

The biocontaminants and complexity of damp indoor spaces: more than what meets the eyes

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Abstract

Nine types of biocontaminants in damp indoor environments from microbial growth are discussed: (1) indicator molds; (2) Gram negative and positive bacteria; (3) microbial particulates; (4) mycotoxins; (5) volatile organic compounds, both microbial (MVOCs) and non-microbial (VOCs); (6) proteins; (7) galactomannans; (8) 1-3- β -D-glucans (glucans) and (9) lipopolysaccharides (LPS – endotoxins). When mold species exceed those outdoors contamination is deduced. Gram negative bacterial endotoxins, LPS in indoor environments, synergize with mycotoxins. The gram positive *Bacillus* species, *Actinomycetes* (*Streptomyces*, *Nocardia* and *Mycobacterium*), produce exotoxins. The *Actinomycetes* are associated with hypersensitivity pneumonitis, lung and invasive infections. Mycobacterial mycobacterium infections not from *M. tuberculosis* are increasing in immunocompetent individuals. In animal models, LPS enhance the toxicity of roridin A, satratoxins G and aflatoxin B1 to damage the olfactory epithelium, tract and bulbs (roridin A, satratoxin G) and liver (aflatoxin B1). Aflatoxin B1 and probably trichothecenes are transported along the olfactory tract to the temporal lobe. Co-cultured *Streptomyces californicus* and *Stachybotrys chartarum* produce a cytotoxin similar to doxorubicin and actinomycin D (chemotherapeutic agents). Trichothecenes, aflatoxins, gliotoxin and other mycotoxins are found in dust, bulk samples, air and ventilation systems of infested buildings. Macrocyclic trichothecenes are present in airborne particles <2 μ m. Trichothecenes and stachylysin are present in the sera of individuals exposed to *S. chartarum* in contaminated indoor environments. Haemolysins are produced by *S. chartarum*, *Memnoniella echinata* and several species of *Aspergillus* and *Penicillium*. Galactomannans, glucans and LPS are upper and lower respiratory tract irritants. Gliotoxin, an immunosuppressive mycotoxin, was identified in the lung secretions and sera of cancer patients with aspergillosis produced by *A. fumigatus*, *A. terreus*, *A. niger* and *A. flavus*.

Keywords

Bacteria, construction defects, mold, mycotoxins, particles

Introduction

Damp or wet building materials occur from a variety of circumstances: water intrusion from floods, hurricanes, construction defects, roof leaks, condensation, appliance and plumbing leaks, poorly designed foundations, etc. Furthermore, building materials can become wet during storage, transportation and/or construction. For simplicity, we will use the phrase ‘water intrusion’ as an all encompassing term.

Water intrusion into buildings permits amplification of growth of fungi, bacteria and protozoa (Andersson et al., 1997; Gorny, 2004; Gorny et al., 2001, 2002; Hirvonen et al., 2005; Peltola et al., 2001a,b; Rintala et al., 2001, 2002, 2004, Yli-Pirila

et al, 2004). The increased health risks and economic impact from microbial growth resulting from indoor dampness are recognized as significant public health problems requiring attention and remediation (Bernstein et al., 2008; Cox-Ganser et al., 2005; Fisk et al., 2007; Genuis, 2007; Mudarri and Fisk, 2007; Nevalainen and Seuri, 2005). The bio-contamination resulting from water intrusion includes: (1) molds; (2) bacteria; (3) microbial particulates; (4) mycotoxins; (5) volatile organic compounds (non-microbial

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[MVOCs] and microbial [VOCs]); (6) proteins (e.g. secreted enzymes, haemolysins and siderophores); (7) galactomannans (extracellular polysaccharides or EPS); (8) 1-3-D- β -glucans (glucans) and (9) endotoxins (lipopolysaccharides [LPS]). In this communication, we review indoor biocontaminants resulting from water intrusion and their associated toxicity to animals and humans. It is apparent that the potential additive and synergistic effects of multiple contaminants in the indoor environment have been largely overlooked, except in experimental animal models (Huttunen et al., 2004; Isalm and Pestka, 2006; Islam et al., 2002, 2007; Zhou et al., 1998, 1999, 2000). The study of health risks to humans from exposure to molds have been limited to respiratory disease (asthma) in adults and children (Antova et al., 2008; Jaakkola and Jaakkola, 2004; Rydjord et al., 2008). In this paper, we also review the peer-reviewed research that points to the impacts on human health, including neurological, respiratory and immune systems and other organs, from exposure to damp indoor spaces.

Molds

Fungal contamination as a major contributor to sick building syndrome has been reviewed. The significant factors for mold growth are water, temperature and substrate (Li and Yang, 2004). Water activity (a_w) represents available water in a substrate. It is expressed as a decimal fraction of the amount of water present in a substrate that is in equilibrium with relative humidity. Molds that grow at various a_w are classified as xerophilic (xerotolerant), mesophilic and hydrophilic. The xerophilic molds include species of *Penicillium*, *Aspergillus* and *Eurotium* that grow at $a_w < 0.8$. Mesophilic molds grow at a_w 0.8-0.9 and include *Alternaria*, *Cladosporium*, *Phoma*, *Ulocladium* and *Epicoccum nigrum*. The hydrophilic molds include *Chaetomium globosum*, *Fusarium*, *Stachybotrys chartarum*, *Memnoniella echinata*, *Rhizopus stolonifer* and *Trichoderma spp.* at $a_w > 0.9$. Thus, the genera of mold identified indoors are indicative of the extent of water intrusion. Ergosterol and mycotoxins are indicators of mold growth (Hippelein and Rugamer, 2004; Li and Yang, 2004).

Molds grow on surfaces as well as in hidden areas such as in carpet, behind wall paper, inside interior and exterior walls, in attics, in subflooring, etc. They thrive on wet building materials rich in carbohydrates. Molds take nutrients from dead organic material (wood, dry wall, paint, paper, glues, etc.) by secreting

digestive enzymes into the matrix upon which they are growing. It is estimated that approximately 50% of the mold growth in damp indoor environments is hidden, e.g. within walls cavities, carpets, etc. Molds are present in the ventilation systems of contaminated homes, buildings and automobiles (Ahearn et al., 1996, 2004; Li and Yang, 2004).

Certain species of molds are more abundant (amplified) indoors vs outdoors. These include *Aspergillus flavus*, *versicolor*, *sydowii*, *niger* and *fumigatus* and *Penicillium chrysogenum*, *brevicompectum*, *citrinum* and *decumbens*, *Chaetomium*, *Epicoccum*, *Fusarium* and *S. chartarum*. *Cladosporium* species are often equally abundant outdoors and indoors. The comparison of total mold spore counts from indoor to outdoor samples is not an adequate method to test for mold contamination. Air sampling is only a snapshot of an indoor environment that fluctuates according to various parameters, e.g. human activity, air conditioning, temperature, opened/closed windows, etc. The extent of mold and other microbial growth must be determined from a combination of samples that include bulk, wipe, air, carpet dust and wall cavity sampling. Next, the frequency (percentage) of various species of *Aspergillus*, *Penicillium*, *Stachybotrys*, etc., in the indoor vs the outdoor samples must be determined. This approach will reveal that several of the aforementioned molds have amplified indoors when compared to outdoors. The profile of indoor mold may be constant when compared to the outdoor profile. However, certain species of *Aspergillus* and *Penicillium*, as mentioned above, will be dominant indoors vs outdoors (Schwab and Straus, 2004; Straus et al., 2003; Wilson and Straus, 2002). For example, the authors have observed situations in which *Penicillium* species were at 100% in the indoor air and bulk samples, while outdoor levels were <12%. Moreover, in other samples, *Aspergillus* species were greater indoors (46%) vs outdoors (<6%). The US EPA has developed the polymerized chain reaction (PCR) DNA technology to identify 130 of the major indoor fungi to the species level and has licensed several companies to utilize the method (USEPA, 2007).

As an example, the role of air speed equivalent to normal human activity on the release of spores from mold colonies has been reported in bench studies (Gorny 2004; Gorny et al., 2001, 2002; Tucker et al., 2007). Low air speeds cause an initial release of spores from colonies of *S. chartarum*, *Aspergillus niger* and *versicolor*; *Penicillium chrysogenum* and *melinii*, and *Cladosporium sphaerospermum* and

cladosporioides. The spore release per square centimeter during the first 10 min was lowest for *C. cladosporioides* (<500 spores); followed by *S. chartarum* (4000 spores) and *Aspergillus* and *Penicillium spp.* (10,000 spores each). After the initial release, additional spore releases did not occur with *Stachybotrys* and *Cladosporium*, while those of *Aspergillus* and *Penicillium* slowly declined for the duration of the 70 min of observations (Tucker et al., 2007). The proportion of released amounted to 0.2% (*S. chartarum*); 0.8% (*C. cladosporioides*); 1.1% (*A. niger*) and 1.8% (*P. chrysogenum*) of total spore mass of each mold. These observations demonstrate that dry spore molds (*Aspergillus* and *Penicillium*) more readily release their conidia when compared to sticky clusters of spores of *S. chartarum*.

Moderately to heavily damaged homes in the aftermath of Katrina had elevated levels of *Aspergillus*, *Penicillium* and *Paecilomyces* (Chew et al., 2006; Rao et al., 2007b). Moreover, molds detected in water-damaged building materials include *A. versicolor*, *A. sydowii*, *Trichoderma viride*, *S. chartarum*, *Chaetomium globosum*, multiple species of *Penicillium*, *Acremonium*, *Cladosporium*, *Phoma*, *Aureobasidium*, *Phialophora* and yeast (Reijula, 2004).

Rodent lungs have been used to test the adverse effects of various components of common indoor molds. Proteases, isosatratoxin-F, and spores of *S. chartarum* cause inflammatory and cytotoxic effects in the lungs of juvenile mice. Among the adverse effects are alterations and morphological changes in Type II alveolar cells (Rand et al., 2002), release of interleukin 1 β (IL-1 β), IL-6, IL-8 and tumor necrosis factor α (TNF- α) with neutrophilia, granuloma and reduced collagen IV (Pestka et al., 2008; Yike et al., 2007) and a decrease in alveolar space (Rand et al., 2003). Moreover, spores from indoor species of *Aspergillus* and *Penicillium* cause lung eosinophilia, neutrophilia, release of inflammatory cytokines (IL-6, TNF- α), vascular leakage, elevated LDH, Th-2 inflammatory responses and other cytotoxic damage in mouse lungs (Cooley et al., 1998, 2000, 2004; Jussila et al., 2002b; Schwab and Straus, 2004).

S. chartarum consists of two chemotypes: one produces trichothecene mycotoxins, while the other releases spirocyclic atranones. Both cause inflammation in mouse lungs (Flemming et al., 2004). *S. chartarum* is a slimy greenish black mold that does not readily release spores. Thus, the presence of its spores in the indoor air and bulk samples signals either dried disturbed colonies and/or contamination. The spores of *Stachybotrys* are

rare findings in outdoor air (Cooley et al., 1998; Li and Yang, 2004; Schwab and Straus, 2004; Shelton et al., 2002).

Another issue that has been overlooked is the role of molds in chronic upper and lower respiratory tract disease. Chronic rhinosinusitis (CRS) appears to be a non-immunoglobulin E (IgE) immunological inflammatory response to fungi with nasal eosinophilia and the release of toxic major basic protein has a favorable response to intranasal amphotericin B (Kern et al., 2007; Ponikau et al., 2005, 2006; Sasama et al., 2005). *Cladosporium*, *Aspergillus*, *Alternaria* and *Penicillium* were frequently cultured from nasal polyps with a histologic type of fibro inflammation present in over 60% of patients vs controls. Fungi were commonly cultured during the hot and humid environment of summer time from the polyps (Shin et al., 2007). In addition, *Alternaria*, *Aspergillus* and *Cladosporium* proteases interact with nasal epithelial cells activating protease receptors (PARs 2 and PARs 3) enhancing the production of chemical mediators and migration of eosinophils and neutrophils into nasal polyps (Shin et al., 2006). The condition involves exaggerated humoral response of both TH1 and TH2 types. Peripheral mononuclear blood cells (PMBCS) from CRS patients produce significantly elevated IL-5 and IL-13 to *Alternaria* and *Cladosporium* antigens and increased levels of IgG antibodies to *Alternaria* (Shin et al., 2004). Also, the antimicrobial peptide, cathelicidin LL-37, is up-regulated by antigens of *Aspergillus* (fourfold) and *Alternaria* (sixfold) in CRS patients as well as up-regulated surfactant protein (Ooi et al., 2007a,b).

Molds may infect and/or colonize. Rao et al., (2007a) reported eight cases of colonization of New Orleans immunocompetent residents with *Syncephalastrum*. The organism was isolated from clinical specimens of sputum, BAL, endotracheal aspirates and nasal swabs. Also, the existence of aspergillosis in immunocompetent and immunocompromised humans is not questioned (Lewis et al., 2005a,b; Raja and Singh, 2006; Samarakoon and Soubani, 2008; Strelling et al., 1966). Several other zygomycetes are capable of causing human disease (Ribes et al., 2000). Mucormycosis of immunocompetent individuals with involvement of the gastrointestinal tract, skin, paranasal sinuses, necrotizing fasciitis and pericardium has been described in India (Jain et al., 2006; Prasad et al., 2008).

Pulmonary aspergillosis and clinical update of the disease has been recently reviewed (Zmeili and

Soubani (2007). The recognized clinical conditions are aspergilloma, pulmonary aspergillosis (non-invasive), invasive aspergillosis (IA), chronic necrotizing aspergillosis (CNA) and allergic bronchopulmonary aspergillosis (ABPA). Aspergilloma (fungus ball) occurs in individuals with pre-existing lung disease (tuberculosis, sarcoidosis, bronchiectasis and cysts). The fungus ball exists in pre-existing cavities in diseased lungs. It contains fungal hyphae, inflammatory cells, fibrin, mucous and tissue debris. Other organisms causing fungal balls are zygomycetes and fusarium. Diagnosis of pulmonary aspergilloma is usually based upon clinical history and radiographic features. Approximately 50% of sputum cultures are positive for fungi. The development of IA is usually rapid in immunocompromised individuals (e.g. cancer chemotherapy, organ transplant and haematopoietic stem-cell transplantation [HSCT]) with high mortality in neutropenic (50%) and HSCT (90%) patients. CNA is semi-invasive, resulting from infections of the lungs and runs a slow progressive course. APBA is hypersensitive to *Aspergillus* antigens usually in individuals with asthma or cystic fibrosis who are dependent upon chronic corticosteroid therapy. APBA is an inflammatory condition involving hypersensitivity Type I and III immune responses. The pathology is poorly understood while chronic granulomatous conditions exist in the lungs of affected individuals.

IA by *A. fumigatus* have been reported in immunocompetent children. Strelling et al., (1966) describe the deaths of a brother (14 months) and sister (4 years) from acute pulmonary aspergillosis and review the literature. The two children developed acute fever, cough and breathlessness with yellowish-brown (haemoptysis) mucus, after playing in a barn. Cultures from the lungs and barn materials isolated *A. fumigatus*, while tissue sections of the lungs revealed branching fungal hyphae. The doctors' review of the literature described additional deaths and disease from aspergillosis as follows: (1) brother (5 years) and sister (11 years) living on a farm; (2) 20-day-old infant; (3) 18-day-old infant; (4) 7-year-old child (sex not given); (5) boy (6 years) and (6) girl (7 years) who recovered. The cerebellum and frontal lobes were involved in cases 5 and 6.

Immunocompetent adults may develop non-invasive or invasive *Aspergillus* infections. Non-invasive aspergillosis involves aspergilloma of the lungs visible on computed tomography (CT) scan with a solitary nodule or mass. Microscopically granuloma and cavity lumen

hyphae are present (Kang et al., 2002). On the other hand, IA may infect the lungs as well as other organs. The lungs can be almost completely consolidated with granuloma (Hillerdal et al., 1984; Reijula and Tuomi, 2003), bilateral hilar prominence (Parameswaran et al., 1999), bilateral fibrinous pleural adhesion and extensive parenchymal destruction (Zuk et al., 1989). Blood-stained mucous in bronchi and massive haemoptysis may also be present (Parameswaran et al., 1999; Zuk et al., 1989). Invasion of the tracheobronchial tree can also occur (Mohan et al., 2006). Individuals with asthma or chronic obstructive pulmonary disease (COPD) on either short-term or prolonged corticosteroid therapy (oral, inhalation, intravenous [i.v.]) contract IA mostly from *A. fumigatus* followed in order by *flavus*, *terreus*, *niger* and *nidulans* (Ali, et al., 2003; Ganassini and Cazzadori, 1995; Samarakoon and Soubani, 2008; Smeenk et al., 1997; Trof et al., 2007). Disseminated IA to the skin and bone (spondylodiscitis) in a patient with a pulmonary nodule has been described (Domergue et al., 2008), while it involved the lung, liver and spleen in another documented patient (Raja and Singh, 2006). Paranasal sinus involvement, perforation of the nasal septum and invasion of the palate was described in one patient (Khatri et al., 2000; Raja and Singh, 2006; Samarakoon and Soubani, 2008), while another had paranasal, orbital involvement with intracranial extradural extension via the maxillary division of the trigeminal nerve (Subramanian et al., 2007). IA can result in dissemination to the central nervous system (CNS; Garcia et al., 2006; Palanisamy et al., 2005). CNS complications in one person involved headache, nausea, motor impairment and cognitive decline due to progressive cerebellar lesions. After treatment with high doses of itraconazole (1600 mg/day), the patient recovered with only mild cerebellar motor impairment (Palanisamy et al., 2005).

Finally, diabetes mellitus, corticoid steroids therapy, COPD and antibiotics are risk factors for developing IA. Corticosteroids are immunosuppressive. Treated alveolar macrophages (AM) can internalize mold conidia (Philippe et al., 2003). However, the corticosteroids inhibit reactive oxidant intermediates, e.g. NADPH oxidase, as well as the production of cytokines TNF- α and IL-1 (Kamberi et al., 2002; Philippe et al., 2003; Taramelli et al., 1996). Although the conidia are internalized, the killing of conidia by the inhibited AM is significantly reduced, allowing the development of IA (Brummer et al., 2001; Gangneux et al., 2008; Philippe et al., 2003). Corticosteroid use is a major risk factor for the increase in IA in

non-neutropenic cases (Gangneux et al., 2008; Trof et al., 2007). The use of corticosteroids to treat IA becomes more perilous when the toxic metabolite, gliotoxin, which is produced by several genera of molds, is considered. Gliotoxin is an immunosuppressive mycotoxin produced by *A. fumigatus*, *terreus* and *niger*, several *Penicillium* species, *Trichoderma virens* and *Candida albicans*. It has been detected in the sera and lungs of both mice and humans with aspergillosis (Gardiner et al., 2005; Lewis et al., 2005a,b). Thus, therapy-induced immunosuppression probably leads to fungal metabolite immune suppression. For more information on gliotoxin, see the below category entitled 'Mycotoxins'.

Th-1 cell-mediated immunity was believed to be the major defense against fungal infections, while Th-2 humoral immunity plays a minor role (Blanco and Garcia, 2008). However, recent information suggests that Th-17 cells and IL23/IL17 are important in *Aspergillus* infections and fungal pathology (Romagnani, 2008; Romani et al., 2008; Tesmer et al., 2008; Zelante et al., 2007, 2008). In this scenario, IL-23/IL-17/TGF- β worsen the infection, while IL-6 has a protective role. The regulatory pathway in the pathogenic inflammation to molds involves the kynurenines (Belladonna et al., 2006; Romani and Puccetti, 2008). In addition, the acute phase long pentraxin 3 (PTX3) appears to have a role in the inflammatory process caused by molds (Gaziano et al., 2004).

In mice, the Th-17 cell develops from naive CD4 T cells, while in humans its origin maybe from Tregs or Th-1 cells (Romagnani, 2008). Th-17 was initially described in autoimmune mouse models of autoimmunity: encephalomyelitis (EAE) and collagen-induced arthritis (CIA). Human Th-17 cells promote disruption of blood-brain barrier tight junctions, promote CNS inflammation and kill human neurons through recruitment of CD4+ lymphocytes (Kebir et al., 2007). Furthermore, the interleukin, IL-17, secreted by Th-17 lymphocytes is elevated in the sera and diseased tissues from various chronic inflammatory diseases: e.g. Chron's disease, lupus erythematosus and rheumatoid arthritis. However, in autistic children, plasma IL-17 is not elevated, while IL-23 is decreased (Enstrom et al., 2008). It is also likely that Th-17 cells and IL-17 are involved in severe asthma complicated by bacterial infections independent of IgE-mediated allergic disorders (Romagnani, 2008).

The pentraxins are a family of multimeric pattern-recognition proteins. They are divided into short (C-reactive protein) and long (PTX3) pentraxins

(Mantovani et al., 2008)). Long PTX3 expression is induced in response to inflammatory signals at sites of inflammation. It is secreted by endothelial cells, monocytes/macrophages, dendritic cells (DCs), smooth muscle cells, fibroblasts and is stored in neutrophil granules (Imamura et al., 2007; Jaillon et al., 2007; Savchenko et al., 2008). Long PTX3 is expressed in individuals with chronic systemic inflammation (Muller et al., 2001; Savchenko et al., 2008). PTX3 is an acute-phase protein produced at sites of infections and is thought to have a protective role against microbial infections, e.g. bacteria, fungi, viruses (He et al., 2007). However, over expression of long PTX3 is associated with more severe lung injury and correlates with the state of severity of critical illness as well as organ failures (He et al., 2007; Mauri et al., 2008; Muller et al., 2001; Suliman et al., 2008). Thus, in a mouse model of aspergillosis depending upon the therapeutic dose, PTX3 either exacerbated or improved the state of pulmonary inflammation (Gaziano et al., 2004). Finally, long PTX3 is expressed in the CNS of mice following instillation of LPS and during infections by either *C. albicans* or *Cryptococcus neoformans* (Polentarutti et al., 2000).

Positive gram and gram negative bacteria

Gram positive and gram negative bacteria have been isolated from damp indoor spaces. They are briefly reviewed.

Gram Positive Bacteria

Gram positive bacteria have been isolated from water-damaged building materials. *Actinomyces* (Actinobacteria) including several species of *Streptomyces*, *Nocardia* and *Mycobacterium* were cultured from indoor air and dust as well as from moldy, water-damaged materials (Peltola et al., 2001a,b; Rautiala et al., 2004; Rintala et al., 2001, 2002, 2004; Torvinen et al., 2006). Several species of both potentially pathogenic and saprophytic of *Mycobacteria* were isolated from workplace air during remediation (Rautiala et al., 2004). Some of the identified species belonged to the *Mycobacterium avium* complex and are potential human pathogens. It was noted by the authors that the mycobacteria are slow growing. The *Actinomyces* are potential human pathogens. The reporting of these infections in the United States is not required; therefore, it is impossible to determine disease prevalence.

Table 1. Toxic metabolites produced by bacteria isolated from water-damaged materials and indoor air

Metabolite	Disease	Organisms	Health concerns
Valinomycin	Unknown	<i>Streptomyces griseus</i>	Mitochondrial poison
Leptomycin B	Unknown	<i>Streptomyces species</i>	Inhibition of inducible nitric oxide synthetase
Toxic peptide	Unknown	<i>Bacillus amyloliquefaciens</i>	Depolarized trans-membrane. Decreased ATP and NADH cell death
Mitochondrial toxin	Unknown	<i>Bacillus pumilus</i>	Disruption of mitochondrial membrane
Mitochondrial toxin	Unknown	<i>Nocardiopsis species</i>	Disruption of mitochondrial membrane
Cytostatic compounds	Unknown	Co-culture of <i>S. chartarum</i> and <i>S. californicus</i>	Cytotoxic compounds that are just as toxic as doxorubicin and AMD

Streptomyces californicus produces spores approximately 1 µm in mean aerodynamic diameter that can penetrate deep into alveolar spaces of the lungs. Intrathecal instillation of spores in mice caused inflammation characterized by increase concentrations of TNF-α, IL-6, LDH, albumin and haemoglobin in bronchoalveolar lavage fluid (BAL) and sera (Jussila et al., 2001). Moreover, following repeated exposures to the spores in a dose-response study, the inflammation was systemic, involving recruitment of neutrophils, macrophages and activated lymphocytes into the airways and decreased numbers of spleen cells. The dose response was non-linear. BAL from the mice also contained increased concentrations of albumin, total protein, LDH and activated lymphocytes. It was concluded that *S. californicus* spores are capable of causing both lung inflammation and systemic immunotoxic effects (Jussila et al., 2002a, 2003). It is interesting that *Streptomyces* produce anthracyclines, e.g. daunorubicin and doxorubicin, drugs widely used in chemotherapy (Arcamone, 1998; Arcamone and Cassinelli, 1998). The anthracyclines cause apoptosis of activated and non-activated lymphocytes as well as a decrease of mature T and B cells in mice. The T and B cell depletion was most severe in the spleen, moderate in lymph nodes and least in the thymus (Ferraro et al., 2000). In addition, various species of this genus are the source for a variety of antibiotics (Gunsalus, 1986).

The inflammatory and cytotoxic affects in vitro of indoor air bacteria compared to mold spores have been reported. The bacteria tested were *Bacillus cereus*, *Pseudomonas fluorescens* and mold tested were *Streptomyces californicus*, *A. versicolor*, *P. spinulosum* and *S. chartarum*. The bacteria caused the production of IL-6 and TNF-α in mouse macrophages. Only the spores of *S. californicus* caused a production of nitric oxide (NO) and IL-6 in both mouse and

human cells. Of the molds, only *S. chartarum* caused the production IL-6 in human cells. The overall potency to stimulate the production of proinflammatory mediators decreased in order as follows: *Ps. fluorescens*, > *S. californicus*, > *B. cereus*, > *S. chartarum*, > *A. versicolor*, > *P. spinulosum*. There was a synergistic response of TNF-α and IL-6 after coexposure with *S. californicus* with both trichodermin and 7-α-hydroxytrichodermol. These observations indicate that bacteria in water-damaged buildings should also be considered as causing inflammatory effects on occupants (Huttunen et al., 2004; see Table 1).

The synergism and interaction of *S. californicus* and *S. chartarum* on mouse macrophages have been reported. Spores from these two organisms were tested for the effects on macrophages as follows: spores isolated from co-cultivated cultures, mixture of the spores from separate pure cultures and the spores of each organism. Spores isolated from the co-cultures were compared to the mixture of spores and were more cytotoxic than either the mixture of spores or the spores from each organism. Co-cultured spores caused increased apoptosis of the macrophages by more than fourfold. Cells arrested at G2/M stage of the cell cycle were increased nearly twofold. In contrast, the co-cultured spores significantly decreased the ability of the spores to trigger the production of NO and IL-6 by the macrophages. Thus, co-culturing of the two organisms resulted in microbial interactions that significantly potentiated the ability of spores to cause apoptosis and cell cycle arrest (Penttinen et al., 2005). In a follow-up study, the same authors (Penttinen et al., 2006) compared the cytotoxicity of the co-cultured spores (*S. californicus* and *S. chartarum*) to that of chemotherapeutics (doxorubicin, phleomycin, actinomycin D and mitomycin C) produced by *S. californicus*. The co-cultured spores mediated apoptosis, cell cycle arrest at the

S-G2/M phase and caused a fourfold collapse of mitochondrial membrane potential. In addition, a sixfold increase in caspase-3 activation and DNA fragmentation was observed. The cytotoxicity of the co-cultured spores was similar to that caused by doxorubicin and actinomycin D. It was concluded that the co-culture of the two organisms caused the production of unknown cytotoxic compound(s) that evoked immunotoxic effects similar to chemotherapeutic drugs. In conclusion, these studies demonstrate that spores from *S. californicus* are cytotoxic to mouse macrophages. More importantly, the co-cultivation of *S. californicus* and *S. chartarum* results in a spore mixture that is more toxic than the spores of each organism cultured individually. Additional attention must be paid to the synergism that probably occurs in the microbial mixture that is present in water-damaged buildings. Moreover, the spores of *S. californicus* were more toxic to mouse macrophages than was a mixture of spores from co-cultures with various molds (*A. versicolor*, *P. spinulosum* and *S. chartarum*). *S. californicus* spores alone were more potent inducers of inflammatory and cytotoxic responses than any combination of co-cultivated spore mixtures. In addition, co-culture of *S. chartarum* and *A. versicolor* produced a synergistic increase in cytotoxicity with no effect on inflammatory responses of the macrophages (Murtoniemi et al., 2005). Finally, *S. griseus* strains isolated from indoor environments produce a toxin, valinomycin, which causes mitochondrial swelling, damaged mitochondrial membranes, and disrupted the mitochondrial membrane potential of boar sperm (Andersson et al., 1997; Peltola et al., 2001a). In addition, the *Nocardiosis* strains isolated from indoor water-damaged environments are toxigenic and produce a mitochondrial toxin(s) that damages the mitochondria of boar sperm (Peltola et al., 2001a,b). In conclusion, these studies demonstrate that spores from *S. californicus* are cytotoxic to mouse macrophages. More importantly, the co-cultivation of *S. californicus* and *S. chartarum* results in a spore mixture that is more toxic than the spores of either organism cultured individually. Additional attention must be paid to the synergism that probably occurs in the microbial mixture that is present in water-damaged buildings. Finally, *Nocardia* isolated from water-damaged building materials also cause cytotoxicity.

Streptomyces species are associated with farmer's lung disease (allergic alveolitis). Infections (*Streptomyces*) occur most frequently in immunocompromised

individuals and people with diabetes mellitus and/or corticosteroid therapy. However, co-infection with *Aspergillus* in cases of chronic granulomatous disease following exposure to aerosolized mulch has been reported (Siddiqui et al., 2007). Diagnosis is difficult because of mimicry of other diseases (Acevedo et al., 2008; Che et al., 1989; Kagen et al., 1981; Kapadia et al., 2007; Kofteridis et al., 2007; Madhusudhan et al., 2007; Quintana et al., 2008; Roussel et al., 2005). Finally, *Streptomyces spp.* can cause mycetoma, a condition most endemic around the Tropic of Cancer, but also occurs worldwide, in the United States, Asia, and Latin America (Quintana et al., 2008; Welsh et al., 2007). The organisms are aerobic, produce chalky aerial mycelia and granules of different sizes, textures and colors. *Streptomyces* do not stain with haematoxylin and eosin, but are gram positive and acid fast stain.

Nocardia are aerobic and infectious (nocardiosis), producing pulmonary disease, skin infections, lymphocutaneous lesions and brain abscesses (Bennett et al., 2007; Mauri et al., 2002; Shook and Rapini, 2007). The genus contains approximately 15 known species. The species identified in human pulmonary and systemic infections include *asteroides*, *pseudo-brasilensis*, *otitidis-cavriarum*, *abscessus*, *farcinica*, *nova*, *transvalensis* (Bennett et al., 2007; Georghiou and Blacklock 1992; Groves, 1997; Kennedy et al., 2007; Yourke and Rouah, 2003). *N. cyriacigeorgica* recently was identified as an emerging pathogen in the United States and probably worldwide (Schlaberg et al., 2008). Lymphocutaneous, subcutaneous mycetoma with sulphur granules and superficial skin infections also occur (Shook and Rapini, 2007). *N. asteroides* was identified with pneumonia and empyema (thoracis) in a healthy 40-day-old neonate after presumed inhalation exposure (Tantracheewathorn, 2004). *Nocardia* are gram positive and stain partially with acid fast. Serological tests are not available. Predisposing factors are immunocompromised individuals, pre-existing lung disease, corticosteroid therapy and diabetes mellitus (Bennett et al., 2007; Georghiou and Blacklock, 1992; Mari et al., 2001). As occurs with *Streptomyces*, the disease process can exhibit mimicry. Case reports of immunocompetent patients include brain abscesses (Chakrabarti et al., 2008; Dias et al., 2008; Kandasamy et al., 2008), spinal cord abscess (Samkoff et al., 2008), mimicry of metastatic brain tumor (Kawakami et al., 2008), ventriculitis/choroid plexitis (Mongkolrattanothai et al., 2008), lymphangitis (Dinubile, 2008), lung abscesses (Mari et al., 2001; Martinez et al., 2008;

Tada et al., 2008), endophthalmitis (Ramakrishnan et al., 2008) and sternal osteomyelitis with mediastinal abscess (Baraboutis et al., 2008). It is recommended that 16s recombinant DNA (rDNA) sequencing should be used to identify infections of novel bacteria (Woo et al., 2008).

Mycobacteria are common in moisture-damaged building materials (ceramic, wood and mineral insulation) and their occurrence increase with the degree of mold damage (Rautiala et al., 2004; Torvinen et al., 2006). They are environmental (soil, water, sewage) opportunistic gram positive bacteria capable of causing hypersensitivity pneumonitis as well as cervical lymphadenitis in children. Mycobacteria have been isolated from water systems, spas, hot tubs and humidifiers and are resistant to disinfection (Primm et al., 2004; Torvinen et al., 2007). The Centers for Disease Control and Prevention (CDC) has implicated *M. avium*, *terrae* and *immunogenum* in outbreaks of hypersensitivity pneumonitis (Falkinham, 2003a,b). *M. terrae* isolated from the indoor air of a moisture-damaged building induced a biphasic inflammatory response after intrathecal instillation into mouse lungs. There was an initial increase in TNF- α and IL-6 at 6 hour to 3 days, followed by a second phase at 7 to 28 days (Jussila et al., 2002a,b).

The genus *Mycobacterium* consists of approximately 117 species of which 20 are potential human pathogens. They cause non-tuberculous mycobacteria (NTM) lung disease (American Thoracic Society, 2007). *M. avium-intracellulare* organisms are increasingly significant pathogens in North America, causing a pulmonary infection named MAC (*M. avium* complex). *M. kansasii*, *chelonae* and *fortuitum* are other important pathogens (Agrawal and Agrawal, 2007; Fritz and Woeltje, 2007; Fujita et al., 2002; Kuhlmann and Woeltje, 2007; Iseman et al., 1985). According to the American Thoracic Society, 2007, 'The minimum evaluation for NTM should include the following: (1) chest radiograph or, in absence of cavitation, chest high-resolution computed tomography (HRCT) scan; (2) three or more sputum specimens stained for acid-fast bacilli (AFG) analysis; and (3) exclusion of other disorders such as tuberculosis. Clinical, radiographic and microbiologic criteria are equally important and all must be present to make a diagnosis of NTM lung disease. The following criteria apply to symptomatic patients with radiographic opacities, nodular or cavitary, or HRCT scan that shows multifocal bronchiectasis with multiple nodules. These criteria fit best with *M. avium* complex (MAC), *M. kansasii* and

M. abscessus. There is not enough known about NTM of other species to be certain that these diagnostic criteria are universally applicable to all NTM respiratory pathogens. A microbiologic diagnosis includes one of the following: (1) positive cultures from two separate expectorated samples; (2) positive culture from at least one bronchial wash; (3) trans-bronchial or other lung biopsy with mycobacteria histopathologic features. Patients suspected of having NTM lung disease but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded. NTM is on the rise worldwide. Mycobacteria have been isolated from water-damaged building materials from indoor environments. Finally, individuals treated with corticosteroids are at an increased risk.

M. ulcerans is a significant human pathogen that causes Buruli ulcer (BU). Cases of BU have been reported worldwide with the greatest burden of disease occurring in West and Central Africa. Its transmission source is not fully understood, but it may be waterborne. The disease is characterized by progressive, severe necrotizing skin lesions that do not respond to antimicrobial therapy and may require either surgical excision or amputation as treatment. *M. ulcerans* is an intracellular pathogen. It produces a polyketide-derived macrolide, mycolactone. Mycolactone is cytotoxic at 2 ng/mL and is the organism's virulence factor. *Mycobacterium scrofulaceum* and *kansasii* and other mycobacteria produce a less cytotoxic (33 to 1000 μ g/mL) lipid chemical when tested on fibroblast in vitro (Daniel et al., 2004; Yip et al., 2007). The gram positive toxic organisms identified in indoor environments also include *Bacillus spp*, *Nocardia spp*. and *Streptomyces spp*. (Peltola et al., 2001a,b). Mycobacteria have been isolated from damp indoor environments (Falkinham, 2003a,b; Jusilla et al., 2001, 2002a).

Examples of additional gram positive bacteria are species of *Atrhrobacter*, *Bacillus*, *Cellumonas*, *Gordona* and *Paeniibacillus* (Andersson et al., 1997). *Bacillus simplex* and *Amyloliquefaciens* isolated from moisture-damaged buildings produce surfactin (lipopeptide) and peptides that adversely affect cell membranes and mitochondria (Mikkola et al., 2004, 2007). Finally, there were elevated concentrations of *Staphylococci* and *Actinomycetes* in a water-damaged home in which a 3-month-old infant died from a Reye's-like syndrome, with mitochondrial damage resulting in decreased enzymatic activity of complexes I-IV. Mitochondrial DNA mutation testing of the infant resulted in negative

findings for known mitochondrial diseases. This home also contained several species of *Aspergillus*, *Penicillium* and *S. chartarum* (Gray et al., in preparation).

Gram negative bacteria: Gram negative bacteria have also been identified in water-damaged buildings. These bacteria produce endotoxins (LPS) and are potentially infectious, particularly species of *E. coli*, *Enterobacter* and *Pseudomonas* (e.g. *aeruginosa* and other spp.). Other gram negative bacteria are species of *Agrobacterium*, *Caulobacter*, *Stenophomonas* and *Chryseomonas* (Andersson et al., 1997). Gram negative bacteria are ubiquitous in the environment and have been isolated from contaminated ventilation systems, humidifiers, carpeting, drywall, etc., in large numbers in water-damaged buildings. Pet fecal matter from dogs and cats and sewage are two sources of gram negative bacteria. They release endotoxins that can cause a variety of symptoms as well as pulmonary inflammation in building occupants (see endotoxins; Martinez, 2007a,b; Rylander 2004; Simpson et al., 2006; Yang, 2004). Finally, bioaerosols of *Staphylococcus aureus*, multi-antibiotic-resistant and non-resistant strains, have been isolated from healthy residential homes (Gandara et al., 2006).

Particulates

Colonies of fungi and bacteria shed particulates into the indoor air ranging from nanoparticles to 9 µm or larger. For convenience of this discussion, the particulates will be divided into large and small particle fractions. The larger particles are >2 µm consisting of spores and hyphal fragments. They contain mycotoxins, antigenic material, enzymes, haemolysins and other potentially toxic metabolites with adverse effects on the lungs of mice and rats. Hyphal fragments of *S. chartarum* and other genera of molds probably caused pulmonary bleeding in infants (Dearborn et al., 2002; Etzel et al., 1998; Flappan et al., 1999; Novotny and Dixit, 2000). *S. chartarum* was isolated from the lung of a child with pulmonary bleeding and haemosiderosis (Elidemer et al., 1999). Spores, hyphal fragments and extracts from several genera of molds cause inflammatory changes in the lungs and nasal passages (Brieland et al., 2001; Rand et al., 2002, 2003, 2005; Schwab and Straus, 2004; Yike et al., 2005, 2007).

The shedding of fine particles (<2 µm) from fungal and bacterial growth results from human activity, e.g. radio, TV, talking, walking, etc., which creates vibrations at frequencies from 1 to 20 Hz and air

movement (Gorny, 2004; Gorny et al., 2002). The vibrations along with air velocity release spores, hyphal fragments, and fine particulates. The fine particles are up to 320 times more numerous than the large particulates, depending upon mold species and velocity of air. Furthermore, the fine particulates also contain biocontaminants (mycotoxins, endotoxins, antigens, haemolysin, etc.) produced by fungi and bacteria (Brasel, et al., 2004, 2005a,b; Van Emon et al., 2003) and are immunogenic (Gorny, 2004).

The mean diameter, size and density of particulates, particularly nanoparticles, determine the deposition in the nasal cavity and levels of the tracheobronchial tree. Particles <5 µm are deposited in alveolar spaces (Oberdorster et al., 2004; Peters et al., 2006). Nanoparticles mainly deposit in alveoli and transfer into the systemic circulation and distribute to other organs, including the brain (Calderon-Garciduenas et al., 2004, 2008a,b,c; Elder and Oberdorster, 2006; Nemmar et al., 2001; Peters et al., 2006). Transfer into the brain via the olfactory nerve is probable with mycotoxins as well as cadmium, other chemicals, drugs and viruses (Calderon-Garciduenas et al., 2004, 2008a,b,c; Eriksson et al., 1999; Islam et al., 2006, 2007; Larsson and Tjalve, 2000; Peters et al., 2006). As an example, children and young adults exposed to severe air pollution in Mexico City have deposits of particles in the olfactory mucosa with transport along the olfactory tract bulb that show up-regulation of markers of inflammation in the frontal cortex, hippocampus, cerebellum and alteration of the blood-brain barrier (Calderon-Garciduenas et al., 2004, 2008a,b,c). In addition, the translocation of ultrafine particles to the olfactory bulbs and extra-pulmonary organs was observed in rats (Oberdorster et al., 2004) and humans (Peters et al., 2006) demonstrating that fine particles target the brain and other organs, e.g. blood vessels, cardiovascular system and kidneys. Evidence for endothelial inflammation and damage in children was characterized by increased TNF-α, prostaglandin E2 (PGE2), C-reactive protein and increased endothelin-1 and down-regulation of soluble adhesion molecules (Calderon-Garciduenas et al., 2008c). Finally, air pollution leads to brain inflammation resembling Alzheimer-like pathology as well as neurocognitive deficits in young adults and children (Calderon-Garciduenas et al., 2004, 2008a). These authors also demonstrated fine particles within RBCs adjacent to capillary endothelium in the brain. In conclusion, exposure to fine particles present in damp indoor spaces (Gorny, 2004) that have been proven to contain

trichothecenes (Brasel et al., 2005a,b; Gottschalk et al., 2008) and other toxic metabolites (Johanning et al., 2002a,b) must be considered as probable sources of human neurocognitive abnormalities, described below, Mechanism of Neurological Injury.

Mycotoxins

Mycotoxins are produced by some fungi (Campbell et al., 2004; Jarvis, 2002; Li and Yang, 2004; Nielsen, 2003). Mycotoxin production is influenced by substrate composition, water activity and temperature. It is crucial to inventory indoor molds to species in order to assess if toxigenic molds are present. Exposure of occupants mainly results from inhalation and, to a lesser extent, skin absorption and ingestion. Molds produce mycotoxins during rapid growth (Straus, personal communication). At low concentrations, they cause mycotoxicosis in humans and animals. The mycotoxins causing disease include aflatoxins, ochratoxin A, trichothecenes, citreviridins, fumonisins and gliotoxins (Bennett and Klich, 2003; Peraica et al., 1999; Richard 2007). Mycotoxins can regulate the immune system up or down as well as inhibit synthesis of protein, RNA and DNA (Bok et al., 2006; Stanzani et al., 2005). Moreover, they can form DNA adducts (Peng et al., 2007; Pfohl-Leskowicz et al., 2007), protein adducts (Campbell et al., 2004; Vojdani et al., 2003a,b; Yike et al., 2006) and cause oxidative stress (Gardiner et al., 2005; Peng et al., 2007) as well as mitochondrial directed apoptosis (Chan, 2007; Stanzani et al., 2005). Some of the animal and human health concerns from mycotoxin-producing fungi are listed in Table 2.

Conjugation of mycotoxins to human serum albumin and detection of the conjugates have been reported. Aflatoxin B1-albumin adducts occur with up to 350 pg of AFB1-lysine equivalent/mg albumin (Wild et al., 1990). The conjugation is reported to be permanent and irreversible (Nassar et al., 1982). Humans form aflatoxin-albumin conjugates equivalent to similar conjugates formed in animals sensitive to the mycotoxin (Wild et al., 1996). Aflatoxin-albumin adducts are present in children with impaired growth (Gong et al., 2004) and in cases of acute aflatoxicosis (Azziz-Baumgartner et al., 2004). Genetic polymorphism in glutathione S-transferases affects adducts level. Individuals with glutathione S-transferase M1 (GSTM1) null had increased levels of adducts versus individuals with normal GSTM1 enzymatic activity. This enzyme conjugates aflatoxin B1 8,

9-epoxide to albumin (Chen et al., 2000; Sun et al., 2001; Wojnoski et al., 2004). In addition, polymorphism in CYP3A5 and CYP3A affects aflatoxin-albumin adduct levels. CYP3A5 haplotypes with high enzyme activity had increased levels compared to individuals with low activity. The effect was more evident in individuals with low CYP3A4 enzyme activity (Wojnoski et al., 2004). More recently, attention has been directed towards the study of *S. chartarum* and trichothecenes. Albumin conjugates with satratoxin G have been demonstrated. As many as 10 satratoxin molecules adduct with albumin at lysyl, cysteinyl and histidyl amino acid residues of the protein. Satratoxin G-albumin adducts were identified in the sera of exposed humans and rat pups (Yike et al., 2006). In addition, antibodies to satratoxin H were present in the systemic circulation of humans exposed to *S. chartarum* (Vojdani et al., 2003a,b).

The neurotoxic mycotoxins include ergot alkaloids, trichothecenes, citreviridin, patulin, fumonisins and tremorgens. The neurotoxic effects of the tremorgens in laboratory animals are on the brainstem, stellate ganglion and Purkinje cells of the cerebellum. The tremorgens can affect neuroreceptor sites (e.g. gamma aminobutyric acids [GABA] and inositol 1, 4, 5-trisphosphate receptor), inhibit acetylcholinesterase, and release excitatory neurotransmitters (e.g. glutamate aspartate, GABA, serotonin) (Campbell et al., 2004; Chen et al., 1999; Land et al., 1987; Selala et al., 1989; Valdes et al., 1985). In humans, the tremorgens verrucologen and fumitremogen C produced by *A. fumigatus* have been implicated in wood trimmer's disease, characterized by alveolitis and tremors (Land et al., 1987). Verrucologen decreases GABA levels in the mouse brain (Hotujac et al., 1976).

Fumonisin-contaminated corn tortillas have been linked to an increased risk of neural tube defects and fetal death in residents along the Texas-Mexico border (Missmer et al., 2006). These mycotoxins inhibit ceramide synthase causing an accumulation of bioactive intermediates of sphingolipid metabolism (sphinganine and sphingoid bases). They also interfere with folate transport and cause craniofacial defects in mouse cultures and in utero. The administration of folic acid or a complex sphingolipid was preventative with respect to the in utero defects (Marasas et al., 2004).

Intrathecal instillation of extracts of *P. brevicompactum* and *chrysogenum* that contained mycophenolic acid and roquefortine C in mice at concentrations of the mycotoxins ranging from 0.5 to 12.5 nM/g body weight caused inflammation within 6 hours at

Table 2. Mycotoxins produced by toxic molds

Metabolite	Disease	Organisms	Health Concerns
Gliotoxin	Invasive aspergillosis	<i>Aspergillus fumigatus</i> , <i>terres</i> , <i>flavus</i> , <i>niger</i> , <i>Trichoderma virens</i> , <i>Penicillium spp</i> , <i>Candia albican</i>	Immune toxicity, immune suppression, neurotoxicity
Aflatoxin B1; kojic acid; aspergillic acid; nitropopionic acid	Carcinogenesis	<i>Aspergillus flavus</i>	Liver pathology and cancer; immune toxicity; neurotoxicity
Fumigaclavines; fumitoxins; fumitermorgens; verruculogen; gliotoxin	Aspergillosis	<i>Aspergillus fumigatus</i>	Lung disease; neurotoxicity; tremors; immune toxicity
Ochratoxin A	BEN Urinary tract tumors; Aspergillosis	<i>Aspergillus niger</i> <i>Penicillium verrucsum</i>	Immunosuppression BEN Lung disease
Ochratoxin A Penicillic Acid; Xanthomegnin; Viomellein; Vioxanthin	Urinary tract Tumors	<i>Aspergillus ochraceus</i>	Nephropathology
Sterigmatocystin	Carcinogenesis	<i>Aspergillus versicolor</i>	Liver pathology and cancer
5-methoxysterigmatocystin	Unknown	<i>Chaetomium globosum</i>	Cytotoxicity Cell division
Chaetomiums; Chaetoglobosum A and C	Unknown	<i>Memnoniella echinata</i>	Carcinogenesis? Reproductive toxin Hypersensitivity? Protein synthesis inhibition
Griseofulvin; Dechlorogriseofulvins	Unknown		Cytotoxic; mutagen
Trichodermin; Trichoderma	Unknown	<i>Penicillium brevicompactum</i>	Immune toxicity; cytotoxic;
Mycophenolic acid	Unknown	<i>Penicillium expansum</i>	
Botryodiploidin	Unknown		Tremors
Patulin; citrinin			
Chaetoglobosin			
Roquefortine C			
Verrucosidins	Unknown	<i>Penicillium plonicium</i>	Tremors, cytotoxicity; Nephropathology
Penicillic acid			
Nephrotoxic glyco-peptides			
Trichothecenes	Unknown	<i>Trichoderma species</i>	Trichothecene toxicity Immunotoxicity
Trichodermol			
Trichodermin			
Gliotoxin; Viridin			
Fumonisin	CNS birth defects	<i>Fusarium verticillioides</i> (aka <i>moniliforme</i>)	Neural tube defects in animals and humans
Spirocyclic	Pulmonary bleeding	<i>Stachybotrys chartarum</i>	Respiratory bleeding Protein synthesis inhibition
Drimanes; roridin			Neurotoxicity
Satratoxins (F, G, H)			Cytotoxicity
Hydroxyroridin E			Immune toxicity
Verrucarins J			
Trichodermin			
Dolabellanes			
Altrones B, C;			
Stahybotrylactams			

BEN; Balkan Endemic Nephropathy

concentrations of mycotoxins. Cellular and chemical markers of inflammation were elevated, including macrophages and neutrophils, MIP-2, TNF and IL-6 concentrations in bronchoalveolar lavage fluid (BALF). A dose response was seen for mycophenolic acid (macrophages) and MIP-2. In addition, brevianamide A induced cytotoxicity with increased LDH concentrations. Albumin, a marker of pulmonary capillary vascular leakage, was also elevated in the BALF (Rand et al., 2005). Finally, zearalenone and zearalenol are estrogenic compounds already associated or correlated with increased incidence of infertility, abortion and uterine prolapse in livestock (Zinedine et al., 2007). They probably have estrogenic action in humans exhibited by precocious puberty (Leffers et al., 2001; Massart et al., 2008).

Mycotoxins have been detected in the air and building materials following water intrusion. Sterigmatocystin produced by *A. versicolor* was detected in 2 of 11 carpet dust samples from water-damaged homes (Englehart et al., 2002). Bulk samples from a Finnish building with moisture problems were analyzed for 17 different mycotoxins. Sterigmatocystin was present in 24% of the samples. Trichothecenes were detected in 19% of the materials as follows: Satratoxin G or H (five samples); diacetoxyscirpenol (five samples); 3-acetyldeoxynivalenol (three samples) and deoxynivalenol, verrucarol or T-2 tetraol in an additional five samples. Citrinine was found in three samples. *A. versicolor* was present in most sterigmatocystin-containing samples. *Stachybotrys spp.* were present where satratoxins were detected (Tuomi et al., 2000). Screening of dust samples from the ventilation system of office buildings revealed the presence of the trichothecenes, T-2 toxin, diacetoxyscirpenol, roiridine A and T-2 tetraol (Smoragiewicz et al., 1993). Satratoxin G and H were identified in buildings with dampness in Denmark (Gravesen et al., 1999) and Germany (Gottschalk et al., 2008) and the United States (Hodgson et al., 1998). Finally, Johanning et al. (1996, 1999, 2002a,b) demonstrated that indoor air of *S. chartarum* contaminated structures is cytotoxic in an in vitro MTT (-(-4, 5-dimethylthiazolyl)-2, 5-diphenyltetrazolium bromide) assay. MTT is a colorimetric assay that involves the reduction by mitochondria of living cells of the yellow MTT to purple formazan. Trapped particulates from the indoor air of moldy buildings contain macrocyclic trichothecenes (satratoxins) and spirocyclic lactones. However, mycotoxins produced by other genera of molds in the indoor air cannot be ruled out. Thus, the MTT

cytotoxicity assay responds to mycotoxins, e.g. gliotoxin, fumonisins, aflatoxins, patulin, etc., as well as Type A and B trichothecenes (Hanelt et al., 1994; Schultz et al., 2004; Smith et al., 1992; Visconti et al., 1991; Yike et al., 1999).

The authors of this paper were involved in sampling of three homes. Molds isolated and cultured from bulk samples obtained from the three homes revealed mycotoxins as follows: Home 1: satratoxins H and G, isosatratoxin F, roridin, 1-2, E and isororidin, epoxydolabellane A, MER 503; aflatoxin B, sterigmatocystin and cyclopanzoic acid; Home 2: roquefortine C, sterigmatocystin and 5-methyloxysterigmatocystin; and Home 3: sterigmatocystin, MER 503 and dolabellanes (Neville, P-K Jarvis unpublished reports). An 18-month-old male child in one of the homes died from pulmonary bleeding. In the other two homes, two women and a 7-year-old boy developed permanent neurocognitive deficits as well as increased sensitivity to various odorous chemicals. The latter three had changes in quantitative electroencephalograms (QEEG) involving the frontal cortex as well as other regions of their brains. The neurocognitive deficits were shown by testing performed by neuropsychologist Raymond Singer, PhD Santa Fe, New Mexico.

Airborne macrocyclic trichothecenes in contaminated buildings, control buildings and outdoor air were investigated (Brasel et al., 2005a,b). The Quant Tox Kit manufactured by Envirologix was utilized to detect satratoxin G and H, verrucarol, verrucarol and isosatratoxin F by an ELISA method with roridin A as the control. Air samples were collected using a Spin Con PAS bioaerosol sampler. The air samples were pulled through multistage polycarbonate filters of 5.0, 1.2 and 0.4 μm . The mycotoxins were present in all particulate fractions, particularly 0.4 to 1.2 μm . Briefly, macrocyclic trichothecene concentrations present in the fine particle fractions ranged from <10 to >1300 pg/m^3 , significantly greater ($p < .001$) than detection in control buildings and outdoor air. In addition, the trichothecenes were detected in the sera of symptomatic occupants of the same buildings vs controls ($p < .05$; Brasel et al., 2004). More recently, elevated macrocyclic trichothecenes were reported in flooded moldy dwellings in which *S. chartarum* was present (Charpin-Kadouch et al., 2006). Additionally, Bloom et al. (2007), using gas chromatography as well as HPL with tandem mass spectrometry, tested for the presence of trichothecenes (verrucarol, trichodermol, satratoxins G and H, trichodermol, gliotoxin, aflatoxins and sterigmatocystin) in

building materials and dust from water-damaged buildings and homes. Of 62 samples, 45 were positive for mycotoxins, three of eight settled dust samples and five of eight air dust samples were positive for macrocyclic trichothecenes and sterigmatocystin. Additionally, concentrations of various mycotoxins were as follows: building materials (gliotoxin at 0.43-1.12 pg/mg; sterigmatocystin at 4.9-50,000 pg/mg; trichodermol at 0.9-8700 pg/mg; verrucarol at 8.8-17,000 pg/mg and dust samples (aflatoxin B1 at 32.0-13,500 pg/cm²; sterigmatocystin at 3.6-10,900 pg/cm²; trichodermol at 6.5-170 pg/cm²; verrucarol at 25-3,400 pg/cm²; gliotoxin at 400 pg/cm²). In addition, verrucarol and sterigmatocystin were found in dust samples from Katrina homes (Bloom, 2008). Also, airborne satratoxin G and H were demonstrated in a contaminated home utilizing a 0.8- μ m filter and LC-MS/MS (Gottschalk et al., 2008). More recently, hydrophilic fungi and ergosterol were shown to be associated with respiratory illness in a water-damaged building (Park et al., 2008). Ergosterol is a biomarker for the assessment of mold damage (Foto et al., 2005; Hippelein and Rugamer, 2004). In conclusion, mycotoxins in damp indoor environments become airborne in both large (spores, hyphae fragments) and fine particles. They are also present in bulk in dust samples from the same buildings. In conclusion, multiple mycotoxins, e.g. trichothecenes, aflatoxins, gliotoxin, are prevalent in water-damaged homes and buildings.

The epipolythiodioxopiperazines (ETP) are a class of fungal toxins produced by several different genera of mold (Gardiner et al., 2005). One of the most abundant ETP is gliotoxin produced by *A. fumigatus*, *niger*, *terreus*, *flavus*, *Trichoderma virens*, *Penicillium spp.* and *C. albicans* (Gardiner et al., 2005; Lewis et al., 2005b). Gliotoxin is a virulence factor in invasive *A. fumigatus* in mice and probably for humans (Kupfahl et al., 2008; Lewis et al., 2005a,b; Sugui et al., 2007). Gliotoxin is an immunomodulating toxin with suppressive activity (Mullbacher et al., 1986; Sutton et al., 1994). It inhibits macrophage and polymorphonuclear cell function and generation of alloreactive cytotoxic T cell. The toxin inhibits the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), an integral part of the inflammatory immune response and controls expression of some cytokines. Finally, gliotoxin and other ETPs are mitochondrial poisons resulting in reduction of adenosine triphosphate (ATP) by hyper-polarization of the mitochondrial membrane and causing apoptosis (Gardiner et al., 2005; Pardo et al.,

2006). Gliotoxin has been identified in the lungs and sera of mice and cancer patients with aspergillosis (Lewis et al., 2005a). The percentage of *Aspergillus* species isolated from cancer patients with IA secrete gliotoxins as follows: *A. fumigatus* – 93%; *A. niger* – 75%; *A. terreus* – 24%; and *S. flavus* – 4% (Lewis et al., 2005b). Moreover, the production of gliotoxin by clinical and environmental isolates of *A. fumigatus* has been confirmed in Germany and Austria (Kupfahl et al., 2008). The percentage of *A. fumigatus* isolates that produced gliotoxin was clinical isolates – 98%; environmental isolates – 96%. The toxin was also detected in decreasing frequency in other isolated species: *A. niger* – 56%; *A. terreus* – 37%; and *A. flavus* – 13%. In conclusion, these observations make it imperative that more attention should be paid to *Aspergillus* species as well as other genera of molds and their production of gliotoxin. The need for an increased awareness of these molds is apparent with respect to the exposure of humans who have risk factors of corticosteroid usage, COPD, diabetes mellitus, pre-existing illnesses as well as altered immune function, e.g. autoimmune diseases.

Mechanism of neurological injury

Three independent sets of information have been used to discuss a plausible mechanism for neurological impairment observed in humans exposed to contaminated air. The first set includes clinical observations on humans exposed to water-damaged environments. The second entails animal experiments demonstrating neurological injury from mycotoxins instilled into the olfactory mucosa. The third set of data involves clinical and pathology of brain injury to children and young adults exposed to the polluted air of Mexico City.

Clinical findings in patients exposed to water-damaged buildings: Both central and peripheral neuropathy have been reported in individuals chronically exposed to damp indoor environments (Campbell et al., 2003; 2004; Crago et al., 2003; Gordon and Cantor, 2004, 2006; Gray et al., 2003; Kilburn, 2003, 2004; Rea et al., 2003). Briefly, exposed individuals develop peripheral neuropathy with autoantibodies directed against several neural antigens (Campbell et al., 2004). Toxic encephalopathy involves multiple symptoms, including loss of balance, recent memory decline, headaches, light-headedness, spaciness/disorientation, insomnia, loss of coordination (Gray et al., 2003; Kilburn 2003,

2004; Rea et al., 2003). Exposed individuals had alterations in QEEG involving the frontal cortex and other regions of the brains (Crago et al., 2003) coupled with neurocognitive decline (Crago et al., 2003; Gordon and Cantor, 2004, 2006; Kilburn, 2003, 2004) as well as significant changes in various neurological measurements (declines in simple reaction and choice reaction times, increased body sway with eyes open and closed, increased latency of blink reflex, and decreased grip strength, among others (Kilburn, 2003, 2004). The probable explanation of the causative mechanism comes from both animal models and humans exposed to air pollution.

Instillation of mycotoxins into the olfactory mucosa of rodents: Satratoxin G, roridin A and aflatoxin B1 instilled into the olfactory area cause sensory olfactory neuron loss, nasal and brain inflammation and neurotoxicity. The mycotoxins are transported into the brain along the olfactory tract leading to inflammation and damage in the tract and the olfactory bulbs. Tritium labelled aflatoxin B1 at 0.2, 1 or 20 μg was intranasally instilled in rats and followed by autoradiography and spectrometry. The mycotoxin was bioactivated in the olfactory/nasal mucosa and transported along the olfactory tract to the bulbs. Twenty-four hours after instillation, the olfactory epithelium was disorganized and undulating with pyknotic nuclei, shrunken cytoplasm and transport of the labelled aflatoxin to the olfactory bulbs. The pathology was still present at 5 days post instillation at 20 μg (Larsson and Tjalve, 2000). Satratoxin G was instilled into the olfactory mucosa in mice at 5 and 25 $\mu\text{g}/\text{kg}$ body weight. Apoptosis of olfactory neurons occurred along with the release of proinflammatory cytokines TNF- α , IL-6, IL-1 and MIP-2 in the nasal airways, ethmoid turbinates and olfactory bulbs. Marked atrophy of the olfactory nerve and glomerular layers of the bulb were observed (Islam and Pestka, 2006; Islam et al., 2006). Similarly, roridin A instilled into the olfactory mucosa of mice at 500 $\mu\text{g}/\text{kg}$ body weight induced apoptosis of olfactory neurons, atrophy of the olfactory epithelium and olfactory bulbs. The kinetics of the reported pathology was potentiated by the simultaneous exposure to lipopolysaccharide (Islam et al., 2007). Also, lipopolysaccharides enhance the hepatotoxicity of aflatoxin B1 in rats (Barton et al., 2001; Luyendyk et al., 2002, 2003). Finally, C-14 aromatic carboxylic acids are transferred unchanged into the brain and olfactory bulbs following intranasal instillation in mice (Eriksson et al., 1999). These observations point towards at least

one probable mechanism for the encephalopathy observed in humans exposed to the biocontaminants in damp indoor spaces.

Children and young adults living in Mexico City: Additional evidence for the role of particles and associated toxins as causation in the onset of toxic encephalopathy is derived from observations of children and young adults residing in Mexico City. Particulate matter in polluted outdoor air consists of fine and ultrafine particles to which toxins are adsorbed.

Autopsies were performed on children and young adults who had died suddenly and who did not have familial or personal history of neurological disease. Inhaled particles were observed by electron and light microscopy. They were distributed to organs (liver, spleen, kidneys, brain, within RBCs and heart), via the systemic circulation and/or by macrophage and dendritic cell activity and via the olfactory mucosa. Observations on the brains showed marked up-regulation of inflammatory markers in the frontal cortex, olfactory bulb, substantia nigrae, vagus nerve and disruption of the blood-brain barrier. Pathological observations included deposition of ultrafine particles, accumulation of amyloid β -42, α synuclein and increased expression of COX2 in the brains. These findings were observed in the frontal cortex, olfactory bulb, substantia nigrae and vagus nerve of affected individuals (Calderon-Garciduenas et al., 2004, 2008a,b,c; Peters et al., 2006). The pathology resembled that of Alzheimer- and Parkinson-like diseases (Calderon-Garciduenas et al., 2004; 2008b).

Clinically healthy children exposed to air pollutants have systemic inflammation and endothelial damage with significant increases in inflammatory markers (TNF- α , PGE2, C-reactive protein, IL-1 β , endothelin-1) with a concomitant down-regulation of soluble adhesion molecules (Calderon-Garciduenas et al., 2008c). Finally, exposed children exhibited significant deficits in short- and long-term cognition with neuropsychological testing. Over 50% of them had magnetic resonance imaging (MRI) findings of prefrontal white matter hyperintense lesions. Concomitantly exposed canines had the same MRI changes and increases in COX2 inflammatory markers, i.e. neuroinflammation (Calderon-Garciduenas et al., 2008a).

In conclusion, published observations point towards the role of fine particles in the exposure of occupants in water-damaged structures to mycotoxins and other biocontaminants (see below Endotoxins and MVOCs/VOCs). The observations include (1) particulates

<1.5 μm contain trichothecenes and are associated with growth of the mold (Brasel et al., 2005a,b); (2) the trichothecenes were detected in the sera of symptomatic individuals occupying the *S. chartarum* contaminated structures (Brasel et al., 2004); (3) trichothecenes and other mold by-products are present in particles <2 μm in other settings and are cytotoxic in the MTT assay (Johanning et al., 2002a,b); (4) trichothecenes are in the urine, blood, nasal and lung secretions of individuals exposed to molds in water-damaged homes (Croft et al., 1986; 2002; Hooper, 2008, personal communication); (5) finally, the blood concentrations of the haemolytic protein (stachylysin) of five symptomatic individuals exposed to *S. chartarum* averaged 371 nanograms/mL (Van Emon et al., 2003) and (6) toxic strains of *Bacilli*, *Nocardia* and *Streptomyces* were isolated from indoor air in the particle range of 0.56 to 2.1 μm (Peltola et al., 2001a,b).

VOCs and MVOCs

In general, VOCs and MVOCs are present in the indoor environment. Some of the sources for VOCs are building materials, cleaning agents, personal care products (perfumes), paints, furnishings, microbial growth, etc. (Kim et al., 2007; Lee et al., 2005). In addition, fungi and bacteria also produce VOCs, usually referred to as microbial MVOCs. The composition MVOCs varies according to substrate, humidity and species (Claeson and Sunesson, 2005; Gao and Martin, 2002; Gao et al., 2002; Korpi et al., 1999; Nilsson et al., 2004; Sunesson et al., 1996). The emitted MVOCs include limonene, hexanol, acetone, butanone, pentanone, 2-ethyl-1-hexanol, 1-butanol, 3-methyl-1-butanol, 2-methyl-1-propanol, terpineol, 2-heptanone, 1-octen-3-ol, dimethyl disulfide, 2-hexanone, 3-octanone, 2-pentylfuran, aldehydes, ammonia and various amine compounds (Claeson and Sunesson, 2005; Gao and Martin, 2002; Gao et al., 2002; Li and Yang, 2004; Nilsson et al., 2004; Korpi et al., 1999; Sunesson et al., 1996). For the sake of further discussion, the MVOCs and VOCs will be considered as VOCs.

Porous materials act as a sponge-adsorbing VOC, the latter from which re-emission occurs. Thus, regardless of the origin of the VOCs, adsorption to indoor dust, particles and porous surfaces occurs. Inhalation of dust and particles leads to deposition of the VOCs in the olfactory mucosa as well as the respiratory tract (Gorny, 2004; Nilsson et al., 2004; also see above fine particulates). Indoor VOC concentrations are higher than outdoor concentrations,

increasing human exposures to toxins (Kinney et al., 2002; Wallace et al., 1991). Children living in dwellings with elevated VOCs from microbes have a higher prevalence of asthma, fever, wheezing and irritation of the eyes (Elke et al., 1999). Fungal-related VOCs in damp buildings have been associated with increased nasal biomarkers of inflammation (cationic proteins, myeloperoxidase and albumin), increased blinking and a decrease in forced vital volume (FVC) (Walinder et al., 2001, 2005). In addition, fungal colonization of fiberglass insulation leads to the distribution of VOCs through the air conditioning system, which may be related to sick building syndrome (Ahearn et al., 1996, 2004). In conclusion, more attention needs to be paid to the contributions of VOCs to the adverse health effects in individuals residing in water-damaged building.

Extracellular proteins, enzymes, siderophores and haemolysins and pulmonary haemorrhage

Molds excrete extracellular enzymes and proteins to digest and absorb nutrients from substrates that include lipases, proteinases, chitinases, amylases, esterases, phospho-lipases, siderophores and haemolysins, among others (Birch et al., 2004; Donohue et al., 2005, 2006; Hu et al., 2004; Kudanga et al., 2007; Mellon et al., 2007; Moon, et al., 2006; Schretti et al., 2007; Vesper and Vesper, 2004; Vesper et al., 2004; Yike et al., 2007). Inhaled microbial proteinases cause inflammation in the respiratory tract, activating protease receptors with production of IL-6, IL-8 and release of IL6, IL-8, PGE2, granulocyte-macrophage colony-stimulating factor (GM-CSF). Neutrophils and eosinophils are recruited (Asokanathan et al., 2002; Chiu et al., 2007; Reed, 2007; Shin et al., 2006; Yike et al., 2005, 2007). In addition, siderophores that bind iron have a distinct role in *A. fumigatus* infections (Schretti et al., 2007).

An outbreak of infantile pulmonary haemosiderosis in Cleveland was associated with *S. chartarum*. A haemolysin (stachylysin) and a siderophore were identified from strains of *Stachybotrys* isolated from the infants' homes and from a lung of a child with pulmonary haemorrhage (Dearborn et al., 2002; Elidemer et al., 1999; Vesper et al., 2000). The Cleveland cases were criticized by the CDC for statistical errors and limitations in sampling procedures during the initial evaluation of the affected homes (CDC, 2000). However, recent observations indicate that species of mold other than *S. chartarum* secrete haemolysins.

Several of the mold genera were isolated from the dust of the Cleveland case homes. They were identified to species by quantitative polymerase chain reaction. The isolates were tested for the production of haemolysins (Vesper and Vesper, 2004). Eleven species of *Aspergillus*, ten species of *Penicillium*, two species of *Ulocladium*, *Paecilomyces variotii*, *Memnoniella echinata*, *Scopulariopsis brevicaulis*, *Trichoderma longibrachiatum* and *viride* and *S. chartarum* were demonstrated to cause haemolysis of sheep's blood agar. Haemolysins were more often produced by the fungi from homes with pulmonary haemorrhage (42%) than from reference homes (10%). These observations emphasize the complexity of damp indoor spaces and broaden the possible biological agents responsible for the adverse health effects to occupants of water-damaged indoor environments.

Galactomannans (EPS)

Galactomannans are cell wall polysaccharides consisting of a mannose back bone with galactose side groups. Other sugars include glucose, rhamnose, arabinose and xylose. They are highly branched with 1-2, 1-5 and 1-6 linkages and are released from the cell wall during growth (Notermans and Soentoro, 1986; Notermans et al., 1987, 1988). EPS are antigenic with 1-5 linked β -D-galactofuranosides being immunodominant from *Aspergillus/Penicillium* species (Kamphuis et al., 1992; Notermans et al., 1988). Antibodies against EPS have been detected in the sera of animals and humans (Notermans et al., 1987, 1988). EPS are present in the sera of immunocompromised organ transplant patients with IA (Pfeiffer et al., 2006). In addition, antigenic EPS are produced by species of *Rhizopus*, *Mucor*, *Rhizomucor*, *Absidia corymbifera* and *Syncephalastrum racemosum* (De Ruiter et al., 1992). EPS are readily detected in house dust of homes with reported dampness and are associated with respiratory symptoms in children (Douwes et al., 1999, 2003, 2006). They and 1-3- β -D-glucans are good markers for the overall level of fungal concentrations in dust and as a surrogate for estimating airborne fungal exposure (Chew et al., 2001). Thus, EPS are additional biocontaminants in damp indoor spaces and appear to be associated with respiratory symptoms in children.

1, 3- β -D-glucans

The 1, 3 β -D-glucans (glucans) are diagnostic markers for fungal infections, particularly, *Aspergillus* species, systemic candidiasis, and other fungi (Kondori

et al., 2004; Pazos et al., 2005; Pickering et al., 2004). However, PCR DNA analytical tests give earlier and more specific diagnostic results for infections (Khan et al., 2007; Musher et al., 2004; Rantakokko-Jalava et al., 2003).

The glucans have been demonstrated in the indoor air and dust and their presence is related to fungal growth and possible intrusion from outdoor sources (Chew et al., 2001; Douwes et al., 2006; Gehring et al., 2001; Rylander, 1999, 2004). The glucans cause airway inflammation. They have been identified in bronchoalveolar lavage fluid from individuals with acute eosinophilic pneumonia (Kawayama et al., 2003; Thorn and Rylander, 1998). Inhalation of glucans by healthy individuals caused an increase in eosinophilic cationic protein, TNF- α and a reduction of peripheral blood eosinophil numbers (Thorn et al., 2001). Similar observations have been reported in guinea pigs and mice treated with glucans (Fogelmark et al., 2002). In contrast, blood leukocytes from healthy volunteers and patients allergic to house dust glucans enhance the release of IgE and histamine in vitro (Holck et al., 2007). Thus, the effects of inhaled glucans may be different in eosinophilic pneumonia cases vs healthy and allergic individuals when tested in vivo compared to in vitro assays. Airway inflammation in adults with chronic exposure to glucans is associated with increased prevalence of atopy, a slight increase in myeloperoxidase and a decrease in forced expiratory volume (FEV₁; Thorn and Rylander, 1998). Moreover, children exposed to glucans in dust at home and at school have variability in pulmonary peak flow values as well as signs of airway inflammation (Douwes et al., 2000; Rylander, 1997, 1999; Rylander et al., 1998) and have a higher incidence of infections (Rylander, 2004). Finally, nasal deposition of glucans is not associated with acute inflammation with respect to an increase of the chemo-attractant eotaxin and eosinophils in nasal lavage fluid (Beijer and Rylander, 2005). Inflammatory response to 1-3 β -D-glucans involves toll-like receptors 2 (TLR2) and TLR4 receptors, MYD88 and Dectin-1 (Hohl et al., 2005; Meier et al., 2003; Wang et al., 2002). Finally, antibodies against glucans have been demonstrated in humans and animals exposed to molds (Kamphuis et al., 1992; Notermans et al., 1987, 1988). The detection of glucan antibodies suggests that inhalation of glucans and/or colonization/infection has occurred. In either event the antibodies to glucans demonstrate an immune response unrelated to IgE sensitivity. Also, glucans are in the blood of

patients with deep invasive mycosis and fungal febrile episodes and can be used to diagnose infections (Kedzierska, 2007; Miyazaki et al., 1995; Obayashi et al., 1995; Pickering et al., 2004). Additional work is needed to determine the role of glucans in respiratory inflammation. However, children seem to be more susceptible to exposure.

Endotoxins

Endotoxins are LPS complexes of the outer cell wall of gram-negative bacteria, usually pathogens such as *E. coli*, *Salmonella*, *Shigella* and *Pseudomonas*, etc. The LPS are maintained within the outer cell wall until autolysis of the bacteria, which releases them into the surrounding environment. They are pyrogenic (fever producing), antigenic and cause inflammation through the activation of the complement system via CD14 protein, the TLR4-signaling pathway and release of inflammatory cytokines, e.g. TNF- α . CD14 protein binds LPS and transfers them to the TLR4 receptor. Clinical or experimental outcomes include fever, leukopenia, hypoglycemia, hypotension, impaired perfusion of essential organs (brain, heart, kidney), activation of C3 and the complement cascade, bleeding, intravascular coagulation, septic shock and death. In addition, LPS also cause an increased production of the long pentraxin PTX3 (Cunningham et al., 2005; Imamura et al., 2007) and in the maturation of dendritic cells evoking Th1 and Th17 responses (Iwamoto et al., 2007). LPS are present in the indoor environment of normal and water-damaged homes and buildings (Douwes et al., 2006; Gorny, 2004; Gorny et al., 2002; Park et al., 2000, 2006; Rao et al., 2007b).

In transgenic mouse models, endotoxins interact with the TLR4-signaling pathway, CD14 phenotype, TNF- α and other factors leading to increased airway inflammation (Jung et al., 2006; Martinez, 2007a,b; Togbe et al., 2007). In addition, in vitro and in vivo animal models of neurological diseases have shown that intra-peritoneal (i.p.), i.v. and intracerebral administration cause expression of proinflammatory markers of microglia (Qin et al., 2004) as well as the induction of oligodendrocyte injury via TLR4 (Lehnardt et al., 2002). Intracerebral or systemic administration of endotoxin exacerbates microglial inflammatory response and increases neuronal cell death in ME7 prion mouse model (Cunningham et al., 2005). Moreover, systemic inflammation (e.g. infectious states) appears to be involved in chronic

neurodegenerative disease (e.g. Alzheimer, Parkinson). The increased synthesis of inflammatory cytokines and other mediators during infections and/or systemic LPS challenge promote an inflammatory response that may contribute to the progression of chronic neurological disease (Cunningham et al., 2005; Godbout et al., 2005; Perry, 2004; Polentarutti et al., 2000). Co-exposure of mice to vomitoxin and LPS caused a synergistic increase in TNF- α messenger RNA (mRNA) as well as plasma TNF- α and IL-6. Marked cell death (apoptosis) and loss occurred in the lymphatic organs, thymus, Peyer's patches, spleen and bone marrow (Islam et al., 2002; Zhou et al., 1999, 2000). The priming of mice with LPS lowered the dosage of deoxynivalenol causing up-regulation of inflammatory cytokines (IL- α and - β , IL6 and TNF- α) and massively increased the thymus apoptosis (Islam et al., 2002). Similarly, in vitro priming of TLR of murine macrophages and human whole blood cultures renders macrophages sensitive to exposure to mycotoxins and other xenobiotics. The LPS-sensitized macrophages have an increased production of mRNA of IL-1 β , IL-6 and TNF- α after exposure to deoxynivalenol (DON), satratoxin G and zeralenone (Pestka and Zhou, 2006). Also, administration of aflatoxin B1 and endotoxin to rats augments liver sinusoidal damage and clotting by converting soluble fibrinogen to insoluble fibrin clots (Luyendyk et al., 2003). Finally, nasal inflammation, inflammatory cytokine production and atrophy of the olfactory nerve and olfactory bulbs in mice are enhanced by the co-administration of LPS and roridin A (Islam et al., 2007). In conclusion, mold agents and LPS exposure are synergistic with adverse effects on organ systems, including the brain, leading to a systemic inflammatory response.

Inhaled LPS causes adverse airway responses in healthy individuals as well as individuals with asthma and other respiratory conditions. Healthy volunteers challenged with LPS had variable airway responsiveness (Kline et al., 1999). Eight sensitive subjects had at least a 20% decline in the FEV₁, at a dose of 6.5 μ g or less, while 11 hyporesponsive subjects maintained an FEV₁ at least 90% after inhaling 41 μ g of LPS. Peripheral monocytes from the hyporesponsive individuals released fewer IL-6 and IL-8 than the sensitive subjects.

The interaction between the environment and lung responsiveness is a complicated gene-environment interaction (Martinez, 2007a). The interactions involve TLR2 and -4 and IL-1 receptors as well as

polymorphism of CD14 protein (Liebers et al., 2008; Martinez, 2007b; Simpson et al., 2006). In addition, down-stream adaptor molecules, e.g. My88 and TRAM, are also involved (Tanimura et al., 2008). Furthermore, other genes (e.g. IL-13, DEFB1, TLR2, TRL4) seem to have a role in the phenotypic complex condition referred to as asthma. Apparently, IgE-mediated conditions are not the norm, while the role of IL-4, IL-5, eosinophils, and neutrophils are difficult to control (Martinez, 2007a,b). Thus, children with CC genotype at -159 of CD14 have a decreased risk of allergic sensitization to endotoxins while having an increased risk of non-atopic wheezing (Simpson et al., 2006). Also, it has been shown that the CC allele of CD14 is a risk factor for allergic phenotypes at a low concentration of endotoxins, whereas the TT allele is a risk factor for higher concentrations of LPS (Martinez, 2007b). In conclusion, gene and air pollution interactions in asthma and endotoxins are complex and require more genome-associated studies with better assessment of exposure and phenotype (London, 2007).

In conclusion, synergism between endotoxins and mycotoxins has been demonstrated in vitro and in animal models. As discussed above, LPS enhance the damage to the olfactory epithelium, tract and bulb of roridin A in mice. In addition, exposure to LPS and aflatoxin B1 enhances liver toxicity in rats. Treated animals had damage to sinusoidal cells and hepatocytes with increased alanine aminotransferase and fibrin deposition (Barton et al., 2001; Luyendyk et al., 2002, 2003). Oral administration of vomitoxin with simultaneously injected LPS in mice produced a significant enhancement of TNF- α , IL-6 and IL-1 β in spleen cells (Zhou et al., 1999). A similarly designed study resulted in an increase of apoptosis of lymphocytes in the spleen, thymus and Peyer's patches (Zhou et al., 2000). Finally, in vitro priming of murine and human whole blood macrophages enhances the proinflammatory cytokine production (Pestka and Zhou, 2006). Two questions arise from these observations: (1) What role does the genetic polymorphism CD14 protein have in synergism of LPS and mycotoxins? (2) Are the children with CD14 CC genotypes more or less sensitive to the inflammatory conditions caused by mycotoxins?

Discussion and Conclusion

Damp indoor spaces create environments in which molds and gram negative and positive bacteria

flourish. In the process of normal organism growth or in response to a change in environmental conditions (e.g. less moisture, human activity, etc.), the microorganisms produce a variety of biocontaminants that impinge upon occupants. A comprehensive review of published peer-reviewed literature, as we have done, clearly shows evidence of deleterious effects on occupants exposed to indoor biocontaminants. Data from in vitro and animal models support this conclusion. The weight of the findings lies with multiple authors publishing in a variety of professional journals, who have arrived at similar conclusions. For example, asthma in adults and children as well as clusters of rheumatic conditions have been attributed to fungal and bacterial contaminants (Jaakkola and Jaakkola, 2004; Luosojarvi et al., 2004; Myllykangas-Luosujarvi et al., 2002; Nevalainen and Seuri, 2005; Park et al., 2008). Neurological sequelae have been reported to include peripheral and central neuropathy, alterations in QEEG and neurocognitive deficits (Campbell et al., 2003, 2004; Crago et al., 2003; Gordon and Cantor, 2004, 2006; Kilburn, 2003, 2004; Rea et al., 2003). In addition, multi-organ symptoms are present in occupants (Croft et al., 1986, 2002; Gray et al., 2003; Hodgson et al., 1998; Johanning et al., 1996, 1999; Rea et al., 2003). Finally, trichothecenes and stachylysin were demonstrated in the sera of individuals exposed to *S. chartarum* (Brasel et al., 2004; Van Emon et al., 2003). These observations and others cited in this review indicate that a systemic inflammatory response is occurring and the synergism of the biocontaminants, particularly LPS and mycotoxins, probably plays a significant role in this response.

Regardless of the sizeable body of evidence documented in scientific and medical literature, the major focus of governmental agencies and medical universities has been directed towards allergies and asthma in regard to mold exposures. However, the literature indicates otherwise. Occupants exposed to multiple biocontaminants in indoor environments develop multi-organ symptoms indicating that a systemic inflammatory response is occurring. A general systemic inflammatory is characterized by the presence of proinflammatory agents (TNF- α , IL-1, myeloperoxidase, C-reactive proteins, neutrophils, lymphocyte activation markers, etc.) in the systemic circulation (Rylander, 2004). Furthermore, when the synergism and interactions of the biocontaminants are considered, it can only be concluded that multiple systemic health effects in humans and animals are not only

occurring but are scientifically and medically explicable. For example, the toxic interactions between LPS and mycotoxins are synergistic in vitro and in vivo. Additional examples include cytotoxicity of spores from co-cultured *S. chartarum* and *S. californicus*. The toxic effects mimic chemotherapeutics doxorubicin and actinomycin D. The gram positive *Actinomycetes* (*Streptomyces* and *Nocardia*) and other gram positive bacteria produce exotoxins that damage mitochondria. *Streptomyces*, *Nocardia* and *Mycobacterium* species are potential human pathogens with corticosteroids, diabetes mellitus, COPD and immunocompromised conditions as risk factors. *Streptomyces* and *Mycobacterium spp.* cause hypersensitivity pneumonitis. Of concern is the rise of biocontaminant-related diseases worldwide, which must be paid heed. According to the American Thoracic Society, NTM is increasing in immunocompetent individuals. Since *Mycobacterium* is a common environmental contaminant, attention should be paid to both indoor and outdoor sources. In addition, IA is also on the increase in immunocompetent patients. The risk factors for IA are corticosteroids, diabetes mellitus, COPD and extensive use of antibiotics. It is important to understand that corticosteroids inhibit the oxidative pathways of AM, which are the first line of innate immune system defense against foreign organisms. Finally, gliotoxin, a virulence factor, is produced by both clinical and environmental isolates of *A. fumigatus*, *A. terreus*, *A. niger* and *A. flavus*. Furthermore, gliotoxin has been identified in the sera and lung secretions in humans and mice with aspergillosis. We must determine the significance of gliotoxin in water-damaged buildings and its correlation with the rise of IA in immunocompetent individuals.

Currently, the concept of Th1/Th2 interactions in inflammatory response to molds is under challenge. Apparently, mouse and human Th17 cells, IL-17, IL-23 and related mediators have a key role in promoting inflammation and impair antifungal immune resistance in lungs and CRS (Romagnani, 2008; Romani and Puccetti, 2008; Romani et al., 2008; Zelante et al., 2007). Interestingly, tryptophan catabolites (kynurenines) and mouse Treg T cells have a protective effect in taming overzealous exaggerated inflammatory responses. IL-17 and IL-23 pathway down regulates the tryptophan catabolism (Belladonna et al., 2006; Romani et al., 2008). Other advances in understanding the inflammatory response to bacteria and molds are occurring rapidly. Long PTX3 (prototype protein of pentraxin) is essential for

resistance to *A. fumigatus* and other pathogens (Gaziano et al., 2004). PTX3 is released from lung epithelial cells, dendritic cells, macrophages and neutrophils by TNF- α , IL-10 and endotoxins (Doni et al., 2006; Imamura et al., 2007; Jaillon et al., 2007). Increased expression of PTX3 leads to an enhancement of acute lung injury and inflammation (Gaziano et al., 2004; Han et al., 2005). On the other hand, in a mouse model of aspergillosis, administration of appropriate doses of PTX3 gave complete resistance to infection and reinfection. The protective effect was similar or superior to that observed with liposomal amphotericin B or deoxycholate amphotericin B. In addition, PTX3 accelerated recovery of phagocytosis and Th1 lymphocytes with a concomitant decrease in inflammation. Interestingly, PTX3 potentiated the therapeutic efficacy of sub-optimal doses of deoxycholate and amphotericin B (Gaziano et al., 2004). Thus, recent advances in research have revealed that reactive proteins (PTX3) and Th17 lymphocytes impart pathology observed in chronic inflammatory conditions in humans and rodents. The recent information clearly demonstrates that non-IgE allergic mechanisms have a major role in chronic inflammation caused by microbial infections (Chenz and O'Shea, 2008; Gaziano et al., 2004; He et al., 2007; Iwamoto et al., 2007; Korn et al., 2007; Mauri et al., 2008; Muller et al., 2001; Romagnani, 2008). At least two of the mediating factors are long PTX3 and IL-17. It appears from the reviewed literature that long PTX3 is the inflammatory reactive protein that should be monitored in a variety of chronic diseases.

In conclusion, the medical profession worldwide should add to its basic curriculum detailed information on the health effects of the multi-biocontaminants present in water-damaged buildings. Diagnostic tests should be developed and recommended to determine the nature of building-related illness, e.g. allergy, hypersensitivity pneumonitis, encephalopathy, fungal infections, bacterial infection, etc. Finally, the medical profession must recognize the importance of immediate removal of occupants from the toxic environment. Government agencies and medical universities need to increase research to continue to further solidify knowledge regarding health impacts that multi-biocontaminants have on human and animal occupants. Preventing exposure to indoor biocontaminants is the most effective way for society to avoid the illnesses they cause. When exposure has already occurred, immediate removal of the occupant(s) from the contaminated environment is paramount and will

minimize further damage to health. Proper diagnoses will enable affected individuals to either remediate the contaminated structures, if possible, or locate other housing and/or work environments. Increased awareness of the potential health hazards of indoor biocontaminants is the first step in managing – and ultimately reducing – the illnesses they induce. As pointed out in the preface to this issue, “If everything has to be double-blinded, randomized and evidence-based, where does that leave new ideas?” (Kilburn, 2009).

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Declaraton of Conflict of Interests

Dr Thrasher is an independent consultant without a monetary affiliation with public or private organizations. He has been involved as an expert witness in both plaintiff and defense cases involving toxic exposures to a variety of contaminants. He is currently the Director of Toxicology for the National Toxic Encephalopathy Foundation, a non-profit corporation, located in Las Vegas, Nevada, USA. Ms Crawley recently joined the office of Dr Thrasher. She is not affiliated with public or private organizations. She reviews and extracts medical records of individuals exposed to toxins. She assists and counsels people who have post-traumatic stress syndrome.

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