

Excess dampness and mold growth in homes: An evidence-based review of the aeroirritant effect and its potential causes

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ABSTRACT

Exposure to fungi produces respiratory disease in humans through both allergic and nonallergic mechanisms. Occupants of homes with excess dampness and mold growth often present to allergists with complaints of aeroirritant symptoms. This review describes the major epidemiological and biological studies evaluating the association of indoor dampness and mold growth with upper respiratory tract symptoms. The preponderance of epidemiological data supports a link between exposure to dampness and excess mold growth and the development of aeroirritant symptoms. In addition, biological and clinical studies evaluating potential causal substances for the aeroirritant effect, notably volatile organic compounds (VOCs), are examined in detail. These studies support the role of VOCs in contributing to the aeroirritant symptoms of occupants of damp and mold-contaminated homes.

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Key words: Adverse health effect, aeroirritant, allergy, evidence based, fungi, mold, nonallergic rhinitis, respiratory symptoms, toxicity, volatile organic compounds

Fungi produce a broad array of effects on human health. Exposures to outdoor and indoor fungi have been associated with allergic respiratory disease, systemic toxic syndromes, and infections.¹ Epidemiological studies have linked exposure to a damp indoor environment with adverse health effects.² Excess mold growth commonly associates with a damp indoor environment, and exposure to indoor mold itself has been cited in large studies as a predictor of adverse health outcomes.² Well-established routes of exposure to mold components as a cause of adverse health effects, such as allergic respiratory disease, account for some of the adverse symptoms experienced by patients. In addition, there appear to be many people who develop a transient aeroirritant effect from exposure to indoor dampness and molds, separate from the development or worsening of allergic disease.^{3,4} The aim of this study was to review the scientific evidence evaluating the aeroirritant effects of dampness and mold growth and to consider the most likely biological explanations for these effects, focusing on the potential role of volatile organic compounds (VOCs).

METHODS

A narrative review was prepared based on available literature. A search using the Pubmed database was performed to identify studies evaluating the link between a damp and/or mold-contaminated indoor environment and upper airway irritant symptoms. Search terms included “dampness,” “mold,” “fungus,” “irritant,” “upper airway symptoms,” “rhinitis,” and “eye irritation.” Studies were included if upper airway symptoms, such as rhinitis, eye irritation, or throat symptoms, were included as an end point. Studies evaluating only lower airway symptoms or other putative mold-related symptoms (*i.e.*, neurological) were excluded. Pediatric and adult studies were analyzed separately. Hierarchy of evidence was subjectively graded using standard criteria for evaluating clinical studies.^{5,6}

For evaluation of the effects of volatile organic compounds on human subjects, both basic science and clinical studies were identified *via* Pubmed with search terms including “volatile organic compounds,” “microbial VOCs,” (MVOCs) “VOC,” “irritant,” “fungus,” and “mold.” Higher level evidence was used where available, but out of necessity, small-scale and laboratory studies were included also because of a lack of high-quality evidence in some subject areas.

Mold-Related Health Effects

Molds can cause diverse health effects, related to the type of exposure and unique characteristics of an individual’s physiological response. It is important to dif-

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ferentiate the better known effects of molds on human health from the common, but less well-described, aero-irritant effects.

Allergic and Other Immunologic Respiratory Disease. Allergic sensitivity to fungi is common, with 3.6% of the general population⁷ and 22–38% of asthmatic patients^{8–10} possessing specific IgE for indoor and outdoor fungal allergens. For outdoor fungi, most notably *Alternaria*, epidemiological studies have linked daily outdoor spore counts with asthma outcomes including frequency of symptoms^{11,12} and exacerbations.^{13–15} In some studies, indoor fungus exposure as measured by spore counts is associated also with allergic sensitization and rhinoconjunctivitis symptoms,¹⁶ as well as asthma symptoms in sensitized patients.^{17,18} However, not all patients exposed to indoor or outdoor mold develop allergic sensitization. In addition, not all patients who develop respiratory symptoms after exposure to indoor mold possess specific IgE to fungal allergens. Aside from allergic rhinitis and asthma associated with fungal allergen exposure, immunologic reactivity to fungi also plays a pathological role in the well-characterized but relatively rare diseases of hypersensitivity pneumonitis, classic allergic fungal sinusitis, and allergic bronchopulmonary aspergillosis.

Mycotoxicosis. Exposure to large doses of toxins produced by fungi can result in overwhelming acute systemic illness.¹⁹ Contamination of cereal by ergot alkaloids produced by the fungus *Claviceps purpurea* led to ergotism with gangrene during the Middle Ages.²⁰ More recently, *Aspergillus*-derived aflatoxins in contaminated nut and cereal products have led to mass poisonings in India and Kenya in the last 45 years.¹⁹ The media popularized the term “toxic mold” after a cluster of 10 cases of acute idiopathic pulmonary hemorrhage occurred in Cleveland in 1993. An initial review suggested that the cases were associated with common exposure to *Stachybotrys chartarum*, but subsequent analysis showed this was not the cause.²¹ Nonetheless, the terms “toxic mold” or “black mold” often are associated in the public mind with indoor mold exposure.

It has been difficult to correlate levels of detectable *Stachybotrys chartarum* conidia and its associated mycotoxins in the air of mold-contaminated homes with symptoms, which has led to the general idea that there may be little contribution by mycotoxins to irritant respiratory disease.²² However, recent studies have demonstrated *S. chartarum* mycotoxins on respirable mold fragments,²³ suggesting an underestimate of the burden of airborne mycotoxins in previous epidemiological studies.

Infection. Common infections due to fungi include dermatophyte skin infections and yeast-related vaginosis. The causative agents for these conditions usually are not found in significant quantities in air or surface sampling of the home environment. Only in severely immunocompromised patients, *e.g.*, recipients of organ transplants or those with HIV/AIDS, can a range of opportunistic infections commonly occur because of fungi.

Aeroirritation. Common symptoms of patients exposed to a damp environment include upper and lower respiratory complaints. An Institute of Medicine expert panel performed a comprehensive review of the relevant literature and found an association between exposure to a damp indoor environment and cough, wheeze, and nasal and throat symptoms.² In addition, the same expert panel found that epidemiological studies associate the presence of mold in a damp indoor environment with cough, wheeze, and nasal and throat symptoms. In the setting of an allergy clinic, patients commonly present with upper airway symptoms resembling these complaints. The question often arises whether a damp and/or moldy indoor environment may be contributing to symptoms despite the absence of documented IgE-mediated allergic sensitivity. A review of the evidence evaluating the validity of such an assertion will help the allergist make informed decisions regarding treatment of symptoms, whether mold remediation may be necessary, and how to allay the anxiety of concerned patients.

Several large epidemiological studies have found an association between exposure to a damp indoor environment and/or the presence of mold in the indoor environment with irritant upper airway symptoms. These symptoms include irritated eyes, rhinorrhea, nasal congestion, and throat irritation. These epidemiological studies often assessed for other conditions as well, and this review of the literature will focus on upper airway symptoms suggesting aeroirritation, both in adults and children.

Population Studies in Adults. Several cross-sectional studies have found a significant correlation between exposure to a damp indoor environment and the presence of eye, nose, and/or throat irritation symptoms. These studies have been performed in a variety of countries and in both new and old building environments. Multiple studies also have found a dose-response relationship between the number of indicators of dampness present and aeroirritant symptoms.

Engvall *et al.*²⁴ surveyed 3241 adults in 261 buildings in Sweden and determined rates of high humidity indicators, such as moldy odor and history of water leakage, in the past 5 years. They found an odds ratio (OR) of 1.92 (CI, 1.78–2.07) for presence of nasal symp-

toms, and an OR of 4.42 (CI, 4.09–4.77) for throat irritation in association with these dampness indicators. There was a finding analogous to a dose response in that an increase in the number of signs of dampness incrementally increased the OR of having respiratory symptoms.

Wan and Li²⁵ performed a questionnaire study on office workers in buildings in Taiwan. Twelve hundred thirty-seven subjects were surveyed, and they found an OR of 1.34 for eye irritation when stuffy odor or mold was present. The OR increased to 3.14 if water damage, stuffy odor, and mold were present, and was 5.03 if four measures of dampness were present. All of these findings were statistically significant. This again indicated a dose-response-type relationship, this time between eye irritation and dampness in the building. Statistically significant relationships were not found for nasal congestion and runny nose.

A study by Wieslander *et al.*²⁶ evaluated 95 hospital workers, both by recording reported symptoms and by performing a medical examination and measurement of nasal lavage, acoustic rhinometry, and tear film stability. Working in a damp building (as indicated by presence of dampness in the concrete floor) was found to be associated with an OR of 1.10 (CI, 1.15–1.45) for nasal symptoms and 1.29 (CI, 1.02–1.18) for eye irritation symptoms. Mold contamination and MVOCs (discussed later) in the various buildings were of relatively low levels, with total MVOCs measured at $<1 \mu\text{g}/\text{m}^3$.

Koskinen *et al.*²⁷ studied occupants of 310 random homes in Finland. Moisture in the home was assessed by site visit with specially trained personnel, as well as by occupant-assessed current or past mold presence in the home. Six hundred ninety-nine adults were surveyed for respiratory and other symptoms; rhinitis (OR, 1.89; CI, 1.15–3.11) and sore throat (OR, 2.40; CI, 1.56–3.69) were significantly associated with presence of mold. Sore throat (OR, 1.46; CI, 1.03–2.08) and sinusitis, but not rhinitis (OR, 1.06; CI, 0.71–1.59), were significantly associated with surveyor-assessed moisture. However, in the parallel study evaluating the children in these homes,²⁸ rhinitis was strongly associated with surveyor-assessed moisture (OR, 4.31; CI, 1.80–10.34), as was sore throat (OR, 2.34; CI, 1.13–4.86).

Given the possibility that reporting bias may affect the description of symptoms for subjects also reporting mold in their homes, Pirhonen *et al.*²⁹ performed a survey-based study and then controlled for markers of a “complainer” predisposition. Their initial findings were that several symptoms were positively associated with the presence of mold in the home in their random sampling of 1460 Finnish adults. Among these were rhinitis, with an OR of 1.69 (CI, 1.31–2.18), and eye irritation (OR, 1.52; CI, 1.18–1.96). However, lumbar backache and recurrent stomach ache, two conditions that should be pathophysiologically unrelated to mold

exposure, also were found to be associated. Removing the subjects with reported stress and/or depression, who might be expected to be affected by reporting bias, did not affect the significance of the findings. The investigators adjusted their data by removing the “complainers” from the analysis and still found eye irritation (OR, 1.69; $p < 0.05$) to be significantly associated with presence of mold, whereas rhinitis became a nonsignificant trend (OR, 1.21; $p = \text{NS}$).

Recently, an analysis of 50 patients referred for evaluation of mold-related illness has been published.³ Thirty-three patients were found to have plausible nonmold-related causes of their complaints or nonphysiological bases for their symptoms, and 17 patients (34%) were found to have symptoms thought related to aeroirritant effects of indoor mold.

Although more studies of dampness and indoor health have focused on older dwellings, Saijo *et al.*³⁰ surveyed 317 occupants of newly built houses in Japan. Occupants related whether they had symptoms including eye, nose, and throat/respiratory complaints. The investigators found that condensation on windowpanes and visible mold growth were associated with eye, nose, and throat/respiratory symptoms in a statistically significant manner. There also was a dose-response effect, in that when both dampness factors were present, the ORs increased compared with the presence of either condensation or mold growth alone. If both factors were present, for eye symptoms the OR was 4.36 (CI, 1.60–11.9), for nose symptoms the OR was 3.70 (CI, 1.42–9.60), and for throat/respiratory symptoms the OR was 3.45 (CI, 1.23–9.66). Their conclusion, as was the conclusion of the authors in several other studies reviewed here, was that the presence of dampness and/or visible mold growth in the indoor environment was significantly associated with irritant eye and/or nose symptoms in adults.

Population Studies in Children. Several epidemiological studies have addressed the question of whether a damp indoor environment correlates with adverse respiratory health effects in children. In addition to cross-sectional studies, longitudinal studies and nested case-control studies in children provide higher-level evidence supporting a causative role for indoor dampness and mold growth in producing aeroirritant symptoms.

Zacharasiewicz *et al.*³¹ surveyed parents about their 6- to 9-year-old children to determine the rates of nasal symptoms relating to exposures in the indoor environment. Two thousand and eight hundred forty-nine children were analyzed, and the investigators found an increased OR of 1.51 (CI, 1.31–1.74) of having nasal symptoms if there was dampness/mold present at home. A study in Canada by Dales and Miller³² correlated itchy eyes and nose irritation with reported mold growth in the homes of 403 elementary school children,

with an OR of 1.81 (CI, 1.02–3.24) for risk of these symptoms. In addition, controlling for level of dust mites and endotoxin did not eliminate the association. Bornehag *et al.*³³ performed a cross-sectional survey of 10,851 1- to 6-year-old children to assess the prevalence of rhinitis symptoms in relation to environmental dampness. Rhinitis symptoms significantly correlated with visible dampness, condensation, floor moisture, and history of water damage. Another cross-sectional study of 20,016 children in Italy found that rhinoconjunctivitis was associated with early exposure to visible mold or dampness, with an OR of 1.46 (CI, 1.13–1.89) after adjusting for confounding variables.³⁴

A nested case control study within a prospective longitudinal cohort also found that home dampness correlated with respiratory complaints in children aged 7–8 years old.³⁵ Within the cohort, 781 children with respiratory complaints were identified and matched with controls. It was found that, among other risk factors, long-term exposure to dampness significantly correlated with respiratory symptoms (OR, 2.98; CI, 1.10–8.28).

A study by Jaakkola *et al.*³⁶ highlighted the importance of mold odor in assessing fungal contamination. Surveys were sent to parents of 1- to 6-year-old children, and 2568 children were included. Along with several other respiratory symptoms, nasal congestion (OR, 1.94; CI, 1.15–4.98) was associated with all of the determinants of dampness/mold, which included history of water damage, presence of moisture and visible mold, and perceived mold odor at home. However, perception of mold odor had a stronger association with nasal congestion (OR, 2.39; CI, 1.15–4.98) and nasal excretion (OR, 2.38; CI, 1.13–4.99). In addition, water damage over 1 year before the survey had a strong correlation with nasal congestion (OR, 4.60; CI, 2.57–8.22) and nasal excretion (OR, 3.19; CI, 1.64–6.19).

A study published as part of the Danish Mold in Buildings Program found a significant correlation between levels of mold colony-forming units in settled dust and eye and throat irritation in 13- to 17-year-old adolescents.³⁷ Nasal irritation was not significantly associated. One thousand fifty-three children were surveyed in the cross-sectional study, which found the significant correlation even after adjusting for numerous confounding variables such as presence of asthma, hay fever, recent airway infection, and psychosocial factors.

Finally, a recent longitudinal study³⁸ has added stronger evidence that moisture damage and its related higher fungal contamination levels have a causal effect on upper airway symptoms in children. Children aged 6–17 years old were assessed for upper airway symptoms in moisture-damaged schools before and after either complete or partial remediation efforts. Trained engineers assessed the level of water damage before

and after remediation, and airborne fungal concentrations were recorded. In the study, authors found that there were statistically significant decreases in stuffy nose, rhinitis, sore throat, cough, and eye symptoms after mold and water damage remediation had been performed. In addition, airborne fungal contamination and building moisture were lower after remediation in parallel with the decrease in symptoms. As a control, another group of children was assessed at a school that underwent partial remediation, which caused no significant improvement in moisture or fungal contamination. In these children, there was no improvement in upper airway symptoms. This study suggested not only that a damp environment is associated with upper airway symptoms, but also that remediation efforts may be effective in reversing those symptoms. In addition, it endorses the notion that aeroirritant symptoms are transient if the source of the aeroirritants is removed. Other reports also suggest that mold remediation efforts may be successful in reducing mold spore levels³⁹ and mold-related respiratory symptoms.⁴⁰

Potential Offending Substances

The finding that exposure to a damp indoor environment and/or indoor mold is associated with adverse respiratory symptoms prompts an evaluation of the types of mold-associated compounds that potentially could be responsible for the effect. Any candidate compound must be able to interact with the respiratory tract to produce symptoms. As such, one requirement for potential offending substances is that they have the ability to become airborne in sufficient quantities to cause health effects *via* inhalation. Several types of mold-related compounds may become airborne. Most commonly considered in the practice of allergy/immunology are mold spores, which contain allergenic mold proteins and cause respiratory symptoms in patients with mold-related IgE hypersensitivity. However, most patients presenting with upper airway symptoms in relation to indoor mold exposure do not have IgE-mediated hypersensitivity to molds. This prompts a consideration of nonallergenic but potentially irritating substances produced by molds.

The β -D-glucans have been proposed as one possible agent causing aeroirritant symptoms, but, currently, there are limited epidemiological data available to evaluate their contribution to respiratory disease.⁴¹ Mycotoxins, mentioned previously, may associate with respirable fungal fragments,²³ which could theoretically produce aeroirritant symptoms. Additional epidemiological studies are needed to evaluate this possibility. Another group of compounds are VOCs, called MVOCs when produced by fungi or bacteria. VOCs have the quality of becoming easily airborne and are

known to produce irritant nose and eye symptoms, as discussed later. Because of these features, VOCs are an attractive candidate as an agent producing aeroirritant symptoms in the damp indoor environment where mold is present.

Aside from the contributions of mold-related compounds to aeroirritant symptoms, other factors in the damp indoor environment, such as bacterial mVOCs and decaying debris (*i.e.*, human skin scale, food products, insects, water-damaged building materials, carpeting, furniture, and other porous personal possessions) could theoretically contribute to the symptoms of subjects in these studies.

β -(1 $\rightarrow$ 3)-D-Glucans. These compounds are structural components of the cell walls of fungi. Glucans are polyglucose moieties that persist after death of the fungus. Concentrations of β -(1 $\rightarrow$ 3)-D-glucans are elevated in concordance with the amount of mold present in a given location.⁴¹ Studies have been performed with both animals and humans to assess the effect of β -(1 $\rightarrow$ 3)-D-glucan exposure on airway inflammatory markers. Young *et al.*⁴² instilled increasing doses of β -D-glucans into the tracheas of rats and found dose-dependent increases in neutrophil influx and nitric oxide production. Wan *et al.*⁴³ showed that β -D-glucans can potentiate ovalbumin-induced production of IgE antibodies in mice.

In humans, exposure of 26 subjects to aerosolized curdlan, a glucan, produced nasal and throat irritation but no changes in forced expiratory volume at 1 second or airway hyperreactivity.⁴⁴ However, nasal instillation of glucans in another experiment failed to produce symptoms or eosinophil influx.⁴⁵

Limited epidemiological studies have evaluated the correlation between exposure to glucans and upper airway symptoms.⁴¹ The results have been inconsistent, with some studies showing a positive correlation between glucan exposure and nose or eye symptoms⁴⁶ and others showing no association.⁴⁷⁻⁴⁹ In general, although the data are limited, the preponderance of epidemiological studies have been unable to show consistently that exposure to β -D-glucans correlates with irritant upper airway and/or eye symptoms.

A recent study has been suggested that endorses the lack of effect of mold particles, such as those that contain glucans, on irritant symptoms.²² Roponen *et al.*⁵⁰ studied 11 healthy male sawmill workers and the relation of their occupational exposures to production of proinflammatory cytokines. In these subjects with no history of irritant or other respiratory symptoms, they found no difference in the reports of symptoms while at work or on vacation and no difference in proinflammatory cytokine levels in nasal lavage, including nitrites, TNF- α , IL-4, IL-5, and IL-6. The small size of the study ($n = 11$) limited its power to find a

difference, and the confidence intervals of the results were several times larger than the measured values. Interestingly, the only statistically significant correlate was between the concentration of TNF- α in nasal lavage fluid and the concentration of total terpenes as well as individual terpenes in the work environment. Terpenes are VOCs (discussed later), and it is interesting that among measured exposures such as fungal spores, inhalable dust, endotoxin, and terpene VOCs, the only association with increased TNF- α production was the VOC concentration. Similar studies performed in a large number of symptomatic individuals while in damp home environments would be highly illustrative albeit difficult to accomplish.

VOCs and MVOCs. MVOCs are small molecules produced as a byproduct of metabolism by numerous microbial organisms. In composition and physicochemical properties, they resemble nonmicrobially derived VOCs, differing primarily in their production source. VOCs derive from such sources as paint, solvents, and petroleum products. The strong odor and often accompanying irritant sensation associated with being in a freshly painted room is likely caused by the effects of VOCs.⁵¹ A longitudinal study of professional painters suggested that exposure to VOCs in paints is associated with development of airway symptoms.⁵²

Molds produce a number of organic compounds, including alcohols, aldehydes, and sulfur-containing chemicals, many of which are volatile. MVOC production results in the musty and pungent odors associated with indoor mold growth.^{53,54} Examples of MVOCs include 3-methyl-1-butanol, 1-hexanol, 1-octen-3-ol, 2-heptanone, and 3-octanone. Although other organisms, such as bacteria, produce MVOCs, the discussion here will be limited to general characteristics of VOCs as well as studies of mold-associated MVOCs.

Aeroirritant Effects of VOCs: Characteristics and Threshold Dose. VOCs act as odorants and irritants. Olfactory stimulation results from interaction between VOC molecules and receptors in the olfactory groove. The irritant effect has afferent and efferent paths. Sensory nerve fibers in the nasal mucosa carry irritative signals *via* the pathways for common chemical sense, through the trigeminal, glossopharyngeal, and vagus nerves.⁵³ This stimulation results in the sensation of irritation as well as mucous hypersecretion. Some of the symptoms (nasal and throat irritation and cough) that have been associated with exposure to mold in a damp indoor environment resemble the irritant effects caused by VOCs in controlled laboratory circumstances.^{53,55}

The dose-response curve of the irritant effects of VOCs has been studied in animal and human models. Korpi *et al.*⁵⁶ exposed mice to increasing concentrations of individual and a mixture of VOCs, while measuring

the concentration required to reduce the respiratory rate. Respiratory depression is representative of the irritant effect as manifested in rodents and correlates with the threshold concentration for nasal irritation in humans.⁵⁷ The study found that all of the VOCs were able to elicit a respiratory response, and a mixture of five VOCs together elicited a response at a lower overall concentration than any of the compounds individually. In humans, a comparison of subjects with normal olfaction to anosmics found odor and irritant thresholds, respectively, for numerous VOCs.⁵³ Odor thresholds ranged from the 1 part per million (ppm) range (*i.e.*, 4-heptanol with an odor threshold of 8.2 ppm) to hundreds of ppm (*i.e.*, 2-propanol, 503 ppm). Pungency or irritant thresholds in anosmics averaged approximately one to two orders of magnitude higher values; *e.g.*, 4-heptanol had a pungency threshold of 335 ppm and 2-propanol had a pungency threshold of 18,135 ppm. Measurements were made instantaneously after exposure, and it was not possible to extrapolate what effect longer-term exposure at lower levels may have had. Another study found that nasal pungency and ocular irritation (which can be assessed using longer duration exposure) occurred at a relatively similar concentration of VOCs.⁵⁸ Specific individual VOCs and mixtures of VOCs had different thresholds for odor and irritation. In general, longer carbon chain lengths of VOCs corresponded with a lower nasal detection threshold.⁵⁸

The authors of the studies mentioned previously suggest that longer duration exposure to VOCs may produce symptoms at a lower concentration than the instantaneous experiments indicate. In a damp indoor environment, the duration of exposure is likely to be longer than in the laboratory setting, and longer duration experiments would be more representative. Although odor sensation produces tachyphylaxis over time, irritation does not. In a controlled exposure to the VOC 2-ethylhexanol, olfactory symptoms decreased, nasal irritation remained unchanged, and eye irritation increased in subjects over a 4-hour exposure.⁵⁹

Hempel-Jorgensen *et al.*⁶⁰ studied the effect of exposure to single and mixed VOCs on eye symptoms. Healthy volunteers were exposed to increasing concentrations of VOCs, starting at a concentration of either 312.5 or 423.0 ppm and increasing to a highest value of either 3125 or 2311 ppm. Sensory irritation intensity was recorded. For all VOC mixtures, a dose-response curve was seen for eye irritation. The concentration required to produce eye irritation varied depending on the VOC mixture, but for two of the three mixtures, a mean 50% irritation intensity level was seen at ~1000–1500 ppm concentrations. In a damp indoor environment, the specific composition of MVOC production and, importantly, the concentration, would affect the intensity of ocular exposure and irritant symptoms.

Long-term exposure has not been studied in a similarly controlled way.

In summary, VOCs produce olfactory stimulation at low concentrations, but at higher concentrations, eye and nose irritation develop. Dose-dependent irritant effects have been found in both animal and human studies. Most experiments have evaluated mostly short-term effects of relatively high concentrations of VOCs. The limited data available suggest that long-term exposure may produce irritation at a lower overall VOC concentration than that required for short-term effects.

Concentration of VOCs in the Ambient Environment. The studies described previously support the potential for VOCs to cause irritant symptoms of the nose and eyes. MVOCs, because they are chemically identical in many cases, should have similar effects. However, to be responsible for symptoms, VOCs and/or MVOCs must be present in a sufficient concentration in the damp indoor environment. Recently, the level of current knowledge about VOCs in the ambient environment has been highlighted,²² with some studies postulating that the levels of MVOCs in the damp indoor environment are too low to cause irritant symptoms.

One cited study, by Pasanen *et al.*,⁶¹ performed a theoretical computation to estimate the probability that ambient VOCs might cause irritant symptoms. Lacking information regarding actual irritation thresholds in humans for several of the VOCs that were modeled, theoretical irritation potency was determined based on a mathematical calculation derived from VOC exposure studies in mice. They estimated that ambient VOC concentrations in the range of hundreds of micrograms per cubic meter to a few milligrams per cubic meter would be required to cause irritant symptoms. They compared measurements of VOC concentrations in damp and mold problem buildings performed in previous studies to these mathematically derived recommended indoor air levels. The authors found that in most calculations, levels of VOCs in the problem buildings would be unlikely by prediction of this model to cause irritant symptoms. Theoretical calculations of predicted effects, without actually measuring irritation potency of VOCs, will provide low-grade evidence for or against VOCs as potential irritants. The relevance of a calculated VOC irritation potency to human health is unknown.

Mathematical modeling does not usually provide information adequate to guide patient care but may guide estimates useful in generating hypotheses and designing studies. Several epidemiological studies have begun to address the question of ambient VOC levels by measuring them in indoor environments. Miller *et al.*⁶² sampled 52 Canadian homes in which the occupants had reported "respiratory health problems

and/or allergic reactions to indoor air for which no satisfactory cause could be determined." Air samples were analyzed for VOCs, airborne particle content, and fungal colony-forming units. On average, homes contained 12–13 types of VOCs. VOC estimates ranged from 0.08 to 1.89 mg/m³, with a mean concentration of 0.68 mg/m³. Four houses had a VOC concentration of >2 mg/m³. In general, concentrations of VOCs did not correlate well with other measurements of levels of fungal burden. The study avoided sampling rooms that had obvious nonfungus-related VOC sources, such as perfume bottles, glue, or fresh paint, but, clearly, there are nonfungal sources of VOCs in any sampling of indoor air. The range of VOC concentrations was consistent with levels needed to cause irritant symptoms in laboratory experiments.

Saijo *et al.*³⁰ assessed symptoms in occupants of newly constructed homes in Japan. Aside from the association with dampness and mold growth discussed previously, in this study authors found that concentrations of each of seven VOCs individually measured, as well as total VOC levels in the home, significantly correlated with symptoms after adjusting for age, gender, smoking, pets, time in the dwelling, size of household, and allergy or asthma history. Total VOC levels were associated with an increased OR of 9.79 (CI, 1.67–57.5) for eye symptoms. The range of VOC mean concentration was 2.3–325.5 µg/m³ for each individual compound, and the overall mean total VOC level was 482 µg/m³ for houses when toluene was measured and 221.9 µg/m³ when it was not measured. These levels are considerably lower than some estimates (as mentioned previously) felt to be theoretically required to cause irritant symptoms. Also important to note is the enhanced concentration of VOCs released from building materials. It is interesting to hypothesize that dampness may synergize with new building materials to enhance VOC levels in the air.

An epidemiological study in West Virginia⁶³ studied the question of whether proximity to chemical manufacturing plants and the associated higher levels of VOCs in the air correlated with an increased frequency of respiratory symptoms. Children from 74 schools answered surveys regarding the presence of lower respiratory symptoms as well as acute irritant symptoms. Concentrations of 15 VOCs were measured at the schools. The study did not attempt to quantify MVOCs specifically. They found statistically significant correlations indicating that schools located closer to the manufacturing facilities had children with more physician-diagnosed asthma and wheeze-related symptoms. Acute eye symptoms, but not nose or throat symptoms, correlated with closer proximity to factories. Lower respiratory symptoms had a dose-dependent correlation with increased concentration of VOCs ($p < 0.05$). Acute eye symptoms had a similar trend

that was not statistically significant. For petroleum-related VOCs, a dose effect was seen for each increase of 10 µg/m³ and for process-related VOCs, the dose associated with a change was 2 µg/m³. In this study authors concluded that proximity to VOC-emitting factories was associated with increased respiratory symptoms in a dose-dependent manner.⁶³

There are difficulties in measuring VOCs in indoor air, and aside from their presence as free airborne molecules, association with larger particles such as dust could enhance their delivery to the respiratory tract. For example, a recent study⁶⁴ showed that MVOCs produced in a laboratory setting adsorb to dust particles. As dust particles are respirable, the authors suggest that a portion of MVOCs reaching the respiratory tract could be adsorbed into these larger particles and thereby penetrate the airways more efficiently. Additional studies are necessary to determine whether this may lead to underestimates of VOC burden in indoor air and whether this mechanism may contribute to human health effects.

The summary of these studies suggests that it is difficult to estimate *a priori* the level of an individual VOC that may be sufficient to cause irritant symptoms. The data so far available suggest that, in the presence of newly constructed homes with or without dampness, other damp homes, and locations in proximity to VOC-emitting factories, the total ambient air VOC concentration has been shown to correlate with eye, nose, and other respiratory symptoms. In addition, the possibility of VOCs adhering to larger respirable particles could increase the overall VOC burden in the typical damp indoor environment.

CONCLUSIONS

The presence of indoor mold is a common, if not ubiquitous, phenomenon. At least partially because of reports in the media, patients may have the perception that indoor fungus commonly produces dangerous adverse health effects. Although some patients may have anxiety-based symptoms related to mold exposure out of proportion to the actual risk to health, there remains a large population of patients who do suffer medical problems related to damp indoor home environments. Some of the complaints are those that allergists commonly see in practice, such as cough, wheeze, and upper airway symptoms such as nasal and eye irritations. The allergist's position as the main specialist performing testing (in our case, for IgE-mediated allergy) for possible sensitivity to mold puts us in the unique position of requiring knowledge of a broad spectrum of health effects potentially caused by indoor fungus.

The data reviewed here represent initial steps toward defining the pathophysiological mechanisms for

the aeroirritant effects of damp homes and associated excess mold growth. The delineation of a biological mechanism would allow allergists to approach patients with a rational explanation for their symptoms and at the same time provide reassurance of the transient nature of the effect. Ideally, identifying the true nature of the agents causing the symptoms may alleviate anxiety and help direct appropriate medical treatment and mold remediation efforts.

MVOCs are produced by indoor mold, and VOCs have been linked in controlled experiments with irritant symptoms of the eyes and nose. Additional studies are needed to determine levels of MVOCs in a variety of damp homes and to try to identify the proportion of VOC production that indoor molds contribute. In addition, larger epidemiological studies could address questions of aeroirritation with a directed effort at examining MVOC levels and symptoms. Most of the dose-response studies in humans have identified threshold levels for brief exposures. The typical occupant of a damp home with a heavy indoor mold burden has a much longer exposure and to many more elements in the indoor environment than subjects in experimental settings. The duration of exposure could affect the threshold dose needed to cause symptoms,⁵⁷ and this also should be evaluated in controlled studies, if possible.

In summary, epidemiological studies support the link between a damp indoor environment and mold growth with upper airway irritant symptoms. MVOCs are produced by indoor fungus, and, based on available data, are the most likely candidate compounds as the cause of this aeroirritant effect. Studies have shown that MVOCs produce nose and eye irritant symptoms with a consistent dose-response effect. In addition, the limited epidemiological studies performed to date suggest that VOCs are likely to be present in damp indoor homes at a level sufficient to produce irritant symptoms.

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