AN OVERVIEW OF THE HEALTH EFFECTS DUE TO MOLD EXPOSURE

M Shum*

Exponent, Inc., Menlo Park, CA

ABSTRACT
Several health studies have implicated mold as the cause of respiratory effects, asthma, central nervous system difficulties, and general malaise. Most of these studies have used self-reported data from questionnaires to obtain information on exposures and health outcomes Self-reported exposure is not well-correlated to airborne fungal concentrations, and self-reported symptoms or illnesses are limited in providing sufficient quality data for studying potential adverse health effects of mold. We reviewed those epidemiologic studies that attempted to use more objective measures for both exposure and health assessment. Among these studies, there appears to be a general consensus towards a positive association between mold exposure in indoor environments and respiratory effects. However, many of these studies are limited by small sample sizes, no demonstrations of dose-response relationships, exposure misclassification and other study limitations. Without better studies, a causal association cannot be confirmed at this time.

INDEX TERM
Mold, Fungi, Health effects, Epidemiology, Review

INTRODUCTION
There has been much public and scientific concern over the health effects of mold in indoor environments. Many epidemiologic studies have indicated an association between damp buildings and health effects such as respiratory effects and other non-specific symptoms such as fatigue and headaches. The literature of direct toxic effects of mold is less conclusive. Toxicological effects and case studies have indicated that ingestion or inhalation of large amounts of mold or spores of the quantity found in moldy hay or grain, can cause adverse health effects (Robbins et al., 2000). Ingestion of certain mycotoxins such as aflatoxin has been documented as a hepatocarcinogen. Molds have been implicated in causing three different types of health effects: 1) allergic effects, 2) infections, and 3) toxic effects. Fungi can act as an opportunistic infectious agent among immunologically suppressed populations, but these health outcomes will not be discussed in this paper. Only papers regarding the allergic and toxic effects of molds will be discussed.

METHODS
A DIALOG database (including Elsevier Biobase, Embase, Life Sciences Collection, NTIS, FEDRIP, Env. Bib., Enviroline, Pollution, Biol. & Agric. Index, Paxcal, ICONDA-Intl Construction, Tiosis Previews, Toxfile, TGG Health & Wellness, MEDLINE, CAB HEALTH, and ChemEng & Biotec Abs.)search for health studies about mold and health effects was conducted using the following key words: mold, fungi, fungus, health or adverse effect, human, study, Epidemiology. We analyzed recently published papers (1981 to 2001)

* Contact author e-mail: mshum@exponent.com

reporting human illness as a result of inhaled exposure to indoor molds. Of the 57 papers originally identified, 32 examined human health in relation to mold exposure in indoor environments. We abstracted information about study design, exposure assessment, population studies, outcome ascertained, and study findings in our review of the 32 papers.

RESULTS

Of the 32 studies identified in the search, the majority (26) found an association between mold in indoor environments and increased respiratory and other health effects. Many of the studies relied on self-reported information for exposure and health outcomes. Only studies that included some quantitative measures of both exposure assessment and health evaluation will be discussed in detail (Table 1). Perhaps the most well-known study involves 10 infant cases (1993-96) in Cleveland who were diagnosed with idiopathic pulmonary hemosiderosis (IPH) and 30 controls. A statistically significant association was observed between *Stachybotrys chartarum* and IPH (Dearborn et al., 1999), but recently, the CDC reported that the study was inherently flawed (CDC, 2000). After making corrections, the previously reported association became non-significant. Although there have been other case studies linking *S. chartarum* with IPH (Flappan et al. 1999; Vesper et al., 2000), there is insufficient evidence to conclude an association between *S. chartarum* and IPH.

In a US study of 53 office workers in a "problem" building and 21 controls in a "non-complaint" building, a higher proportion of office workers exposed to *S. chartarum* experienced health problems typical of sick building syndrome compared with controls. However, airborne viable fungal levels were comparable within the "problem" building and to outdoor air fungal levels (Johanning et al., 1996). Although the highest white blood cell (WBC) levels were observed in basement workers where water-damage had occurred, these levels were still within normal range (Robbins et al., 2000). There was an association between fungal exposure and abnormalities of the cellular and humoral immune system, but these differences were small and sometimes not significant (Johanning et al., 1996). In another study in Canada of 59 children classified as living in either "more contaminated homes" or "less contaminated homes" (defined by fungal dust and airborne ergosterol findings), lymphocyte stimulation was observed at a higher rate among those living in contaminated homes (Dales et al., 1998). A Finnish study compared inflammatory mediators of 32 staff from a school with higher airborne mold concentrations and visible mold to eight staff from a control building (Hirvonen et al., 1999). IL-6 and TNF-alpha, as well as pro-inflammatory mediators in nasal lavage fluid were higher in mold-exposed workers than in control subjects. These studies indicate that there may be an inflammatory response occurring in relation to mold exposure.

Hodgson et al. completed a study at a US courthouse and constitutional office building, which had been subject to water intrusion (Hodgson et al., 1998). Air and bulk sampling were only completed in the case building and not in control buildings. There were an increased number of symptoms consistent with interstitial lung disease (ILD) among case building occupants based on a questionnaire survey of 197 individuals, but the odds ratios were often not statistically significant. It is unclear whether toxins from *Aspergillus, Penicillium or Stachybotrys* found in the indoor environment of these case buildings contributed to symptoms. In a case-control study of 26 cases with at least two symptoms of ILD and 24 matched adult controls, there was no difference attributable to environmental exposure, immunological tests were uninformative, and neurophysical tests did not indicate a lower cognitive function among cases (Hodgson et al., 1998).

Table 1. Reviewed publications of mold exposures and health effects

Author	*Population*	*Age (yrs)*	*Country*	*Mold Assessment*	*Health Assessment*	*Health Effect (Author-claimed) (Y/N/Uncertain)*
Bjornsson et al., 1995	88	20-45	Sweden	Air, HDM, Respirable dust	Interview, spirometry, immune, allergy tests	U – Mold and asthma
CDC, 2000	40	<1	US	Air, Inspection	Physician diagnosis	U – *S. chartarum* and IDPH
Dales et al., 1998	59	11 Mean	Canada	Air, Dust	Lymphocyte testing	Y – Mold and lymphocyte stimulation
Dales et al., 1999	403	~10	Canada	Air, Dust, Questionnaire	Overnight cough recorder (n=145); Questionnaire	N
Dotterud et al., 1995	38	7-12	Norway	Air, Inspection, Questionnaire	Skin prick test to determine HDM-sensitive children	U – Dampness and HDM-sensitization
Garrett et al., 1998	148	7-14	Australia	Air, Inspection, Questionnaire	Questionnaire, skin-prick tests	Y – Specific genera and atopy, allergy, respiratory symptoms
Hirvonen et al., 1999	40	26 -58	Finland	Air, Bulk, Inspection	Questionnaire, nasal lavage for NO, TNF-alpha, IL-6	Y – Mold and pro-inflammatory mediators
Hodgson et al., 1998	50	? Adults	US	Air, Inspection, Records	Screening, spirometry, neuropsychological tests, enzyme IgG	Y – Mold and ILD
Huang et al., 1997	44	4-14	US	Air	Questionnaire, nasal smear for eosinophils	Y – Mold and PCLS
Johanning et al., 1996	53	Mean 35	US	Air, Bulk, Mycotoxin	Questionnaire, immune tests	Y – *S. chartarum* and cellular and humoral immune system.
Johanning et al., 1999	22 children 125 adults	<18 >18	US	Air	Questionnaire, immune tests, IgE	U –Molds and respiratory, eye, dermal, CNS symptoms
Li and Hsu, 1997	82	7-15	Taiwan	Air, Questionnaire	Clinical diagnosis	U – Self-reported dampness and allergic disease
Strachan et al., 1990	1000	7	England	Air (n=88), Questionnaire	Medical exam, Spirometry, Questionnaire	U- Reported mold and wheeze

U = an association between mold concentration and health effect was not proven (i.e., only reported mold or dampness associated with outcome)

Authors conclude that the outbreak of disease was likely due to fungal toxins, but this conclusion is largely based on questionnaire-based health assessments, which were likely biased as this building was undergoing remediation and occupants were involved in litigation (Robbins et al., 2000).

A cross-sectional study in Canada examined 403 children close to the age of 10 years old who were chosen randomly from school lists in Canada (Dales et al., 1999). A cough recorder was used overnight in a subsample of 145 homes in conjunction with a health questionnaire. Although, there was an increase in symptom prevalence when mold was reported to be present, objectively measured cough symptoms were not related to airborne ergosterol or self-reported mold/dampness.

In a US study of 22 children under the age of 18 years and 125 adults older than 18 years, there was a greater percentage of respiratory, dermal, eye, central nervous system, and fatigue symptoms among case groups exposed to mold compared to controls (Johanning et al., 1999). However, authors could not analyze for statistical significance due to the limited sample size and different time and location of measurements. The authors admit that the variations in the groups may be partially due to selection bias, biologic differences or survey limitations. Most of the health effect findings were identified in a health questionnaire and were not substantiated in the clinical tests.

A cross-sectional study of 1000 – 7 year old children in the UK showed that questionnaire reports of mold in the home were not correlated with air sampling results (Strachan et al,. 1990). Differences between airborne fungal counts and species were small and inconsistent. For most species, the differences were non-significant between homes of wheezy children and control homes with the exception of mycelia sterilia. The total burden of inhaled mold spores was not an important indicator of wheeze among children in the general population.

A US study of 44 children (4-14 years old) diagnosed with perennial allergic rhinitis and diagnosed as sensitive to at least three mold allergens and not other common household allergens, were investigated to elucidate the relationship between mold exposure and persistent cold-like symptoms (PCLS) over two years(Huang and Kimbrough, 1997) Nasal smears were collected. Twenty-five had PCLS for at least the last two years and 19 did not. The PCLS group had significantly higher mold counts in winter and a higher percentage of eosinophils in nasal smears than controls. The symptom scores for all children correlated positively with mold count in homes, but no threshold of airborne mold for development of symptoms was found. This study based its conclusions on a questionnaire used to identify PCLS.

A case-control study completed in China examined the relationship between allergic disease and mold exposure in 46 asthmatic children (7-15 years old) and 20 atopic and 26 nonatopic children (7-12 years old) (Li and Hsu, 1997). There was an association between self-reports of damp housing conditions and allergic disease. No differences in airborne fungal concentration were indicated between damp and dry homes. No consistent relationships were observed between fungal allergens and atopic diseases among children. Only self-reported exposures (not quantitative exposures) were related to atopic diseases.

In an Australian cross-sectional study of 148 children between the ages of 7 and 14 years old, no association was observed between resident-reported damp housing and spore concentrations (Garrett et al., 1998). Mean total spore concentrations were not significantly

associated with respiratory symptoms. Specific genera were better able to predict health outcome than total spore concentrations, reported dampness or observed dampness. *Penicillium* was marginally associated with asthma and allergy, *Aspergillus* with atopy, and *Cladosporium* with allergy and possibly respiratory symptoms. A small sample size may have limited this study.

In a Norwegian study, generally low concentrations of airborne fungi were found, except in the homes of some HDM-sensitized children. Authors did make any conclusions about an association between airborne fungi and HDM-sensitization (Dotterud et al., 1995). In a Swedish study, authors did not find mold exposure to be an independent risk factor for asthma symptoms (Bjornsson et al., 1995).

DISCUSSION AND CONCLUSIONS

Many studies have indicated an increased prevalence of respiratory and other general symptoms for residents who have reported damp or moldy homes. Most health studies on exposure to molds in indoor air and health effects rely on questionnaires to elucidate mold exposure and health effects rather than rely on exposure monitoring and clinical diagnoses/biomarkers. Studies indicate that questionnaire data for mold exposure is not well correlated to actual mold exposure (Platt et al. 1989; Strachan et al. 1990; Garrett et al. 1998; Ren et al., 2001). Even observation of dampness and visible mold by trained inspectors is not always correlated with airborne mold counts (Verhoeff et al., 1992).

Given the limitation of self-reports and recall bias when relying solely on questionnaire data, we focused our review on studies that attempted to use more objective measures of exposure and health. Most of these studies were cross-sectional or case-control and, information about exposure and health outcome was collected without a clear distinction between the temporal nature of mold exposure and health effects. Many of the conclusions reached by authors in the reviewed studies were based on health outcomes obtained through questionnaires and therefore are subject to the same limitations mentioned previously. Many of these studies were limited by selection and recall bias, small sample size, and possible exposure misclassification. None discussed dose-response relationships in a quantitative manner.

Although studies with objective assessments of exposure and health seem more desirable than questionnaire-based studies, there are inherent problems with air sampling for mold and with identifying an appropriate biomarker for mold-related outcomes. Most methods involve area sampling for a short time-period and may not capture actual exposure to dynamic individuals. In one study, airborne mold concentrations were not well-correlated with damp from a checklist and were not consistent throughout time (Verhoeff et al., 1992). This finding indicates that the use of fungal air sampling in epidemiologic studies may still be limited. Not only does a better sampling method for sampling mold in air need to be developed, appropriate biomarkers need to be validated in order to conduct more informative and well-designed epidemiologic studies. There is no standard method of testing airborne exposure and fungal dose at this time. Until then, it may not be possible to conclude a causal relationship between mold exposure and health effects.

REFERENCES

Bjornsson, E, et al. 1995. "Asthmatic symptoms and indoor levels of micro-organisms and house dust mites." *Clin Exp Allergy* 25(5): 423-31.

Dales, R, et al. 1998. "Influence of residential fungal contamination on peripheral blood lymphocyte populations in children." *Arch Environ Health* 53(3): 190-5.

Dales, RE, Miller, D and White, J. 1999. "Testing the association between residential fungus and health using ergosterol measures and cough recordings." *Mycopathologia* 147(1): 21-7.

Dotterud, LK, Vorland, LH and Falk, ES. 1995. "Viable fungi in indoor air in homes and schools in the Sor-Varanger community during winter." *Pediatr Allergy Immunol* 6(4): 181-6.

Flappan, SM, et al. 1999. "Infant pulmonary hemorrhage in a suburban home with water damage and mold (Stachybotrys atra)." *Environ Health Perspect* 107(11): 927-30.

Garrett, MH, et al. 1998. "Indoor airborne fungal spores, house dampness and associations with environmental factors and respiratory health in children." *Clin Exp Allergy* 28(4): 459-67.

Hirvonen, MR, et al. 1999. "Nitric oxide and proinflammatory cytokines in nasal lavage fluid associated with symptoms and exposure to moldy building microbes." *Am J Respir Crit Care Med* 160(6): 1943-6.

Hodgson, MJ, et al. 1998. "Building-associated pulmonary disease from exposure to Stachybotrys chartarum and Aspergillus versicolor." *J Occup Environ Med* 40(3): 241-9.

Huang, SW and Kimbrough, JW. 197). "Mold allergy is a risk factor for persistent cold-like symptoms in children." *Clin Pediatr (Phila)* 36(12): 695-9.

Johanning, E, et al. 1996. "Health and immunology study following exposure to toxigenic fungi (Stachybotrys chartarum) in a water-damaged office environment." *Int Arch Occup Environ Health* 68(4): 207-18.

Johanning, E, et al. 1999. "Clinical experience and results of a Sentinel Health Investigation related to indoor fungal exposure." *Environ Health Perspect* 107 Suppl 3: 489-94.

Li, CS and Hsu, LY. 1997. "Airborne fungus allergen in association with residential characteristics in atopic and control children in a subtropical region." *Arch Environ Health* 52(1): 72-9.

Platt, SD, et al. 1989. "Damp housing, mould growth, and symptomatic health state." *Bmj* 298(6689): 1673-8.

Ren, P, et al. 2001. "The relation between fungal propagules in indoor air and home characteristics." *Allergy* 56(5): 419-24.

Robbins, CA, et al. 2000. "Health effects of mycotoxins in indoor air: a critical review." *Appl Occup Environ Hyg* 15(10): 773-84.

Strachan, DP, et al. 1990. "Quantification of airborne moulds in the homes of children with and without wheeze." *Thorax* 45(5): 382-7.

Verhoeff, AP, et al. 1992. "Presence of viable mould propagules in indoor air in relation to house damp and outdoor air." *Allergy* 47(2 Pt 1): 83-91.

Vesper, S, et al. 2000. "Evaluation of Stachybotrys chartarum in the house of an infant with pulmonary hemorrhage: quantitative assessment before, during, and after remediation." *J Urban Health* 77(1): 68-85.