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ADVERSE HEALTH EFFECTS OF INDOOR MOLDS.

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INTRODUCTION

In recent years, public attention has become increasingly focused on human health concerns linked with mold (fungi) inside homes and workplaces. Indoor airborne mold exposure has been associated with adverse human health effects in multiple organs and body systems, including: 1) respiratory, 2) nervous, 3) immune, 4) hematological and 5) dermatological systems. Indoor mold exposure can also lead to life-threatening systemic infections in immunocompromised patients.

A qualitative systematic literature review was undertaken in order to examine and appraise the current state of knowledge about indoor mold-linked health effects, and to summarize the available evidence for the use by health professionals. Physicians in particular may encounter patients with common symptoms occurring in particular environments, and understanding of the potential for mold-related health effects is key to the complete investigation of those environments. Physicians and industrial hygienists may be asked to contribute reports to assist the courts in settling suits. In 2002, an estimated 10,000 mold-related cases were pending in US courts (1). Also in 2002, the insurance industry paid out \$2 billion in mold-related claims in Texas alone (2).

Literature was reviewed using the peer-reviewed database, and from recent conferences on indoor molds. The levels of evidence available for each topic varied from Level I (from at least one properly randomized controlled trial) through Level II (from trials without randomization, exceptionally convincing uncontrolled experiments, cohort or case control studies), to Level III (opinion of respected authorities based on clinical experience, descriptive studies, or reports of expert committees) (3).

MOLDS IN THE INDOOR ENVIRONMENT

Fungi (or molds) are ubiquitous in both indoor and outdoor environments and are frequently dispersed by airborne spores. Mold and mold spores require moisture and a food source like cellulose or decaying food to grow (4). As mold spores swell with water and grow, they elongate, forming balloon like protuberances (hyphae) which secrete digestive enzymes and mycotoxins. The fungi then digest the food source to support their growth.

About 100,000 fungal species have already been identified; in fact fungi are estimated to comprise an astounding 25% of the world's biomass (5). Various surveys of homes in North America and Europe have reported that visible mold and/or water damage are common, found in 23 to 98% of all homes examined (6-9). There are no official standards at this time for indoor airborne fungi concentrations. However, indoor fungal levels above a range of 150 to 1,000 colony forming units per cubic meter of air (cfu/m³) are considered to be sufficient to cause human health problems (7,10-2). Numerous reports have documented that indoor air can be contaminated with fungal spore levels well in excess of 1,000 cfu/m³ (13-20). The most common indoor fungal genera collected are Cladosporium, Aspergillus and Penicillium (13-20). Alternaria, Stachybotrys, Rhizopus, Mucor, Wallemia, Trichoderma, Chaetium, yeasts, Botrytis, Epicoccum and Fusarium species are often found indoors as well (13-20).

MOLD RELATED HEALTH SYMPTOMS

Patients have been reporting multiple ill health effects linked to exposures to mold. Studies of more than 1600 patients suffering ill effects associated with fungal exposure were presented at one meeting in Dallas in 2003 (21st Annual Symposium of Man and His Environment, Dallas, TX June 19-22, 2003) (21-25).

To cite a few studies: Lieberman (21) examined 48 heavily mold-exposed patients who had the following health problems: 1) muscle and/or joint pain 71%, 2) fatigue/weakness 70%, 3) neurocognitive dysfunction 67%, 4) sinusitis 65%, 5) headache 65%, 6) gastrointestinal problems 58%, 7) shortness of breath 54%, 8) anxiety/ depression/ irritability 54%, 9) vision problems 42%, 10) chest tightness 42%, 11) insomnia 40%, 12) dizziness 38%, 13) numbness/ tingling 35%, 14) laryngitis 35%, 15) nausea 33%, 16) skin rashes 27%, 17) tremors 25% and 18) heart palpitations 21%. Rea's (23) study of 150 heavily indoor mold-exposed patients found the following health problems: 1) fatigue 100%, 2) rhinitis 65%, 3) memory loss and other neuropsychiatric problems 46% 4) respiratory problems 40%, 5) fibromyalgia 29%, 6) irritable bowel syndrome 25%, 7) vasculitis 4.7% and 8) angioedema 4.0%. These clinical reports suggest there can be multi-system adverse effects of airborne mold. All reported cases had environmental mold exposure consistent with toxic mold exposure.

MECHANISMS OF MOLD-RELATED HEALTH EFFECTS

Fungi can exert ill health effects by 3 major mechanisms: 1) allergy, 2) toxicity, and 3) infection.

1) Allergy and Irritation. At least 70 allergens have been well characterized from spores, vegetative parts and small particles from fungi (0.3 microns and smaller) (26-7). A review of 17 studies revealed that 6 to 10% of the general population and 15 to 50% of atopics had immediate skin sensitivity to fungi (28). Fungi produce beta glucans which have irritant properties (29)

2) Toxicity. Fungi produce a wide variety of toxic chemicals called mycotoxins (4,30-1). Some common mycotoxins include: 1) Aflatoxins - very potent carcinogens and hepatotoxins produced by some *Aspergillus* species, 2) Ochratoxins - nephrotoxic and carcinogenic- produced by some *Aspergillus* and *Penicillium*, 3) Sterigmatocystin- immunosuppressive and a liver carcinogen produced by *Aspergillus* species, especially *A. versicolor* and 4) Trichothecenes produced primarily by *Stachybotrys* and *Fusarium* species, that have been reported to inhibit protein synthesis, cause hemorrhage and vomiting. Fungi also produce beta glucans which have immunological effects (32). The smell of molds comes primarily from volatile organic compounds (33).

Adverse human and animal effects from mycotoxin contaminated foodstuffs have been well recognized since the early 20th century (30,34). But the pathway of mycotoxin injury through inhalation is questioned (35). Since it is unethical to conduct controlled studies on humans with inhaled mycotoxin exposure, only controlled animal exposures and human cohort and case control studies can be used. The literature reveals that significant amounts of mycotoxins (including ochratoxin, sterigmatocystin and trichothecenes) are present in indoor dust (36-39) and dust or fungal particles less than 10 microns in diameter are respirable, thus allowing absorption of mycotoxins through the lungs. (31, 34, 40-1).

Patients exposed to indoor *Stachybotrys* have been found to have measurable blood levels of the *Stachybotrys* hemorrhagic toxin stachylysin (42). Levels of trichothecene mycotoxins in the urine have also been found in significantly higher levels in patients exposed to high indoor fungal levels as opposed to an unexposed control group (43).

Blood ochratoxin levels have been found to be significantly higher in food industry workers exposed to airborne ochratoxin versus unexposed controls (39). These findings support an inhalation pathway for entry of mycotoxins into the body.

3.) Infection. Fungi such as *Candida*, *Histoplasmosis*, *Cryptococcus*, *Blastomyces* and *Coccidioides* can infect immunocompetent people (44). Fungi such as *Trichophyton*, *Candida* and *Malassezia* commonly cause minor skin infections in immunocompetent humans (45).

Serious infections by such fungi as *Candida*, *Aspergillus* and *Pneumocystis* mostly involve severely immunocompromised patients (45-7). In recent years, the incidence of life threatening infections in immunocompromised patients from *Aspergillus* and other common fungi has been growing rapidly (48-9). Invasive aspergillosis is very common among immunocompromised patients with reported incidence rates in the following patients: lung transplants: 17-26%, allogenic bone marrow transplants: 5-15%, acute leukemia: 5-24%, and heart transplant: 2-13% (50-1). Even with strong anti-fungal drugs and intense hospital treatment, mortality rates from invasive aspergillosis range from 50 to 99% in the immunocompromised (52-3).

SAMPLING FOR MOLD EXPOSURE

Indoor fungal sampling is most commonly performed by measuring airborne levels of viable (culturable) or total (viable and non viable) spores (54-5). Some of the airborne viable sampling methods such as Andersen samplers collect air for only a few minutes. Settle plates are an inexpensive method to get a semi-quantitative measure of indoor airborne fungi levels. Viable and non viable airborne spore counts can vary considerably over a period of minutes, so air sampling over several periods of time may be necessary to accurately characterize airborne fungal spore levels (54-5). However, airborne fungi measurements fail to take into consideration mold contamination in dust or surfaces (often visible to the naked eye) and mycotoxins in air, dust and on surfaces (54,56). Therefore testing the settled dust for fungi and mycotoxins has been recommended (54-5). Other techniques such as PCR (Polymerase Chain reaction), ELISA (Enzyme Linked Immunosorbent Assay), and measurement of fungal volatile organic compounds, polysaccharides, ergosterol and beta glucans have also been found useful in assaying indoor environments for molds, their allergens and mycotoxins (54).

INDOOR MOLD EXPOSURE AND HEALTH EFFECTS IN BODY SYSTEMS

1. **Respiratory System.** Many epidemiological studies have noted that residential exposure to molds and/or chronic dampness can increase asthma/wheezing incidence or morbidity in both children and adults (7-9, 57-70). Asthma and related conditions are very common in the US, with an overall prevalence of about 5.4% among all age groups and incidences as high as 27% in inner city children (71). Studies with infants have reported that higher fungal exposures are associated with more wheezing, coughing and respiratory illness (72-3). Higher indoor beta glucan levels have been associated with significantly higher levels of chest tightness and joint pain (74). Non-industrial occupational mold exposure has been reported to be associated with significantly higher levels of asthma, sinusitis, irritated skin and eyes and chronic fatigue (75-9). One study found that patients exposed to high indoor fungal levels had significantly lower lung function than unexposed controls (24). Higher outdoor fungal concentrations have been linked to higher asthma death rates (80) and higher asthma incidence (81-3) in children or young adults. Challenge exposures with *Penicillium* and *Alternaria* extracts equivalent to high outdoor levels of fungi were noted to severely lower lung function in asthmatics (84). Skin sensitivity to *Alternaria* has been linked to much higher risk (Odds Ratio 190, 95% CI of 6.5 to 6,536, $p < 0.0001$) of respiratory arrest (85). Various epidemiological studies have associated skin sensitivity to common indoor fungi and higher asthma incidence or severity (86-90) and higher rates of sinusitis (91).

Airborne fungal exposure is known to cause bronchopulmonary aspergillosis and hypersensitivity pneumonitis, and can cause sinusitis (92-3). An estimated 14% of the US population suffers from rhinosinusitis and related conditions (94). Allergic fungal sinusitis was diagnosed on the basis of fungal growth in nasal secretions and presence of allergic mucin in 93% of 101 consecutive patients undergoing sinus surgery (94). Another study was able to recover and culture fungi from the sinuses of 56% of 45 patients undergoing endoscopic sinus surgery for chronic rhinosinusitis (95). A long term cohort study of 639 patients with allergic fungal sinusitis demonstrated that remedial steps taken to reduce fungal exposure (by utilizing, for example, air filters, ionizers, moisture control and anti- microbial nasal sprays) significantly reduced rhinosinusitis and improved nasal mucosa morphology (22). This study concluded that failure to reduce airborne fungi levels to less than 4 per hour on a settle plate failed to resolve the sinusitis (22). Although, historically, anti-fungal drugs have generally not been recommended for treatment of fungal sinusitis (92-3), recent observational studies have found beneficial effects of oral and nasal medication for sinusitis patients (22,96). Several studies have linked residential exposure to various fungi with hypersensitivity pneumonitis (97-9).

2. **Hematological Effects.** Exposure to high indoor levels of *Stachybotrys*, *Aspergillus* and other fungi has been epidemiologically associated with infant lung hemorrhage (100-4). Although questions were raised after this association was discovered (105), it meets many epidemiologic criteria for causality (106). Acute infant pulmonary hemorrhage can be rapidly fatal; when the infant survives, lung blood vessel damage is present and deposits of hemosiderin will remain in the lung macrophages and can be seen in tissue obtained during bronchoscopy (101). *Stachybotrys* fungi produce a wide range of trichothecene mycotoxins (including satratoxins and T2), several roridin epimers, verrucarins J and B and hemolysin (31,103). A hemorrhagic protein called stachylysin has been isolated from *Stachybotrys* collected from homes of infants with lung hemorrhage (107-8) and from serum of patients with residential *Stachybotrys* exposure (42). It is hypothesized that infants with their rapidly growing lungs are more susceptible to the toxic effects of *Stachybotrys* mycotoxins (109). Studies with *Stachybotrys*-exposed adults have noted a significantly higher incidence of health conditions such as wheezing, skin and eye irritation, flu-like symptoms and chronic fatigue (110). *Stachybotrys* has been isolated from the lungs of a child with pulmonary hemosiderosis (111).

A case study was presented of 16 month-old twins in a mold infested home, one of whom died of pulmonary hemosiderosis (112). High levels of trichothecene mycotoxins were found in the lungs and liver of the dead infant, while high IgG levels to *Stachybotrys* and IgM levels to satratoxin and trichothecenes were found in the serum of the surviving infant. Environmental sampling in the twins home found high levels of satratoxin as well as high levels of spores from *Stachybotrys*, *Aspergillus versicolor* and *Penicillium* (112).

3. **Immune System.** Some studies have reported that indoor fungi-exposed patients have higher serum levels of IgG, IgA and IgM antibodies to common fungi, trichothecenes and satratoxins (113-5). IgG antibodies to 9 common indoor fungi were significantly higher in subjects with sinusitis versus non sinusitis subjects in a moldy school (116). Other studies note no significant increases in fungal IgG (117-8) or fungal IgE (113) in fungi-exposed patients. Indoor fungal exposure has been associated with altered levels of T4, T8 and NK cells and higher levels of autoantibodies (23,25,119-20). Occupants of homes with high indoor glucan exposure had a lower proportion of cytotoxic t-cells (CD8+SF61+) and higher secretion of tumor

necrosis factor than occupants of homes with lower levels of beta glucans (121). Studies of animals given such common mycotoxins as aflatoxins, ochratoxins and trichothecenes orally show considerable immune impairment including depression of T cells, B cells and macrophages (122). Human cell line studies have also found that many mycotoxins can suppress T-cell, B-cell and NK activity at serum concentrations similar to those found in indoor mold-exposed patients (123).

4. Central Nervous System. Two case series of 48 and 150 mold-exposed patients found significant fatigue and weakness in 70 to 100% of cases, and neurocognitive dysfunction including memory loss, irritability, anxiety and depression in over 40% of the patients (21,23). Numbness, tingling and tremor were also found in a significant number of patients (21,23). These signs and symptoms have been described as classic manifestations of neurotoxicity (124).

A study of 43 mold-exposed patients found they performed significantly worse than 202 controls on many neuropsychiatric tests including balance sway speed, blinking reflex, color perception, reaction times and left grip strength ($p < 0.0001$) (125). Quantitative electroencephalogram (qEEG) studies in 182 patients with documented mold exposure also noted significant alterations in brain waves including hypoactivation of the frontal cortex and narrowed frequency bands (126). Higher levels of mold exposure (as measured such factors as by longer time in mold infested area, presence of *Stachybotrys* or higher colony forming units per cubic meter of air) were associated with significantly more abnormal qEEGs as well as significantly worse scores of concentration and motor and verbal skills in these 182 patients (126). A triple headed SPECT brain scan revealed neurotoxic patterns in 26 of 30 (87%) mold-exposed patients (127). An irisorder study of autonomic nervous function in 60 mold-exposed patients found 95% had abnormal autonomic responses of the pupil compared to the population reference range (23). Visual contrast sensitivity studies were often abnormal in indoor mold-exposed patients (23). Additional studies have reported that mold-exposed patients do significantly worse on tests of attention, balance, reaction time, verbal recall, concentration, memory, finger tapping compared to the general population reference range (24, 128-9). Most of these patients also experienced many health problems including chronic fatigue, headaches, insomnia and decreased balance, concentration and attention. Studies of indoor mold-exposed children and adults found significantly more neurophysiological abnormalities versus controls, including abnormal EEGs and abnormal brainstem, visual and somatosensory evoked potentials (25, 130-1).

Lieberman (21) presented a case series of 12 patients who developed tremors following documented heavy indoor mold exposure. Numerous articles have reported domestic dogs developing tremors following ingestion of moldy food (132-4). Territrem b, a mycotoxin produced by the common fungus *Aspergillus terreus*, has been shown to be an irreversible binder and inhibitor of acetylcholinesterase (135).

5. Renal System It is known that ochratoxin-contaminated food is nephrotoxic (136-7). Indoor airborne exposure to ochratoxin may also be nephrotoxic. In a case report of a family presenting with increasing thirst/urination, lethargy, and skin rash, a considerable amount of ochratoxin was found in their house dust. The family recovered after moving to another home (36).

6. Reproductive System The literature suggests a relationship between heavy airborne fungal exposure and reproductive dysfunction. Kristensen et al. (138-139) reported that airborne mycotoxin exposures in Norwegian grain farmers was significantly related to higher rates of pre term deliveries, late term miscarriages and higher rates of endometrial and ovarian endocarcinoma. The veterinary literature finds a strong association between mycotoxins in feedstuffs and reproductive problems (140).

7. Diabetes There is a good deal of evidence which links environmental factors to the triggering of type 1 diabetes. Exposure to viruses, bacteria and mycotoxins such as alloxan, streptozotocin and L-asparaginase have all been linked to the development of type 1 diabetes in animals and humans (141-3). Lieberman (21) reported that in single year, 5 of his patients developed type 1 diabetes following documented heavy indoor mold exposure (21).

DIAGNOSIS AND MANAGEMENT OF POTENTIALLY MOLD-RELATED HEALTH PROBLEMS

A careful medical and environmental history is an essential first step in evaluating a patient for mold related health problems (144-7). Particular attention should be paid to any history of exposure to visible mold and/or water damage at the home or workplace. Environmental sampling for viable spores, total spores, and mycotoxins in the air and dust can provide important exposure information. For a helpful overview of sampling methods, please see Pasanen (54), Macher (148) and Portnoy (149). For an informative guide to the classification, identification and biology of common indoor fungi, please see

Samson (4). Several good guides exist for prevention and remediation of indoor fungi problems (144, 148-51).

For patients suspected of having substantial fungal exposure, a battery of sophisticated laboratory tests have been developed : 1) a basic metabolic panel to test for several important parameters (including electrolytes, blood sugar, liver and kidney status); 2) measurement of antibodies to molds and mycotoxins in serum (113-4); 3) immune tests for autoantibodies, complement, gamma globulins and lymphocyte panels (120),4) urine and blood testing for mycotoxins (43), 5) Visual contrast sensitivity tests, and 6) pupillometry and heart rate variation to assist in evaluation of autonomic nervous system function. The use of: 7) standard neuropsychological tests batteries (23, 128-30), 8) EEG and brain imaging techniques like 9) SPECT and 10) MRI can be very helpful tools in documenting neurological damage (25,125, 127 131, 145). (11) Pulmonary function tests are also useful for patients with respiratory symptoms (24, 124). Failure to perform objective evaluations for accessing system or organ dysfunction account for the presently accepted position that airborne mold exposures have no significant adverse effects (35). If end stage organ damage is suspected, consultation with a specialist may be useful.

Other common indoor environmental exposures should also be considered as a potential source of health problems. Common non-fungal indoor environmental factors include poor ventilation, carbon monoxide from faulty heat sources, leaking natural gas, pesticides, wood smoke, second hand tobacco smoke, petrochemicals such as cleaners/building materials/solvents, formaldehyde from outgassing carpets and building materials, bacteria, and allergens from the fur, feathers, saliva and excrement of common household animals like cockroaches, dust mites, cats, dogs, mice, rats, caged birds, and pigeons. Exposure to ozone, second hand tobacco smoke, cockroach allergens, formaldehyde, and viral infections have been noted to have a synergistic effect with fungal exposure to worsen asthma and rhinitis (152-6).

The most important part of treatment for mold-exposed patients, symptomatic or not, is avoidance of fungal exposure and remediation of mold contamination in the home and workplace. Any water leaks, and damage from flooded or damp areas should be rectified immediately. Non porous surfaces like floors and walls which have visible mold growth should be cleaned. Porous waterlogged materials like carpet and furniture should be discarded. Control of humidity is important to control mold growth. The use of air conditioners and dehumidifiers can significantly reduce summertime indoor airborne mold concentrations (13,157). HEPA air filters can also significantly reduce indoor airborne fungi concentrations (158). For cleanup of severe indoor water or mold problems, use of protective equipment like face masks and/or use of a professional remediation firm may be essential (148-51).

Remediation of water and mold contaminated buildings can significantly improve the health of building occupants. A year-long study was conducted of children with moderate asthma who lived in homes with visible mold. Twenty six of the children had their homes remediated for mold and moisture problems, while 25 other children did not have their homes remediated. Such remediation included such factors as removing visible mold, fixing water leaks, disinfection with bleach in water and using dehumidifiers. Significantly fewer asthma symptoms ($p=0.006$) and asthma emergency room visits ($p=0.003$) were seen in children in the mold remediated homes as compared to the children with non-remediated homes. In addition, the children in the mold remediated homes had significantly drops in cough ($p=0.0003$), wheezing ($p=0.0001$), fatigue ($p=0.0002$), diarrhea ($p=0.0001$) and vomiting ($p=0.0001$) at the end study period compared to baseline levels (159).

Environmental control plays a key role in preventing Aspergillus infections. Several studies have linked hospital construction work to increased rates of invasive aspergillosis (160-63). Environmental controls such as using HEPA filters, sealing rooms, regular cleaning of rooms, and using anti-fungal copper-8-quinolate paint have been shown to both significantly reduce airborne levels of Aspergillus and significantly reduce rates of invasive aspergillosis in immunocompromised hospital patients (158, 161-6). Other recent research has indicated that a large number of Aspergillus spores can spread through water supplies (167) and that cleaning shower facilities can significantly lower airborne levels of Aspergillus (168).

Use of sublingual or fungal immunotherapy by injection has been shown to be beneficial to some patients sensitized to common indoor molds such as *Alternaria* and *Cladosporium herbarium* (169-170). Some studies with laboratory animals suggest that a high quality diet with adequate anti-oxidant vitamins, selenium, phytochemicals, methionine and total protein can reduce the harmful effects of food mycotoxins (171-2).

SUMMARY

There is an accumulated weight of evidence linking indoor airborne mold and/or mycotoxin exposures to multisystem adverse human health effects. History of new neurocognitive symptoms occurring in patients soon after heavy mold exposure, accompanied by objective neuropsychological findings in such patients, adds considerably to the weight of evidence from animal studies, epidemiological research, and case series.

Health care professionals, building managers, homeowners and the general public need to be much more aware of the potential adverse health effects of high indoor fungal exposures and the need for proper building construction, maintenance, and remediation of dampness to prevent such effects. Potentially mold-related illnesses need to be considered in differential diagnoses, and careful exposure histories taken. Prompt removal from exposure to fungal contamination remains the treatment of choice, with some evidence that immunotherapy and nutritional support are also useful. Indoor airborne mold particles can be irritative to the respiratory tract, and fungal spores, antigens, volatile organic compounds, and mycotoxins can be absorbed through the respiratory route to provoke injury by the mechanisms of allergy, toxicity, and infection.

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