verhoeff and Burge, and Peat and Dickerson (17–19). However, they focused mainly on the health effects in children, which may not be relevant for the adult working population (20). Furthermore, several studies assessing mold exposure in the sick building syndrome were included to only a limited extent. This is a systematic review of reports on health effects related to mold growth (or indicators of mold growth) in nonindustrial work sites. Since comparable mold exposure is seen in dwellings, studies that related adult health effects to exposure at home were also reviewed (21).

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INDOOR MOLDS IN NONINDUSTRIAL ENVIRONMENTS

To assess the possible health effects of indoor molds, characterization of the presence and the degree of exposure is crucial. Use of questionnaire information on visible signs or the characteristic smell of molds or dampness is a simple method, but it gives little information about the degree of exposure and involves a risk of reporting bias (22). Inspection by surveyors can provide a standardized assessment of mold growth in terms of the area affected (23).

Settlement plates, dust samples, and air samples can be used to determine viable mold spores. However, these methods have limitations concerning determination of concentrations of viable mold spores in the air representative of time-weighted exposure (24). Settlement plates have failed to adequately collect small spores and have shown little reproducibility, with average coefficients of variance of about 30 percent regarding the number of colony-forming units (CFUs) (2, 25). Dust sampling has resulted in coefficients of variance of between 11 percent and 27 percent (CFU/g dust), and the mean agreement for species isolated has varied from 37 percent to 60 percent (26). Comparable figures have been reported for air sampling (25).

Viable mold counts may represent only a minor fraction of the total number of fungal particles in indoor air because of different survival rates and difficulties in detecting them on growth agar medium. Nonviable and viable spores can contain allergens and mycotoxins, and it may be of importance also to assess the total number of spores (viable and nonviable), even if a high correlation has been found between viable and total mold counts (27).

Levels of β-(1,3)-D-glucan, ergosterol, and extracellular polysaccharides may be other appropriate measures of fungal biomass, even if only measures of extracellular polysaccharides provide information on the fungal species (8). Coefficients of variance of 25 percent and 16 percent have been reported for measurements of β-(1,3)-D-glucan and extracellular polysaccharides, respectively, while relative standard deviations for determining ergosterol have ranged from 5 percent to 27 percent (8, 28, 29).

Total airborne mold counts (viable and nonviable) of 667–570,000 spores/m³ have been reported in dwellings (30, 31). Table 1 presents viable mold exposure levels expressed as CFU per cubic meter (only limited data exist for the other parameters) and shows considerable variation, ranging from 0 to 450,000 CFU/m³, between studies. Furthermore, counts differ by season, and there is a tendency toward higher counts at lower latitudes (in Asia). Generally, viable spore counts are higher outdoors than indoors. Significantly higher counts were reported in buildings with signs of mold growth or dampness than in reference buildings (32–34); however, no or small differences in mold levels have also been shown (21, 23, 25, 30, 35–37). During remediation of moldy buildings (homes or nonindustrial workplaces), mold exposure levels may increase significantly (38).

The predominant mold genera are Penicillium, Cladosporium, and Aspergillus indoors as well as outdoors in all parts of the world. Fungi such as Trichoderma and Stachybotrys, which require high water activity (aw >0.90–0.95) for growth, are infrequent, but high exposure levels may be seen (34). Stachybotrys has been identified more frequently in buildings with mold problems (32, 39, 40).

LITERATURE SEARCH AND STUDY QUALITY EVALUATION

MEDLINE (National Institutes of Health, Bethesda, Maryland) (1968–June 2000) and NIOSHTIC (National Institute for Occupational Safety and Health Technical Information Center; database provided by SilverPlatter Information Ltd., London, United Kingdom) (1977–June 2000) were searched to identify human peer-reviewed studies published in English that related adult health effects to mold exposure in nonindustrial indoor environments. Additional snowball searches were conducted of the bibliographies in the original papers identified initially. A total of 47 articles were identified.

The articles were initially classified as 1) case or cluster reports and 2) analytical studies in populations with no concerns about possible mold-related health effects. The analytical studies were then scored according to six quality parameters, as follows (score value in parentheses): 1) design: cross-sectional (0), longitudinal (1); 2) participation rate: <80 percent (0), ≥80 percent (1); 3) exposure assessment: qualitative (0), quantitative, nonindividual measurements (each measurement representing more than one study subject) (1), quantitative, individual measurements (2); 4) health outcome: self-reported symptoms or weakly defined health outcomes (0), self-reported physician-diagnosed disease or well-defined symptoms (1), physician-diagnosed disease or objective findings (2); 5) potential confounders controlled for: no or limited confounder control (0), comprehensive confounder control that included smoking (1); and 6) exposure-response assessment: no (0), yes (1). Finally, each study was assigned a total sum of scores.

Weighted average odds ratios with 95 percent confidence intervals were computed when appropriate (41). The odds ratio values from each study were weighted by the inverse variance extracted from the confidence intervals, and 95 percent confidence intervals for the meta-odds ratios were computed from the sum of the weights.

CASE AND CLUSTER REPORTS

A total of 19 articles were identified that described patient cases with health effects attributed to mold contamination of the indoor environment or cross-sectional studies conducted in populations because of suspected health effects related to mold exposure in those populations.

Three case reports described a teacher, an office worker, and a married couple, all diagnosed with allergic alveolitis attributed to indoor mold exposure at work or at home (42–44). High levels of viable airborne molds (approximately 5 × 10^4 CFU/m³) dominated by Penicillium species originating from a contaminated ventilation system were detected in the workplace of the office worker (43). No quantitative exposure levels were given for the married couple, but they showed precipitating antibodies against Penicillium species detected in their home (44). Precipitating antibodies against Alternaria, Aspergillus, Botrytis, Cladosporium, Penicil-
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**TABLE 1. Viable mold exposure levels in indoor and outdoor air, in buildings with and without signs of mold growth, and by continent: results from exposure surveys and epidemiologic studies, 1984–2000**

<table>
<thead>
<tr>
<th>Continent</th>
<th>Author, year of publication (reference no.)</th>
<th>Outdoor air samples (CFU/m³)</th>
<th>Indoor air samples (CFU/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Buildings with signs of mold growth</td>
<td>Buildings with no signs of mold growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Europe</td>
<td>Beaumont et al., 1985 (73)</td>
<td>0–15,643</td>
<td>0–12,514</td>
</tr>
<tr>
<td></td>
<td>Björnsson et al., 1995 (31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Holmberg, 1984 (36)</td>
<td>145</td>
<td>7–12,046</td>
</tr>
<tr>
<td></td>
<td>Hunter et al., 1988 (34)</td>
<td>236</td>
<td>&lt;12–23,070</td>
</tr>
<tr>
<td></td>
<td>Hyvärinen et al., 1993 (32)</td>
<td>410†</td>
<td>37–11,000†</td>
</tr>
<tr>
<td></td>
<td>Strom et al., 1990 (21)</td>
<td>30,000</td>
<td>45–3,500$†</td>
</tr>
<tr>
<td></td>
<td>Verheoff et al., 1992 (25)</td>
<td>882#</td>
<td>124–6,248#</td>
</tr>
<tr>
<td></td>
<td>Wieslander et al., 1999 (35)</td>
<td>90–160</td>
<td>80–120</td>
</tr>
<tr>
<td></td>
<td>McGrath et al., 1999 (91)</td>
<td>227–535</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>Miller et al., 2000 (23)</td>
<td>329</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>Nelson et al., 1995 (63)</td>
<td>492</td>
<td>264–696</td>
</tr>
<tr>
<td>Asia</td>
<td>Li and Hsu, 1997 (37)</td>
<td>394‡</td>
<td>530**</td>
</tr>
<tr>
<td></td>
<td>Li et al., 1997 (61)</td>
<td>916</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ooi et al., 1998 (65)</td>
<td>63</td>
<td>5–1,062</td>
</tr>
<tr>
<td></td>
<td>Pei-Chih et al., 2000 (92)</td>
<td>11,464‡</td>
<td>4,689**</td>
</tr>
<tr>
<td></td>
<td>Takahashi, 1997 (93)</td>
<td>219</td>
<td>&lt;13–2,750</td>
</tr>
<tr>
<td>Australia</td>
<td>Dharmage et al., 1999 (33)</td>
<td>811</td>
<td>544</td>
</tr>
<tr>
<td></td>
<td>Garrett et al., 1998 (30)</td>
<td>965</td>
<td>1,036</td>
</tr>
</tbody>
</table>

* CFU, colony-forming units.  
† Autumn.  
‡ Winter.  
§ Offices.  
¶ Homes.  
# Spring.  
** Summer.

*Penicillium, Pullularia,* and *Rhizopus* were shown in the teacher, but no relevant environmental data were available (42). A case of organic dust toxic syndrome in a museum staff handling moldy books was related with high-level exposure to airborne molds (10⁶ CFU/m³ viable molds and 10⁸/m³ total molds) (45). A cluster of 33 cases of granulomatous lung disease in swimming pool lifeguards was related to endotoxin levels in the work environment, but not with fungal levels (46).

Household aggregation of cold and flu symptoms, sore throat, diarrhea, headache, fatigue, dermatitis, intermittent focal alopecia, and generalized malaise have been related to mold exposure since symptoms were reduced after removal of mold-contaminated material (*Penicillium, Trichoderma, Phoma* species, and *Stachybotrys atrata*) from the homes (47, 48). In eight of nine cases of allergic fungal sinusitis, identical mold species were identified in the indoor air as isolated in mucin from the maxillary and ethmoid sinuses of the patients (49).

Reduced bronchial hyperresponsiveness was observed in employees following renovation of a day care institution that significantly reduced exposure levels of β-(1,3)-D-glucan, but this finding was not supported by a study among inhabitants of water-damaged homes (50, 51). No consistent associations between β-(1,3)-D-glucan exposure and inflammatory markers were observed (51).

Among 91 office workers with symptoms thought to be related to the indoor environment, 67 percent showed immunoglobulin G antibodies to one or more of a range of molds, 3 percent showed immunoglobulin E antibodies to *Alternaria*, but none showed immunoglobulin E antibodies to *Penicillium, Candida,* or *Aspergillus* species; however, these findings were unrelated to environmental mold measures (52). An increased sensitivity to *Penicillium chrysogenum, S. atrata,* and *Trichoderma viride* was observed in an experi-
mental histamine release test in 25 subjects with symptoms of sick building syndrome (53). A reduced number of T lymphocytes in 53 employees of an office contaminated with S. atra was reported, but not in the employees with presumably the highest exposure (40).

Increased prevalences of eye, nose, throat, and lung symptoms and of general symptoms were reported among workers and inhabitants of buildings with signs of indoor mold growth and viable mold levels of about 1,000 CFU/m³ or higher (39, 54) as well as less than 300 CFU/m³ (40, 55–57), or they were related to β-(1,3)-D-glucan level (58).

### ANALYTICAL STUDIES

A total of 28 articles based on analytical studies not initiated by concerns about mold-related health effects (or health effects related to other aspects of a sick building) in the study populations were identified. Fifteen studies focused on occupational exposures (35, 59–72) (table 2), and 13 examined samples of the general population for health problems related to exposures at home (31, 73–84) (table 3).

### Design

Except for two longitudinal studies that recorded exacerbations in asthma patients (73) and nasal lavage parameters in school workers (72), all studies used a cross-sectional sampling frame and relied on prevalent symptom reports or case definitions, including the six case-control studies (31, 62, 68, 75, 80, 83). The participation rate was generally high and varied between 57 percent (80) and 100 percent (61, 70).

### Mold exposure

The occupational exposure settings included offices (59, 62, 63, 65, 67–71), day care centers (60, 61, 66), schools (64, 72), and hospitals (35). Exposure information frequently was based on the study participants’ own reports of mold growth or moisture (60, 66, 71, 74–77, 79, 81). In some studies, members of the research team made this assessment (68, 78, 80, 82, 83). Between 5 percent (79) and 75 percent (60) of the study subjects lived or worked in houses with signs of mold growth or moisture problems.

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**Table 2. Epidemiologic studies of health effects related to mold exposure in nonindustrial workplaces, 1990–2000**

<table>
<thead>
<tr>
<th>Author, year of publication, country (reference no.)</th>
<th>Design and study population (no. of participants, response rate)</th>
<th>Exposure (prevalence/exposure level)</th>
<th>Health effects (no. of symptoms reported)</th>
<th>Confounders controlled for in the analysis or by design</th>
<th>Exposure-response assessment</th>
<th>Quality score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gyntelberg et al., 1994, Denmark (59)</td>
<td>Cross-sectional study of office workers (870, 78%)</td>
<td>Viable molds in dust (910 CFU/30 mg), 12 samples</td>
<td>Symptoms (13)</td>
<td>None</td>
<td>Yes, on building level</td>
<td>2</td>
</tr>
<tr>
<td>Hirvonen et al., 1999, Finland (72)</td>
<td>Longitudinal study of school workers and referents (32 and 8, respectively; response rate not reported)</td>
<td>Total viable molds in air and building structures (7–100 CFU/m³, several species detected, &gt;17 samples in index school</td>
<td>Symptoms (10) and nasal lavage parameters (8)</td>
<td>None</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Li et al., 1997, Taiwan (60)</td>
<td>Cross-sectional study of 56 day care centers (612, response rate not reported)</td>
<td>Self-reported mold growth (26%), water damage (49%)</td>
<td>Work-related symptoms (10)</td>
<td>Gender, age, education</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Li et al., 1997, Taiwan (61)</td>
<td>Cross-sectional study of 28 day care centers (264, 100%)</td>
<td>Total airborne viable molds (1,480 CFU/m³), several genera quantified, 28 samples</td>
<td>Work-related symptoms (12)</td>
<td>Gender, age, education</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Menzies et al., 1998, United States (62)</td>
<td>Case-control study of office workers (107 matched pairs, 78%)</td>
<td>Total and viable molds in air and dust (levels not reported), several species determined in air and dust, 214 samples</td>
<td>Cases defined by work-related respiratory symptoms in initial survey; mold-specific skin prick test</td>
<td>Gender, age, atopy, smoking, house dust mites</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Nelson et al., 1995, United States (63)</td>
<td>Cross-sectional study of office workers (646, 70%)</td>
<td>Total airborne viable molds (10–86 CFU/m³), several species determined, 12 samples</td>
<td>Symptoms (19) grouped into four categories</td>
<td>Gender, age, education, contact lens use, smoking, psychosocial factors, and environmental measurements and perceptions</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Norbäck et al., Sweden, 2000 (64)</td>
<td>Cross-sectional study of school personnel (234, 84%)</td>
<td>Total airborne viable molds (310 CFU/m³). Total airborne molds (32 × 10³/m³), several species determined, 48 samples</td>
<td>Nasal symptoms (4); rhinometry (4) and nasal lavage (4)</td>
<td>Gender, age, smoking, atopy, room temperature</td>
<td>Yes</td>
<td>6/4</td>
</tr>
<tr>
<td>Ooi et al., 1998, Singapore (65)</td>
<td>Cross-sectional study of office workers (2,856, 75%)</td>
<td>Total viable airborne molds (63 CFU/m³), 285 samples</td>
<td>SBS† (&gt;1 symptom out of 10)</td>
<td>Several</td>
<td>Yes</td>
<td>3</td>
</tr>
</tbody>
</table>

Table continues
Quantitative levels of viable molds were determined in air (31, 35, 61–65, 67, 69, 70, 72, 73, 82) and dust (59, 62, 67, 84). Individual samples were collected for each study subject on single (31, 82, 84) or repeated occasions at home (73). In studies of workplace exposures, a limited number of measurements frequently characterized exposure conditions common to several workers (between 2,369 workers/14 samples (67) and 109 workers/24 samples (70); however, individual sampling was also used (62). One study used personal sampling (62), while the others relied on stationary sampling. Sampling time varied from 2 minutes (70) to 6 hours (35).

The average concentration of total viable molds ranged from 32 CFU/m³ (67) to 1,480 CFU/m³ (61) when measured in air and between 33 CFU/30 mg (67) and 910 CFU/30 mg (59) when measured in dust. Some studies also reported total airborne mold counts (viable and nonviable) ranging from $6 \times 10^3$/m³ to $35 \times 10^3$/m³ (31, 35).

$\beta$-(1,3)-D-glucan level was measured in a single study (70). Others determined the presence of specific mold species in air or on building structures (35, 61–64, 73, 75, 84).

**Health effects**

**Asthma.** Cases of asthma were defined by a clinical examination (75, 83, 84) or as physician-diagnosed asthma reported by the study subjects (74, 76, 81). A change in peak expiratory flow with reference to mold exposure in patients with known asthma was the outcome measure in one study (73), while others examined peak flow variability or assessed bronchial hyperresponsiveness by decline in forced expiratory volume in 1 second (FEV₁) following methacholine inhalation, according to established criteria (31, 80).

Asthma-related symptoms were defined by using validated questionnaire criteria (31, 80) or were based on self-reports of wheeze or chest tightness, usually as one of several symptoms screened for (61, 63, 66, 74, 76, 78, 82). The prevalence of asthmatic symptoms varied. For example, in the United Kingdom, 10 percent reported wheezing within 14 days (82), while 21 percent of day care workers in Finland reported wheezing within 12 months (66).

**Rhinitis and nasal symptoms.** Different combinations of nasal symptoms such as congestion, discharge, irritation,
itching, sneezing, or dryness or self-reported rhinitis were often included among the health effects assessed (35, 59–61, 64, 66, 69–71, 77, 81, 82). In Finland, 11–14 percent reported nasal dryness, congestion, or discharge during a 12-month period (66); in Sweden, 54 percent reported nasal catarrh, itching, sneezing, or obstruction during 1 week (35).

Measurement of eosinophilic cationic protein, myeloperoxidase, lysozyme, and albumin in nasal mucosa and measures of nasal patency by acoustic rhinometry were used in two studies (35, 64). Tumor necrosis factor alpha, interleukin-6, nitric oxide, inducible nitric oxide synthase, and cell differential counts in nasal lavage were measured in another study (72).

**Other symptoms.** Most occupational studies and some of the studies focusing on home exposures collected information on a variety of throat, eye, and skin symptoms and on different general symptoms. In the studies reviewed, more than 40 different symptoms were reported; often, different studies reported different symptoms for the same organ. Frequent symptoms were eye irritation, tiredness, and headache, which often affected more than 50 percent of the subjects.

**Confounders**

Atopy was controlled for in several studies (62, 64, 66, 68, 71, 77, 79, 81) and house dust mites in the indoor environment in others (31, 62). In numerous studies, analyses were adjusted by gender, age, smoking, pets at home, social status, educational level, number of cohabitants, temperature, type of dwelling, ventilation, psychosocial index, stress, or job satisfaction. However, in others, confounder control was limited (e.g., no control for smoking) (59, 69, 72, 73, 75, 78, 84).

**Exposure-response relation**

Generally, studies that measured mold levels also assessed possible exposure-response relations by using logistic regression analysis or by computing correlation coefficients; however, this procedure was not used by all (69, 72, 73, 84), or analyses were conducted on a building level and not an individual level (59). Some studies relying on qualitative exposure data classified exposure in high and low categories from the extent of mold growth or dampness observed (66, 71, 83). Nonetheless, these classifications were not validated by mold counts.

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### Table 3. Epidemiologic studies of health effects related to mold growth at home, 1985–1999

<table>
<thead>
<tr>
<th>Study, year of publication, country</th>
<th>Design and study population (no. of participants, response rate)</th>
<th>Exposure (prevalence/exposure level)</th>
<th>Health outcome (no. of symptoms)</th>
<th>Confounders controlled for in the analysis or design</th>
<th>Exposure response assessment</th>
<th>Quality score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beaumont et al., 1985, the Netherlands (73)</td>
<td>Longitudinal study of physician-diagnosed asthma patients (6, participation rate not reported)</td>
<td>Indoor and outdoor airborne total viable molds (125–1425 CFU/m³), several genera determined, 826 samples</td>
<td>Change in PEF†, cough or total IgE†</td>
<td>None</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>Björnsson et al., 1995, Sweden (31)</td>
<td>Population-based case-control study (47 cases, 41 referents, 58%)</td>
<td>Total (35 × 10³/m³) and total airborne viable molds (300 CFU/m³), 88 samples</td>
<td>Asthma-related symptoms defined in initial survey, skin prick test, PEF variability, BHR†</td>
<td>Gender, age, smoking, house dust mites, airborne bacteria, air humidity, temperature</td>
<td>Yes</td>
<td>6/5</td>
</tr>
<tr>
<td>Bruneckref, 1992, the Netherlands (74)</td>
<td>Cross-sectional study (6,436, 73%)</td>
<td>Self-reported damp stains (24%) and visible mold growth (15%)</td>
<td>Symptoms and self-reported physician-diagnosed asthma</td>
<td>Gender, educational level, active and passive smoking, gas heater</td>
<td>No</td>
<td>2/1</td>
</tr>
<tr>
<td>Burr et al., 1988, United Kingdom (75)</td>
<td>Family-physician-based case-control study (72 matched pairs, 95%)</td>
<td>Self-reported damp patches and mold growth verified by observations</td>
<td>Physician-diagnosed asthma, mold-specific IgE and skin prick test</td>
<td>None</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Dales et al., 1991, Canada (76)</td>
<td>Population-based cross-sectional study (14,799, 83%)</td>
<td>Self-reported dampness, mold, flooding, or moisture (38%)</td>
<td>Symptoms (5) and self-reported physician-diagnosed asthma</td>
<td>Gender, age, ethnicity, education, crowding, region, occupation, smoking, atopy</td>
<td>No</td>
<td>3/2</td>
</tr>
<tr>
<td>Koskinen et al., 1999, Finland (77)</td>
<td>Population-based cross-sectional study (699, 100%)</td>
<td>Self-reported mold growth (27%) and observed (52%)</td>
<td>Symptoms and self-reported illness (22)</td>
<td>Gender, age, smoking, allergy, pets, gas stove, atopy</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Martin et al., 1987, United Kingdom (78)</td>
<td>Population-based cross-sectional study (358, 73%)</td>
<td>Observed dampness (24%) or mold growth (17%)</td>
<td>Symptoms (several, not specified)</td>
<td>None</td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

Table continues...
Quality assessment

The summary quality scores are presented for each study in tables 2 and 3. Studies that used a combination of self-reported and objective exposure or outcome information were given a combined quality score to reflect this fact. A maximum of eight points was possible. Two studies were scored with the observed maximum of six points (31, 64), while the median was three points.

EXPOSURE-EFFECT RELATIONS

Asthma

Signs of mold growth or dampness. Clinically verified cases of asthma, as well as self-reported cases of physician-diagnosed asthma, were associated with signs of mold growth or dampness (weighted average odds ratio = 1.48, 95 percent confidence interval (CI): 1.32, 1.65) (74–76, 81, 83). This was also the case for asthma-related symptoms (weighted average odds ratio = 1.62, 95 percent CI: 1.54, 1.71) (60, 66, 74, 76, 80) (table 4). No consistent differences were found if exposure characterization was based on self-reports or reviewers’ observations. Martin et al. reported no association with asthma-related symptoms but did not present the estimates (78). Norbäck et al. showed a strong crude association with wheeze/whistling in the chest, attacks of shortness of breath, or nighttime awakening because of breathlessness/tightness in the chest (80). However, if these three sets of asthma-related symptoms were analyzed separately, no associations were observed for the latter two. Williamson observed increasing asthma severity by extent of visible mold growth (83). Bronchial hyperresponsiveness, as measured by methacoline provocation or peak flow variability, showed no association with signs of mold or dampness in the dwellings (80) (table 4).

Viable mold counts. Measures of bronchial hyperresponsiveness or asthma-related symptoms were unrelated to counts of viable molds in air or dust (table 4). Only Platt et al. (82) reported estimates of the association, and a meta-measure was not computed.

Total mold counts. The single study that assessed the impact of total airborne molds (viable and nonviable) showed no association with signs of mold or dampness in the dwellings (80) (table 4).

Rhinitis and nasal symptoms

Signs of mold growth or dampness. Nasal symptoms (congestion, discharge, irritation, itching, sneezing, or dryness) or self-reported rhinitis was associated with signs of...
TABLE 4. Reported relations between mold exposure in nonindustrial workplaces or dwellings and physician-diagnosed asthma, asthma-related symptoms, and bronchial hyperresponsiveness in adults: results of epidemiologic studies, 1988–1997

<table>
<thead>
<tr>
<th>Study, year of publication (reference no.)</th>
<th>Quality score</th>
<th>Outcome</th>
<th>Association*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williamson et al., 1997 (83)</td>
<td>4</td>
<td>Physician-diagnosed asthma</td>
<td>1.70 (0.78, 3.71)</td>
</tr>
<tr>
<td>Burr et al., 1988 (75)</td>
<td>3</td>
<td>Physician-diagnosed asthma</td>
<td>2.5 (1.1, 5.9)†</td>
</tr>
<tr>
<td>Dales et al., 1991 (76)</td>
<td>3</td>
<td>Self-reported physician-diagnosed asthma</td>
<td>1.56 (1.25, 1.95)</td>
</tr>
<tr>
<td>Norbäck et al., 1995 (80)</td>
<td>3</td>
<td>PEF‡ variability or reduction in FEV1‡ following methacholine provocation</td>
<td>No associations, estimates not reported</td>
</tr>
<tr>
<td>Brunekreef, 1992 (74)</td>
<td>2</td>
<td>Self-reported physician-diagnosed asthma</td>
<td>1.29 (0.92, 1.81)§</td>
</tr>
<tr>
<td>Dales et al., 1991 (76)</td>
<td>2</td>
<td>Persistent cough, phlegm, wheeze, wheeze with dyspnea</td>
<td>1.62 (1.48, 1.78)</td>
</tr>
<tr>
<td>Pirhonen et al., 1996 (81)</td>
<td>2</td>
<td>Self-reported physician-diagnosed asthma</td>
<td>1.02 (0.60, 1.72)</td>
</tr>
<tr>
<td>Ruotsalainen et al., 1995 (86)</td>
<td>2</td>
<td>Wheeze</td>
<td>1.28 (0.44, 3.73)</td>
</tr>
<tr>
<td>Brunekreef, 1992 (74)</td>
<td>1</td>
<td>Wheeze</td>
<td>1.63 (1.30, 2.06)</td>
</tr>
<tr>
<td>Norbäck et al., 1995 (80)</td>
<td>1</td>
<td>Wheeze or whistling in the chest, attacks of shortness of breath, or nighttime awakening because of breathlessness or chest tightness</td>
<td>3.9 (1.1, 14.1)</td>
</tr>
<tr>
<td>Li et al., 1997 (60)</td>
<td>0</td>
<td>Wheeze</td>
<td>1.39 (0.84, 2.29)</td>
</tr>
<tr>
<td>Martin et al., 1987 (78)</td>
<td>0</td>
<td>Wheeze</td>
<td>No association, estimate not reported</td>
</tr>
<tr>
<td>Björnsson et al., 1995 (31)</td>
<td>6</td>
<td>Daily PEF variability or reduction in FEV1 following methacholine provocation</td>
<td>No associations, estimates not reported</td>
</tr>
<tr>
<td>Beaumont et al., 1985 (73)</td>
<td>5</td>
<td>Mean daily PEF</td>
<td>No association with indoor mold levels, (highest vs. lowest daily mold counts)</td>
</tr>
<tr>
<td>Björnsson et al., 1995 (31)</td>
<td>5</td>
<td>Wheeze or whistling in the chest, attacks of shortness of breath, or nighttime awakening because of breathlessness or chest tightness</td>
<td>No association, estimate not reported</td>
</tr>
<tr>
<td>Platt et al., 1989 (82)</td>
<td>4</td>
<td>Wheeze</td>
<td>0.01 (p = 0.41)§</td>
</tr>
<tr>
<td>Nelson et al., 1995 (63)</td>
<td>3</td>
<td>Chest tightness, difficulty in breathing, shortness of breath, or wheeze</td>
<td>No association, estimate not reported</td>
</tr>
<tr>
<td>Wood et al., 1988 (84)</td>
<td>2</td>
<td>Physician-diagnosed asthma</td>
<td>Lower mold counts in asthma patients' dwellings than in control patients' dwellings (p = 0.49)</td>
</tr>
</tbody>
</table>

Total airborne molds

<table>
<thead>
<tr>
<th>Study, year of publication (reference no.)</th>
<th>Quality score</th>
<th>Outcome</th>
<th>Association*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Björnsson et al., 1995 (31)</td>
<td>6</td>
<td>Daily PEF variability or reduction in FEV1 following methacholine provocation</td>
<td>No association, estimate not reported</td>
</tr>
<tr>
<td>Björnsson et al., 1995 (31)</td>
<td>5</td>
<td>Wheeze or whistling in the chest, attacks of shortness of breath, or nighttime awakening because of breathlessness or chest tightness</td>
<td>0.8 (0.1, 5.1)</td>
</tr>
</tbody>
</table>

* Odds ratios (95% confidence intervals) unless otherwise noted.
† Crude odds ratio derived from the original data.
‡ PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 second.
§ Men only, similar estimates for women.
¶ Airborne mold levels except for the study by Wood et al. (84), which reported dust levels.
# Correlation coefficient (p value in parentheses).
mold growth or dampness in several studies (35, 60, 66, 77, 81) but not all (71) (table 5). A weighted average odds ratio of 1.84 was computed (95 percent CI: 1.65, 2.04).

**Viable mold counts.** Levels of viable molds in air or dust were associated with nasal symptoms in three studies (59, 61, 70), but this was not the case in the other three (64, 69, 82) (table 5).

**Total mold counts.** No statistically significant association was reported between total mold counts and nasal symptoms of congestion, discharge, itching, or sneezing (64) (table 5).

**β-(1,3)-D-glucan levels.** Wan and Li observed no association between β-(1,3)-d-glucan level and nasal symptoms (70) (table 5).

**Rhinometric or nasal lavage parameters.** None of four rhinometric parameters of nasal patency was related to signs of dampness, but a statistically significant higher lysozyme level in nasal mucosa was observed in employees of damp buildings compared with dry buildings ($p = 0.002$); however, this was not found for eosinophilic cationic protein, myeloperoxidase, or albumin levels (35). Airborne level of total molds (viable and nonviable) was related to nasal patency expressed as the sum of the volumes of the two nasal cavities measured 23–54 mm from the nasal openings but not if measured from 0 mm to 22 mm or if nasal health was examined as the minimal cross-sectional areas of the nasal cavities or as four mucosa parameters (myeloperoxidase, eosinophilic cationic protein, lysozyme, or albumin) (64). Nasal lavage concentrations of interleukin-6 and nitric oxide fell during summer vacation and rose to previous levels in workers of a school with visible mold growth, but this pattern was not seen for tumor necrosis factor alpha and cell differential count (72).

### Throat, eye, and skin symptoms and general symptoms

**Signs of mold growth or dampness.** Consistent associations were found between signs of mold growth or dampness and throat symptoms (soreness, hoarseness, cough, dryness, irritation, or itching), eye symptoms (irritation, dryness, itching, soreness, redness, or swollen eyelids), skin symptoms (dryness, irritation, itching, rash, blushing, or eczema), and general symptoms (headache, fatigue, malaise, nausea, fever and chills, vomiting, and diarrhea) (table 5). Weighted average odds ratio values of 2.06 (95 percent CI: 1.84, 2.29), 1.73 (95 percent CI: 1.63, 1.82), 1.81 (95 percent CI: 1.55, 2.06), and 1.51 (95 percent CI: 1.44, 1.58), respectively, were computed. However, no strong associations were seen for case definitions based on combinations of nose or throat symptoms, lower respiratory tract symptoms, or wider case definitions in accordance with sick building syndrome.

**Viable mold counts.** No consistent pattern indicating increased occurrence of symptoms affecting the throat, eyes, or skin or of general symptoms by measured levels of viable molds in air or dust was apparent (table 5).

**Total mold counts.** The single study that assessed total mold levels reported no association with nasal, throat, or lower respiratory tract symptoms (62). Another study measured total mold levels but presented no results (35) (table 5).

**β-(1,3)-D-glucan levels.** A statistically significant association was found between β-(1,3)-d-glucan level and lethargy or fatigue but not for symptoms affecting the throat, eyes, or skin (70) (table 5).

### Study quality and exposure effect relations

No consistent trend in odds ratios (or other measures of association) was found for asthma, asthma-related symptoms, or nose, throat, eye, or skin symptoms or for general symptoms by study quality score in the four exposure categories (signs of mold growth or dampness, viable molds, total molds, or β-(1,3)-d-glucan). There were indications of an overall trend toward weaker or no association by increasing quality score if the four exposure categories were disregarded. However, this comparison was weakened by many negative higher-quality studies that did not report exposure effect estimates.

### Health effects related to specific mold species

An increased occurrence of airway symptoms was reported in office workers from a building in which *Alternaria* was detected (odds ratio = 4.2, 95 percent CI: 1.1, 16.2), but symptoms were unrelated to *Aspergillus, Cladosporium*, and *Penicillium* species (62). The presence of *Aspergillus* species (detection level, 30 CFU/m$^3$) was related to decreased nasal patency, whereas the presence of *Penicillium* species was associated with increased patency and no association was found for yeasts (64). Airborne levels of *Aspergillus* species showed statistically significant associations with nasal congestion, cough, phlegm, lethargy, and fatigue, but this was not the case for levels of *Penicillium* and *Cladosporium* species or yeast in day care workers (61).

No significant difference in pulmonary complaints related to levels of *Penicillium, Alternaria*, and *Aspergillus* species was reported in another study (73).

### Allergy as a possible mode of action

A positive skin prick test for *Alternaria* species was associated with work-related respiratory symptoms and growth of *Alternaria* species at the worksite, but no such relation was suggested for *Cladosporium* and *Penicillium* species (62). However, specific immunoglobulin E to *Alternaria alternata* was not more frequent in asthma patients with signs of mold growth at home than in asthma patients without such mold growth, but this finding was true for *Penicillium notatum* (75). Indoor mold levels or signs of indoor mold growth were unrelated to positive skin prick tests for common molds (84). Total immunoglobulin E and s-eosinophilic cationic protein were related to mold levels (31). Indicators of atopy did not modify an observed association between signs of mold growth and lower respiratory tract symptoms, which would be expected if allergy is of causal importance (76).
DISCUSSION

The analytical studies reviewed provide strong evidence that signs of mold growth or dampness in nonindustrial workplaces or dwellings are associated with asthma as diagnosed by a physician or on the basis of relevant symptoms and with nose, eye, and skin symptoms; fatigue; or headache. However, no consistent associations were found for objectively assessed exposure to viable molds.

TABLE 5. Reported relations between mold exposure in nonindustrial workplaces or dwellings and throat, eye, nose, and skin symptoms, general symptoms, or mixed-organ symptoms: results of epidemiologic studies, 1987–2000a

<table>
<thead>
<tr>
<th>Study, year of publication (reference no.)</th>
<th>Quality score</th>
<th>Exposure-effect relation (odds ratios (95% confidence intervals) unless otherwise noted) and underlying symptoms (in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signs of mold growth or dampness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dales et al., 1991 (76)</td>
<td>2</td>
<td>Nose: 1.63 (1.46, 1.82) (itching)</td>
</tr>
<tr>
<td>Koskinen et al., 1999 (77)</td>
<td>2</td>
<td>Nose: 1.89 (1.15, 3.11) (rhinitis)</td>
</tr>
<tr>
<td>Pirhonen et al., 1996 (81)</td>
<td>2</td>
<td>Nose: 1.69 (1.31, 2.18) (rhinitis)</td>
</tr>
<tr>
<td>Ruotsalainen et al., 1995 (66)</td>
<td>2</td>
<td>Nose: 1.84 (0.65, 5.18) (dryness)</td>
</tr>
<tr>
<td>Stenberg et al., 1994 (68)</td>
<td>2</td>
<td>Nose: 1.84 (0.65, 5.18) (dryness)</td>
</tr>
<tr>
<td>Wan and Li, 1999 (71)</td>
<td>2</td>
<td>Nose: 0.94 (0.50, 1.77) (congestion or discharge)</td>
</tr>
<tr>
<td>Norbäck and Edling, 1991 (79)</td>
<td>1</td>
<td>Nose: —‡ (irritation or swollen eyelids)</td>
</tr>
<tr>
<td>Wieslander et al., 1999 (35)</td>
<td>1</td>
<td>Nose: 13.0 (3.4, 86)§ (irritation, congestion or discharge)</td>
</tr>
<tr>
<td>Martin et al., 1987 (78)</td>
<td>0</td>
<td>Nose: —‡ (several unspecified symptoms and health problems)</td>
</tr>
<tr>
<td>Li et al., 1997 (60)</td>
<td>0</td>
<td>Nose: 1.52 (1.02, 2.26) (congestion)</td>
</tr>
<tr>
<td>Menzies et al., 1998 (62)</td>
<td>5</td>
<td>Nose: —‡ (congestion, discharge, itching or sneezing)</td>
</tr>
<tr>
<td>Norbäck et al., 2000 (64)</td>
<td>4</td>
<td>Nose: —‡ (congestion, discharge, itching or sneezing)</td>
</tr>
</tbody>
</table>

Table continues
tive measures of bronchial hyperresponsiveness or nasal mucosal parameters, but the studies were few (35, 64, 80). In children, asthma also has been related to signs of mold growth or dampness (18, 19).

The studies provide no consistent evidence that quantitative measures of total or viable indoor molds, β-(1,3)-D-glucan, or specific mold species are associated with asthma disease, asthma-related symptoms, or bronchial hyperre-
sponsiveness. These findings are in line with the fact that the impact of mold exposure on asthma in adults is largely unknown (85), even if single cases of occupational mold asthma have been reported (11, 12). In addition, nose, throat, eye, and skin symptoms; fatigue; headache; or objective nasal parameters were not associated with specific measures of fungal biomass.

The discrepancies in these results may suggest that the quantitative measures of mold exposure were inappropriate, that detection levels in the quantitative studies were insufficient, or that these studies were flawed because of bias. The latter aspect also pertains to the studies relying on qualitative signs of mold growth or dampness. We discuss these aspects one at a time.

**Appropriateness of quantitative measures of mold exposure**

In the studies reviewed, four principally different measures of molds in air or dust were used: total viable mold counts, total mold counts (viable and nonviable), \( \beta \)-(1,3)-D-glucan level, and specific mold species (qualitative or quantitative). Air and dust are the media relevant to examine; dermal absorption or ingestion of surface-contaminated material is not expected to play a significant role, and no difference in exposure-effect relations was observed when exposure assessment was based on air or dust samples.

However, one may question the appropriateness of using viable mold counts as the measure of exposure since higher levels generally are not observed in buildings characterized by mold growth or water damage compared with nonproblem buildings or outdoor air (21, 23, 25, 30, 35–37). This question may also apply to total mold counts; however, for this measure, data are limited. \( \beta \)-(1,3)-D-glucan levels have been associated with signs of mold growth in the indoor environment (70).

Thus, it may be that the measures of exposure applied do not provide a sufficient characterization of mold exposure. On the other hand, they all reflect the extent of molds from recent and current sources in air or dust and are therefore expected to relate to human health effects if a causal effect of indoor molds is present.

Even if molds are obvious causal candidates for the health effects reported by subjects working or living in buildings with signs of mold growth or dampness, there are also other candidates, for example, house dust mites. House dust mites, similar to molds, prefer a humid environment and are well-documented causes of allergic airway disease. Furthermore, house dust mites were related to asthmatic symptoms in the study by Björnsson et al. (in contrast to mold counts) (31) but not in the study by Wan and Li (70). Inhalation of bacterial particles could also, at least partly, explain some of the symptoms, since endotoxin exposure determines the severity of asthma in people allergic to house dust mites (86); however, the studies reviewed do not provide consistent evidence for this hypothesis (31, 61, 64, 70).

**Detection level of the quantitative studies**

The lack of any consistent association between levels of mold exposure and health effects may be due to nondifferential misclassification, since a limited number of mold measurements often were used to classify exposure levels for several workers in large buildings (61, 63–65, 67) or sampling time was brief (70). This limitation may have attenuated real associations, since mold levels show significant variability (25).

If there is a threshold level for mold-related health effects, it may be that the populations in the quantitative studies were exposed below this level. However, no stronger exposure-effect associations were seen in the few studies reviewed with the highest average exposure levels (>1,000 CFU/m\(^3\)) (61, 73).

**Bias in the quantitative studies**

It is expected that subjects with mucosal or respiratory symptoms take precautions to avoid exposures in their dwellings or leave workplaces that have mold and moisture problems. Thus, in cross-sectional studies, which was the preferred design of all but two of the studies reviewed, a possible relation between mold exposure and health effects may be underestimated (87). However, since it is expected that such selection bias would affect studies classifying exposure according to signs of mold growth more than those relying on quantitative measures, this possibility can hardly explain the discrepancy in the results of the studies reviewed.

It is also unlikely with respect to other aspects of study quality, because no systematic deficit in overall quality (design, participation, confounder control, exposure-effect assessment, outcome specificity) was seen for the quantitative studies compared with those relying on qualitative exposure data.

Discrepancies in results could also be seen if generally lower exposure levels were found compared with the qualitative studies. However, this possibility was not supported by the two studies by Björnsson et al. and Norbäck et al. that characterized the same population by both qualitative and quantitative exposure information (31, 80).

**Bias in the qualitative studies**

The major limitation of the reviewed studies relying on self-reports of exposure is the inherent risk of information bias. Pirhonen et al. illustrated this limitation by observing that associations between self-reported home exposures and symptoms disappeared when subjects who had symptoms that could hardly be explained by indoor exposures were excluded from the analyses (81). Others have provided strong evidence of a significant effect of recall bias in studies of health effects due to indoor climate (22, 88), but not all have (82). Researchers’ independent observations of indoor mold growth may to some extent counter this bias, but not in studies with symptoms as the health outcome; symptoms, by definition, are self-reported, and mold growth visible to surveyors is also expected to be visible to study subjects. The
A possible mode of action

If increased levels of molds in indoor environments cause the respiratory and mucosal health effects suggested, immunoglobulin E–mediated allergy is a possible mechanism. However, no consistent support for this mechanism was provided by the few studies that included information on mold exposure, health effects, and skin prick test results or mold-specific immunoglobulin E.

β-(1,3)-glucan induces nonspecific inflammatory reactions (6). Lethargy and fatigue were the only symptoms that showed an association with β-(1,3)-glucan level. However, this association was weak and was reported in only a single study.

Mycotoxins have been detected in buildings in which persons have complained about a sick building. However, reported health effects from this exposure have not been disentangled from other possible causes in the indoor environment (39, 40, 47), and none of the systematic studies reviewed specifically examined mycotoxins.

Overall, we conclude that the weight of evidence indicates that exposure to exceptionally high mold levels may cause allergic alveolitis and inhalation fever, and this finding may be pertinent to buildings severely damaged by extensive and prolonged mold growth. However, the studies we reviewed provide no evidence that increasing levels of viable mold exposure in nonindustrial work environments or dwellings are related to an increasing occurrence of asthma or to nose, eye, and skin symptoms; fatigue; or headache in the adult population, which may be due to inappropriate or insufficient measures of mold exposure. No consistent indications were presented that related total fungal biomass to health effects; however, the studies were few.

Even if the epidemiologic database is insufficient to judge whether mold exposure in nonindustrial environments has adverse health effects on adults, we recommend that work- places be kept clean, well maintained, and dry. Nonetheless, we will be cautious before ascribing asthma; nose, eye, and skin symptoms; fatigue; or headache to mold exposure in our patients’ nonindustrial workplaces.

However, these health problems more often are reported by adults working or living in buildings that have signs of indoor mold growth and dampness. To elucidate possible causal mechanisms, further studies should probably focus on populations experiencing larger mold exposure contrasts than those encountered in nonindustrial environments. Alternative measures are recommended to characterize buildings that have signs of mold growth and dampness. They may relate to molds and their metabolic products such as mycotoxins, but other factors should also be considered, as well as more appropriate exposure assessment strategies. Newly developed objective methods to determine inflammation, such as acoustic rhinometry, nasal lavage, tear fluid sampling, induced sputum, and condensed breath, will be needed in order to study exposure-response relations and to avoid reporting bias in this area of low exposure. The low exposure situation also leads to the need for good control for confounders and exposures outside the buildings studied.

REFERENCES

55. Cooley JD, Wong WC, Jumper CA, et al. Correlation between


