BIOAEROSOLS AND HEALTH EFFECTS: RECOGNITION AND EVALUATION

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Indoor Biological Contaminants - Health Effects, Assessments, and Sampling
Bioaerosol –Related Health Issues

- Complex problems
- Multidisciplinary investigators
- Detailed, comprehensive & interactive evaluation
Multidisciplinary Interaction

- Physician
- Remediator
- IH IEQ Evaluator Bldg Scientist
- Lab
- Insurance Company
- Employer
- Affected Person

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Detailed, Systematic, & Comprehensive Environmental & Medical Investigative Strategy

- Data gathering and definition of scope of problem
- Hypothesis development
- Diagnostic testing
- Remediation/control/treatment
- Test effectiveness of interventions (clearance sampling/medical follow-up)
IAQ Health Determinants

- Complex mixtures of biological, chemical and physical agents
- Varied host vulnerabilities
- Psychosocial dynamics of human interactions
Medical Evaluation and Treatment/Remediation

- Characterize exposure
- Document disease
- Identify causal linkages
- Intervene/manage
Exposure of Building Occupant

- Nature, dose, duration of exposure
- Transmission and exposure routes (inhalation, mucosal, dermal, ingestion)
- Variables affecting absorption, distribution, metabolism, excretion
Variables Affecting Absorption

- Size of particles
- Chemical composition of offending agents
- Activity of occupant (respiratory rate)
- PPE/clothing worn
# Respiratory Deposition of Particles

<table>
<thead>
<tr>
<th>Chemical Characteristics</th>
<th>Anatomic Level</th>
<th>Size</th>
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<tbody>
<tr>
<td>Water Soluble (SO₂ and nitric acid vapors)</td>
<td>Nasopharynx</td>
<td>≥ 10 µm</td>
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<tr>
<td></td>
<td>Larynx</td>
<td></td>
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<tr>
<td>Low Water Solubility (NOₓ and O₃)</td>
<td>Conducting Airways</td>
<td>2.5 - 6 µm</td>
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<td></td>
<td>Distal Airways &amp; Alveoli</td>
<td>0.5 - 2.5 µm*</td>
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<td></td>
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<td>*&lt; 0.5 µm are exhaled</td>
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Host Differences Affecting Susceptibility

- Genetic make-up
- Immune System
- Nutritional status
- Metabolism
- Prior disease
- Reserve capacity of an organ
Subpopulations With Potentially Increased Responsiveness to Indoor Air Pollutants

- Infant/young children
- Elderly
- Chronic respiratory/cardiac disease
- Smokers
- Asthmatics
- Hypersensitivity disease (allergy)
Varied Host Vulnerability: Immune Status

- Hypersensitive
  - immunologic responses to antigens ("foreign" proteins/glycoproteins)

- Immuno-compromised (eg., AIDS, cancer/chemotherapy)
  - infection

- Immunocompetent
  - pre-existing asthma or RADS
Bioaerosols

- Airborne particles, large molecules, or volatile compounds that are living or released from living organisms
  - Reservoir
  - Amplification
  - Dissemination
Indoor Bioaerosols

- Fungi
- Bacteria
  - ↑ gram negative – ↑ moisture
  - ↑ gram positive – inadequate ventilation
- Viruses
- Protozoa
- Allergens (mold, dust mites, pet allergens, rodents & cockroaches)
Microbial Agents

- Intact organisms
- Constituents of cell walls
  - Endotoxin
  - Beta-(1,3)-D-glucan
- Metabolites
  - Microbial volatile organic compounds (MVOCs)
  - Mycotoxins
Health Effects

- Hypersensitivity disease
  - Allergic rhinitis (and sinusitis)
  - Asthma
  - Hypersensitivity pneumonitis (extrinsic allergic alveolitis)
- Inhalation fever
- Infection (↑ed in immunocompromised)
- Toxic
- Irritant
Endotoxin

- Lipopolysaccharide component of gram-negative bacterial outer cell wall
- Exposure to moisture sources, organic dusts, water-based fluids, metal-working fluids, and residential presence of dogs and increased amounts of settled dust
- Epi studies
  - Inhalation fever
  - Granulomatous pneumonitis
  - Non-allergic wheezing
  - "Hygiene hypothesis"-inverse association between early chronic mucosal exposure to LPS and risk of sensitization and allergic disease
Beta-(1→3)-D-Glucans

- Polyglucose polymers in cell walls of fungi, some bacteria and plants
- Immunomodulators
- Epi studies
  - Dry cough/itching skin (Rylander et al. 1992. Indoor Environment 1:263-267.)
- HA
- Fatigue
- Airway eosinophilia (Fogelmark et al. 2001.10(1):9-13.)
MVOCs

- Metabolic product of fungi & bacteria
- Mucous membrane and respiratory tract irritation
- Exacerbation of asthma
- CNS symptoms (HA, concentration difficulty, dizziness) and fatigue
- Symptoms resolve after removal from exposure
Mycotoxins

- Secondary metabolite – non-volatile, low m.w. organic compounds, without a specific role for the fungus that produces it
- Variable production based on nutrient limitation and aeration (unknown for most fungi)
- Spores (viable and nonviable) may produce toxins (and are potentially allergenic)
- Release of inflammatory mediators
- Carcinogens
- Pulmonary macrophage function interference/death
Stachybotrys Chartarum (atra)

- Growth
  - Fastidious, on material with high cellulose and low nitrogen content in settings with significant moisture (cellulose-based agar, moist filter paper medium)
  - Spores in slimy mass (when airborne-significant finding)
- Mycotoxins produced - trichothecenes
Trichothecenes

- Greater than 180 derivatives
- Biomarker studies at initiation
- Most potent small molecule inhibitor of protein synthesis
- Ingestion-immunosuppression/death in animal studies
- Unproven inhalation route effects: dermatitis, cough, rhinitis, nosebleeds, pharyngitis, conjunctivitis, headaches, fatigue, malaise, low-grade fever, focal alopecia, recurrent cold and flu-like symptoms
IOM Summary: Association Between Health Outcome and the Presence of Mold or Other Agents Indoor Environments

- **Sufficient Evidence of a Causal Relationship**
  - no outcomes

- **Sufficient Evidence of an Association**
  - upper respiratory (nasal and throat) tract symptoms
  - asthma symptoms in sensitized asthmatic persons
  - hypersensitivity in sensitized patients
  - cough, wheeze
  - Hypersensitivity pneumonitis in susceptible persons

- **Limited or Suggestive Evidence of an Association**
  - Lower respiratory tract illness in otherwise healthy children

Damp Indoor Spaces and Health, The National Academies Press, 2004
IOM Summary

- Inadequate or Insufficient Evidence to Determine Whether an Association Exists
  - Asthma development, airflow obstruction and lower respiratory illness in healthy Adults, dyspnea, COPD, mucous membrane irritation
  - Acute idiopathic pulmonary hemorrhage in infants
  - Skin symptoms
  - GI tract problems
  - Fatigue
  - Rheumatologic and other immune diseases
  - Inhalation fevers (non-occupational exposures)
  - Cancer
  - Reproductive effects

Damp Indoor Spaces and Health, The National Academies Press, 2004
- Molds are “common”, and are allergens
- For allergic individuals, health effects are limited to rhinitis and asthma; sinusitis may occur secondarily
- Fungal infections are rare, except in immunocompromised
- “Molds growing indoors are believed by some to cause building-related symptoms. Despite a voluminous literature on the subject, the causal association remains weak and unproven, particularly with respect to causation by mycotoxins. One mold in particular, Stachybotrys chartarum, is blamed for a diverse array of maladies when it is found indoors. Despite its well-known ability to produce mycotoxins under appropriate growth conditions, years of intensive study have failed to establish exposure to S. chartarum in home, school, or office environments as a cause of adverse human health effects. Levels of exposure in the indoor environment, dose-response data in animals, and dose-rate considerations suggest that delivery by the inhalation route of a toxic dose of mycotoxins in the indoor environment is highly unlikely at best, even for the hypothetically most vulnerable subpopulations.”

American Academy of Allergy Asthma and Immunology - agreement with ACOEM and IOM
Novel Considerations

- Islam Z et al. 2006. EHP 114(7): 1099-1107 “Single low dose of satratoxin G administered directly into noses of mice selectively killed sensory neurons involved in detecting odors and sending signals to the olfactory bulbs in the brain.”
Classification of Immunologic Reactions
(Gell and Coombs)

Type I: Anaphylactic or Immediate – type hypersensitivity
- Antigen binding to IgE on basophils/mast cells → release of mediators of inflammation

Type II: Cytotoxic Reactions
- IgG or IgM bind to cell – bound antigens → host cell destruction (e.g. newborn Rh hemolytic anemia, immune hemolytic anemia)
Classification of Immunologic Reactions
(Gell and Coombs)

Type III: Immune complex reactions
- Antigens binds to antibodies (IgG or IgM) forming immune complexes in tissues or vasc. endothelium → complement activating, chemotaxis → tissue injury (e.g. serum sickness, types of nephritis)

Type IV: Delayed hypersensitivity
- Mediated by T lymphocytes (cell-mediated immunity) (e.g. HP, contact dermatitis, TB skin test)
Hypersensitivity: Type I Allergic Reaction (Gell and Coombs Classification)

- Immunoglobulin E (IgE) mediated
- Immediate allergic response
- Clinical expressions
  - Rhinitis
  - Asthma
  - Dermatitis
- Most common hypersensitivity response to fungi
Likelihood of Individual Development of Allergic Disease

- **Genetic**
  - Two atopic parents – 47%
  - One atopic parent – 24%

- **Environmental**
  - Magnitude and pattern of allergen exposure
  - Age at which exposure occurs
  - Co-existing factors
Sensitization Requires:

- Genetic capability to respond to Antigen (Ag)
- Sufficient exposure to Ag (oft repeat exposures to high concentrations)
- Time for immune reaction to occur
Sensitization/Challenge

Allergen/antigen

Macrophage (antigen-presenting) secretes interleukins (ILs)

Stim. T lymphocyte secretes ILs

Stim. B lymphocyte with differentiation

Into plasma cells

Produce IgE

IgE binds to basophil in blood

Cells migrate to nasal mucosa & pulmonary interstitium

> Release of vasoactive amines

IgE binds to mast cell in tissue
Rhinitis

- Affects 40 million Americans
- Nasal itching, irritation, and congestion; watery nasal discharge; sneezing; itching of the eyes, ears, and throat; and fatigue
- 38% with rhinitis also with asthma
- 3.8 million lost work days/year
Rhinitis/Sinusitis

- Inflammation of nasal mucosa
- Thickening of nasal mucosa
  - ↑ nasal & pharyngeal drainage (poss. purulent)
- HA; ear, throat, facial pain; halitosis; fever; cough
- Impaired work and learning efficiency
Asthma

- Increased prevalence (approx. 60%) over past 25 years
  - 7.5 % of US adult population
- Most common chronic childhood illness
- Pathology
  - Airway inflammation
  - Mucosal edema
  - Mucous secretion
  - Increased vascular & epithelial permeability
  - Smooth muscle hypertrophy/constriction
- Airway remodeling – chronic inflam. leads to structural changes in the airway wall, e.g. thickening of the sub-basement membrane with deposition of collagen
Asthma

- Manifested by bronchospasm
  (symptoms: cough, chest tightness, wheezing)

- Causation – complex interaction of exposures (e.g. allergens, endotoxin, particulate/chemical irritants) and genes affect pathophysiologic pathways:
  - Atopy (allergic disease)
  - Airway inflammation
  - Airway hyperresponsiveness

- Co-morbidity with allergic rhinitis
Factors Contributing to Increased Asthma Prevalence

- Air pollutant exposure (tobacco smoke, ozone, diesel exhaust) (Gilmour et al. 2006)
- Indoor exposures to allergens and other biologics
- Increased incidence of obesity
- Decreased exercise
- Change in diet
- Decreased exposure in early life (hygiene hypothesis)
- Increased viral respiratory infections
Bioaerosols and Asthma

- **Increased risk of asthma**
    - The prevalence of symptomatic (active) asthma increased with increasing Alternaria conc. in 831 US homes in 75 different locations in US.
  - Thorne PS et al. Endotoxin exposure is a risk factor for asthma: the national survey of endotoxin in United States housing. Am J Respir Crit Care Med. 2005 Dec 1;172(11):1371-7

- **Increased asthma severity**
    - “a statistically significant association between severe asthma and sensitization to molds.”
Hypersensitivity Pneumonitis

- Type IV hypersensitivity reactions
- Repeated exposures to bioaerosols (e.g., Thermophilic actinomycetes, avian antigens, fungi) and chemicals (isocyanates)
- Variable clinical expression 4-8 hrs after exp:
  - cough, dyspnea, fatigue, fever, chills
  - lung exam and CXR-nl or abnl
  - precipitins (IgG) - markers of exp/not dxic
    - do not establish the time or degree of bioaerosol exp.
- Risk of chronic disease, if exp not d/ced

Beckett W et al. Environmental Health Perspectives 113(6):767-770. Exposure to metalworking fluids with microbiologic contamination associated with hypersensitivity pneumonitis
A. Detailed Medical/Environmental History: Cornerstone of Exam
1. Characterize symptoms/illnesses
   - onset, temporal relation to location/activities
   - co-occupants with similar problems
2. Define: - pre-existing disease
   - family history
   - medications
   - behavioral habits (i.e. smoking, alcohol)
3. Characterize bioaerosol, chemical, and particulate specific exposure or ambient conditions (dampness, H₂O intrusion,
   visible mold, odors) in:
   - occupation
   - residence
   - recreation
   with attention to nature, duration, and degree of exposure
Bioaerosol Health Evaluation (cont’d)

C. Diagnostic Testing (Judicious!)
   - Spirometry, full pulmonary function tests with lung volumes and diffusing capacity, challenge testing, peak flow measurements
   - CXR, CT scan, lung biopsy, BAL
   - Allergy testing – skin & RAST, IgE, IgG (sensitivity, specificity, reagents)

D. Review of results of bioaerosol sampling/building investigation
   (possible on-site assessment guided by Industrial Hygienist)

E. Diagnosis of disease, potentially establish causal association with building

F. Treatment of specific health problem

G. Potentially relocate/remove patient from environment
   (severity of exposure or disease, or immunocomp)

H. Remediate environment

I. Evaluate clearance sampling

J. Monitor patient in remediated environment (e.g. symptoms, peak flow)
BRI Health Investigation Tools/Methods

- Interview occupants with complaints (building or health)
- Interview other occupants (unaffected)
- Interview & review records of medical personnel on-site
- Interview building administrators/facilities managers
- Questionnaire survey of entire occupant population
- For potentially “adversely affected” occupants
  - review of medical records
  - discussion with treating physicians
  - interview/direct medical evaluation
Recommendations Based on Flaws of Previous Studies: Let’s make the gray more black and white

- **Exposure characterization:**
  - Evaluate the full spectrum of offending agents present, and include them when making associations with health outcome.

- **Health evaluation:**
  - “The practice of performing large numbers of nonspecific immune-based tests as an indication of mold exposure or mold-related illness is not evidenced based and is to be discouraged.” AAAAI Position Statement, 2006
  - If available and applicable, select objective diagnostic tests which provide pathophysiologic information concerning a specific health endpoint, e.g. pulmonary function studies when assessing asthma.
Achieving Black and White: Scientific Clarity and Professional Ethics

- Collaborative, interdisciplinary, systematic investigations using:
  - relevant animal models
  - objective markers of exposure and illness
  - appropriate epidemiologic techniques
  - examination of confounding factors

- Continue our professional practices with prudent respect for all the potential adverse effects of bioaerosols and with responsibility for the physical and psychological health of the affected individual
Recommended Criteria for Professionals Involved in Bioaerosol Investigations

- Education, experience, certification

- Detailed, systematic, and comprehensive protocol based on:
  - purpose of the investigation
  - exposure potential
  - unique susceptibilities of hosts
  - limitations of sampling/dxic testing and laboratory techniques
  - knowledge and application of the scientific literature

- Presentation of results clearly and understandably

- Communication/collaboration with and respect for other professionals with
  the common goal of assisting the affected individual/s
  (understanding of boundaries of one’s professional expertise)

- Adherence to professional ethics, and agreement with full disclosure of evaluation results
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Dr. Elissa Ann Favata is President and Executive Medical Director of Environmental & Occupational Health Associates, P.A., Cherry Hill, NJ, a private consulting practice providing health risk assessment, clinical medical services, and education. She is Board-certified in both Preventive/Occupational Medicine and Internal Medicine, and is a Fellow of the American College of Physicians, the American College of Preventive Medicine, and the American College of Occupational & Environmental Medicine. Dr. Favata is a Clinical Associate Professor in the Department of Environmental and Community Medicine of The UMDNJ-Robert Wood Johnson Medical School, as well as an Affiliate Member of EOHSI (Environmental and Occupational Health Science Institute). Her principal interests include the study of health effects related to exposure to indoor air contaminants (particularly biologic aerosols) and to chemical toxins/hazardous waste. Clinically, she has performed numerous IAQ health risk assessments in multiple settings, particularly in schools; as well as clinical evaluations and treatment of individuals with indoor air-related health problems for the past 23 years. Dr. Favata’s other professional activities related to indoor air and bioaerosols include: consulting to the New York City Department of Health in preparation of the April 2000 “Guidelines on Assessment and remediation of Fungi in Indoor Environments”; lecturing in U.S. professional settings as well as to European U.S. Army Occupational/Public Health Professionals; and authoring “Emerging Microbial Diseases of the Indoor Environment” in the text Occupational & Environmental Infectious Diseases, 2000. Dr. Favata also serves on numerous state and federal government advisory boards, including the Occupational Health Surveillance and Asthma Advisory Board of the New Jersey Department of Health, in which she serves as co-chair in the section on Clinical & Industrial Hygiene Consultations. Finally, she has also served on the Scientific Advisory Committee on Special Studies of Health Effects of Agent Orange Exposure under the auspices of the U. S. Secretary of Health and Human Services.