ACMT National Journal Club: Scientific Review of Human Health Effects of Indoor Mold Exposure

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Diseases associated with mold

- Cutaneous infections, Systemic
- Allergic
  - Asthma, Hypersensitivity pneumonitis
  - Allergic Bronchopulmonary Aspergillosis
- Toxin related
  - Trichothecenes: T-2 toxin, Satratoxin
    - Inhibitors of protein synthesis (peptidyl transferase)
      - Ingestion: Alimentary Toxic Aleukia
Are respired mold, mold products toxic?

- 1990s: claims that moldy indoor environments led to systemic disease
  - Idiopathic Pulmonary Hemorrhage
  - Systemic complaints, chronic fatigue
  - Cognitive difficulties, memory loss
• Litigation bonanza in early 2000s
  – Ed McMahon settles for $7.2 million, claimed that mold sickened him and his wife and led to death of his sheepdog Muffin
  – California family wins $22.6 million settlement over claim that toxic mold caused brain damage and autism in their infant

• This litigation begins to ebb by mid-2000s
Today’s papers

- Update: Pulmonary Hemorrhage/Hemosiderosis Among Infants-Cleveland, Ohio, 1993-96. MMWR 1997;46:33
- Update: Pulmonary Hemorrhage/Hemosiderosis Among Infants-Cleveland, Ohio, 1993-96. MMWR 2000;49:180
- Indoor mold, toxigenic fungi, and (*Stachybotrys chartarum*): Infectious disease perspective. Clin Microbiol Rev 2003;16:144
Report of 8 cases of pulmonary hemorrhage/hemosiderosis in infants from Rainbow Babies Children’s Hospital in Cleveland OH

- All were black, 7 male
- Only 3 were diagnosed at Rainbow Babies in the decade prior
- Tight geographical cluster
- Report that case control study is underway
• 7 cases of pulmonary hemorrhage/hemosiderosis in infants from Wyler Children’s Hospital in Chicago, IL
  – Reported as a result of the investigation surrounding the cases identified in Cleveland
  – 6 were black, 4 male
  – Preceding 3 years only 1 child diagnosed at Wyler
  – No geographical Cluster
MMWR January 1997

- Case Control of 8 Cases from MMWR report in 1994, plus an additional 2 cases identified after publication.
Case Control Study

- January 1993- December 1994
  - 10 cases, 1 death
  - Aged 6 weeks-6 months
  - Close proximity
  - Water damaged homes
## Case-Control Study
(of infants identified ‘93-’ 94)

<table>
<thead>
<tr>
<th></th>
<th>Case infants (n=10)</th>
<th>Control Infants (n=30)</th>
<th>P-value/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>9/10</td>
<td>15/30</td>
<td>P&lt;.05</td>
</tr>
<tr>
<td><strong>Breastfed</strong></td>
<td>0/10</td>
<td>11/30</td>
<td>OR .2, 95% CI: 0-1.2</td>
</tr>
<tr>
<td><strong>Household smokers</strong></td>
<td>9/10</td>
<td>16/30</td>
<td>OR 7.9, 95% CI: .9-70.6</td>
</tr>
<tr>
<td><strong>Residence with major water damage</strong></td>
<td>10/10</td>
<td>7/10</td>
<td>OR 16.3, 95% CI: 2.6-∞</td>
</tr>
<tr>
<td><strong>Stachybotrys Atra quantity</strong></td>
<td>?</td>
<td>?</td>
<td>OR 1.6, 95% CI: 1-30.8</td>
</tr>
</tbody>
</table>

*Table reconstructed from data presented in text*
...more cases identified...

• Surveillance identified 11 more cases from 1995-1996
  – Similar demographics and clinical presentations
  – 2 deaths

• Review of postmortem examinations of infant deaths from 1993-1995 (172 records)
  – Additional 6 cases identified
    • hemosiderosin laden macrophages in alveoli
    • 3 male, 2 siblings
    • Same demographic
Conclusion of Case-Control Study

• “These findings documented an association between acute pulmonary hemorrhage/hemosiderosis in this cluster of cases and mold growth in their water-damaged homes.”

• “The water damage may have promoted the growth of fungi, including *S. atra*”
Critique of previously published case-control study
  - Characterization of the problem
  - Association with water damage
  - Analysis Methods
  - Sample collection
  - Identification of S. Atra in water damaged homes
Critique #1

– Characterization of clinical problem
  • “Hemosiderosis”
    – Pathological finding not associated with specific disease
    – Therefore retrospectively identified cases & Cleveland cases are not necessarily associated with the original cluster
Critique #2

– Association with water damage
  • Limited descriptive information provided
    – Water damage criteria?
    – Contamination or exposure?
Critique #3

• Analysis Methods
  – Incorrectly calculated airborne calculations of S. Atra (OR 9.8 → 5.5)
  – Delayed sample collection in 1 case (OR 5.5 → 1.9)
  – Illogical age matching (OR 1.9 → 1.5)
Critique #4

• Sample Collection
  – Incomplete blinding
  – Samples collected from inferred case homes were collected differently
    • Aggressive, non-standarized methods used may have falsely inflated the results
Critique #5

- Presence of any *S. Atra* in water damaged homes
  - Similar percentage in case and control homes
Conclusions

• “Serious shortcomings in the collection, analysis, and reporting of data resulted in inflated measures of association and restricted interpretation of the reports. The associations should be considered not proven; the etiology of AIPH is unresolved.”
Aftermath of Cleveland “Cluster of IPH”

- Despite the caution “that further research is needed to determine causality”
  - Near-panic followed
  - Public buildings, schools, etc. were closed
  - Major clean-ups ordered (Hazmat level A)
  - Plethora of litigation
  - Many testing & remediation companies form
Health and immunology study following exposure to toxigenic fungi (*Stachybotrys chartarum*) in a water-damaged office environment. Johanning E, et. al. Int Arch Occup Environ Health 1996;68;207-218

- The setting: a water damaged urban office space that occupies several below ground levels
- The building had flooded and had visibly contaminated sheet rock, insulation, carpeting and ventilation ducts
- The investigation was prompted by workers in office claiming health related effects
• Perform air sampling, surface scrapings for fungi and mycotoxins

• Workers complete a long health questionnaire
  – “Cumulative symptom complex scores....were formed”
  – no definitions, unclear if they have ever been validated
  – authors are not blinded

• Comprehensive battery of immunologic tests
• “Participants under medical treatment for related problems and using medications, i.e., antibiotics, were excluded from the study.”

  – no further discussion or description of the excluded subjects

• Control group: sample of office workers in non-water damaged building

• Workers n = 53 (39 female), controls n = 21 (11 female)

• No clearly defined study question
Air Sampling

- *Cladosporium, Penicillium, Aspergillus* and *Stachybotrys*
- Concentrations are mostly < 120 cfu/m³ with quiescent testing; none to a minority (up to 14%) of isolates are *Stachybotrys*
- Aggressive testing in basement and sub-basement: > 20,000 cfu/m³; 97%+ *Stachybotrys*
- No sampling of control office building
<table>
<thead>
<tr>
<th>Organ system affected</th>
<th>By external comparison:</th>
<th>By internal comparison, according to office location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls $(n = 21)$</td>
<td>Subjests $(n = 53)$ $P^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P^b$</td>
</tr>
<tr>
<td>Respiratory system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper airways</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>Lower airways</td>
<td><strong>43</strong></td>
<td>76**</td>
</tr>
<tr>
<td>Worse in past year</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Skin</td>
<td>19</td>
<td>47*</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>52</td>
<td>70</td>
</tr>
<tr>
<td>Eyes</td>
<td><strong>19</strong></td>
<td>57**</td>
</tr>
<tr>
<td>Constitutional (feverish, adenopathy, flu-like)</td>
<td>5</td>
<td>28*</td>
</tr>
<tr>
<td>“Multiple chemical hypersensitivity”</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td>Chronic fatigue symptoms</td>
<td><strong>5</strong></td>
<td>24**</td>
</tr>
<tr>
<td>Allergy history</td>
<td>48</td>
<td>60</td>
</tr>
<tr>
<td>Infection (within past year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>47</td>
<td>62</td>
</tr>
<tr>
<td>Yeast</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Health worse since employment at problem-building</td>
<td>N/D</td>
<td>51</td>
</tr>
</tbody>
</table>

$P < 0.05$

$**P < 0.01$

$^a$ Difference between external controls and subjects (chi-square)

$^b$ Difference between subjects (internal controls) by office location (chi-square)

$^c$ Trend by Mantel-Haenszel test for linear association
Blood tests

• Multiple tests (>20), multiple comparisons (>40); Tables 4 and 5

• No real differences
  – Table 4: CD3 count significantly lower in subjects (75.7% v 73.5%), statistically but not clinically different
  – Different statistical approach in Table 5, small differences in WBC, CD3 and NK cells
Health Outcomes

• From the 187 item questionnaire they come up with health outcomes
  – Compare these to selected blood tests and several subject variables (Table 6)
• Except for being female and self assessment of poorer health the differences between “exposed” and “un-exposed” are trivial to marginal
Discussion

• Fungal exposure led to abnormalities to cellular and humoral systems "though the magnitude of some differences was small"

• "Higher and longer indoor exposure to atypical fungi and *S. chartarum* or its chemical products appears to be associated with increased immune reactivity and possibly impaired immunity“

• They do not find IgG or IgE antibodies to *S. chartarum* associated to health outcomes: "its possible that the fungal antigens used in lab are not identical to those in problem building..."
Critique

• Control group office mold exposure not measured
• Exposures were for most part up to $10^2$ cfu/m$^3$
  – outdoor environments much greater
  – farming, gardening, landscaping: $10^6$ to $10^7$ cfu/m$^3$
• Statistical differences in some immune parameters appear clinically irrelevant
• No actual physical exams performed on subjects, symptoms and illnesses all self reported on questionnaire
Critique

• Abstract: “It is concluded that prolonged and intense exposure to toxigenic *S. chartarum* and other atypical fungi was associated with reported disorders of the respiratory and central nervous systems....

• Data presented do not demonstrate any difference in CNS symptoms (Table 3 NS)

• CNS toxicity not discussed in their Discussion
Conclusion

• Wet, mold contaminated indoor environments are unpleasant
• No demonstration that a toxic mechanism is taking place or of systemic toxicity
Holland- Disclosure

• As a Medical Toxicologist, I see patients who have been referred by PMD for health effects suspected to be due to toxic mold exposure
• I perform consults as Occupational Physician for client companies with indoor air quality and Sick Building Syndrome investigations
• Have reviewed toxic tort cases, including some with indoor mold exposures and alleged health effects, for both plaintiffs and defendants
• Primary expert witness work has been for defendants
Beware of Toxic Mold
Indoor Air Quality

• Very subjective, high degree of individual variability
• Depends on multiple factors
  – Temperature
  – Humidity
  – VOC’ s: formaldehyde, toluene, aldehydes, ketones, alcohols, esters, AH, etc
  – Combustion gases (CO, SO₂, CO₂)
  – Fresh air exchanges (CO₂ as marker)
  – Bioaerosoles: Fungi, bacteria, dust mites, etc
Indoor Air Quality

• Other factors determining IAQ perception
  – Job satisfaction
  – Pay level
  – Supervisor factors
  – Quality of work environment
  – Stress levels
  – Ambient noise levels
  – Dust control
  – Occupant gender
  – Lighting
  – Availability of windows
Introduction to Molds

• Fungi (yeasts and molds) are ubiquitous in all indoor and outdoor environments
• Account for 25% of the earth’s biomass
  – They were here before we were!
• > 200,000 known species
• < 100 are known human/animal pathogens
• Eukaryotic
• Cell walls contain chitin or cellulose
• Lack chlorophyll, must obtain food from environment
Molds Perform Vital Function

• Degrade and decompose vegetable matter, such as leaves and trees
• Returns necessary nutrients to the soil
• Molds in outdoor air are lower in the winter, and higher in the summer and fall.
  – Snow cover has melted
  – Warm environment promotes fungal growth
  – Leaves from the prior fall are moist and ready to degrade
Molds are Common and Ubiquitous

• US Census Bureau’s 2003 statistics\(^1\):
  – There are over 119 million housing units in the USA, and 4.7 million commercial buildings
  – Nearly all will experience leaks, flooding, or other excessive indoor dampness at some time
• Mold spores exist on virtually all environmental surfaces
• When water intrusion occurs, mold growth usually results
• Therefore, the mold growth serves as a marker for water damage

Stachybotrys, aka “Toxic Mold”

• Common soil fungus
• Fondness for cellulose
  — Outdoor: straw, grasses, etc
  — Indoor: drywall, wallpaper, wood, etc
• Requires heavy moisture
• Tertiary wall colonizer
  — Comes after primary colonizers *Penicillium* and *Aspergillus*
  — Secondary colonizer *Cladosporium*
• Rarely cultured with standard techniques
  — Selective cultures with cellulose agar: yield >30%
Indoor Mold, Toxigenic Fungi, and *Stachybotrys chartarum*: Infectious Disease Perspective

Kuhn DM, Ghannoum MA

CLINICAL MICROBIOLOGY REVIEWS, Vol. 16, No. 1; Jan. 2003, p. 144–172

- Comprehensive review of literature regarding mold and health effects
- Infectious disease perspective
Fungal Mycotoxins Measurement Problems

• Mycotoxin production depends on:
  – Species, temperature, humidity, growth substrate, nutrient levels, and pH

• When mycotoxins are present, they are contained in fungal mass
  – Miniscule quantities on airborne spores
  – *Stachybotrys* spores are contained in wet, slimy mass
  – Very little available for inhalation absorption even in EXTREME fungal overgrowth conditions

• Serologic testing meaningless
  – Ig levels do not correlate with exposure
  – Large amount of cross-reaction between species
  – Presence does not indicate when or how exposure occurred (i.e., past dietary exposure)
Mold-related Allergic Illnesses

• IgE-mediated allergic diseases
  – Atopic patients, allergic to other allergens: pollen, dust, etc.
  – 5% of general population

• Hypersensitivity pneumonitis (HP)
  – Agricultural exposures predominate- Farmer’s lung
    • Actually due to thermophilic bacterial contamination of moldy hay
  – Indoor exposures rarely cause HP
    • Exceptions: Japanese Summer-type
    • Unusual indoor humidity: pools, spa, humidifiers
    • Rarely with contaminated HVAC systems
Allergic Broncho-pulmonary Aspergillosis and Allergic Fungal Sinusitis- AFS

- Fungi colonize abnormal airways (bronchiectatic) or poorly draining sinuses
- The acquired fungal colonization occurs from ubiquitous environmental molds- NOT necessarily from contaminated buildings
- Ongoing allergen exposure then exacerbates allergic Sx
- Probably no increased risks from indoor mold exposures
Mold-related Infectious Diseases

• Primarily in immunocompromised hosts
  – Advanced HIV disease
  – Cancer patients on chemotherapy
  – Organ recipients on immunosuppressive Rx
  – Lymphoproliferative disorders
  – Uncontrolled DM

• No evidence that exposure to buildings with high indoor mold is causative

• Molds are acquired from normal ubiquitous sources

• Rare fungal infections that affect immunocompetent aren’t acquired from indoor air or mold-contaminated buildings (coccidio., histo. cryptococcus)
Fungal Mycotoxins

• Mycotoxins are secondary metabolites
• May confer advantage to fungus by affecting competing organisms
• Many mycotoxins used medicinally:
  – Penicillin
  – Cephalosporin
  – Cyclosporin A
  – Lovastatin
Mycotoxins and Disease
(NB: all are from ingestion)

• Aflatoxicosis: Acute hepatic failure
• Aflatoxin and hepatocellular carcinoma
• Ergotism: St Anthony’s Fire, ergotamine from *C. purpura* mold on rye
• ATA: T-2 from *Fusarium*
  – Humans who ate over-wintered moldy wheat- Russia pre- and during WW II
• Turkey X disease: aflatoxin from *Fusarium*
Production of Trichothecenes by Toxigenic Species

- Factors affecting trichothecene production
  - Strain specificity (genetics)
  - Environmental conditions of their growth
    - Temperature, humidity, growth substrate, growth of other competing microorganisms

- The presence of a toxigenic fungal species is not an accurate indicator of trichothecene production
  - A frequently misunderstood concept
Trichothecenes: Potential Exposure Sources and Pathways

- Trichothecenes in moldy building materials
  - Nanogram quantities reported on surfaces and in bulk samples
  - Trichothecenes have not been quantified in indoor air in epidemiological studies of building-related illness

- Risks from indoor mold contamination:
  - If repeatedly eat moldy building materials
  - Or repeatedly eat large amounts of dust from moldy buildings
Mold-related Mycotoxic Diseases: ODTS

- ODTS: Organic Dust Toxic Syndrome: Silo unloader’s disease, aka “grain fever”
- Exposures to fungi, bacteria, and organic debris with associated endotoxins, glucans, and mycotoxins
- “Thick airborne dust...fog...impossible to see across the room”
- Total microorganism counts have ranged from $10^5$-$10^9$ per cubic meter of air to $10^9$-$10^{10}$ spores per cubic meter
- Represents extreme conditions not encountered in the indoor home, school, or office environment.
Mold-related Mycotoxic Diseases: Recent Scientific Evidence for ODTS


Indoor Mold, Toxigenic Fungi, and *Stachybotrys chartarum*: Infectious Disease Perspective
D. M. Kuhn1,2,3 and M. A. Ghannoum2,3*
CLINICAL MICROBIOLOGY REVIEWS, Vol. 16, No. 1; Jan. 2003, p. 144–172

• Underscored the difficulty measuring mold spores and mycotoxins
• No control homes or buildings are ever measured
• Most studies have *S. chartarum* in building materials as evidence for occupant airborne exposures
• Studies alleging health effects from molds largely are subjective questionnaires, no actual physical exam findings
• Smokers under-reported their smoking effects on children
Indoor Mold, Toxigenic Fungi, and *Stachybotrys chartarum*: Infectious Disease Perspective  
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• Schools closed due to water damage and mold growth usually had lower airborne mold spore counts than in the students’ homes

• Conclusions:
  – No evidence of significant human health effects from mycotoxins in indoor environment
  – there is no well-substantiated evidence linking the presence of *Stachybotrys* to health concerns elaborated in the scientific and lay press.
Comprehensive Reviews of Scientific Evidence of Mycotoxins causing SBS
Comprehensive Reviews of Scientific Evidence of Mycotoxins causing SBS/BRI

- **Page & Trout A/JHAJ 2001:**
  - Reviewed 13 articles alleging mycotoxin exposure as cause of BRI/SBS
  - Concluded: no causal relationship

- **Fung & Hughson 9th Intl Conf IAQ July 2002**
  - Reviewed all literature 1966-2002
  - Toxicity from inhaled mycotoxins not established
  - Allergy, irritation, URI Sx increased prevalence

- **Bardana EJ Immun All Clin N Am 2003**
  - Comprehensive review of literature of mold and health
  - No evidence of mycotoxic cause of BRI/SBS
Review of Scientific Evidence of Mycotoxins causing SBS/BRI

  - Comprehensive review of mold and health
  - Mold-related Sx: irritation, allergy
  - Mycotoxic cause of BRI/SBS never proven in literature

- Terr AI; *Ann Aller Immun* 2001
  - BRI/SBS from inhalation of *Stachybotrys* spores not supported by literature

- Assouline-Dayan et al; *J Asthma* 2002
  - Mold exposure cause mucosal irritation
  - No long-term effects
  - No evidence for non-mucosal pathology
Review of Scientific Evidence of Mycotoxins causing SBS/BRI

• Terr AI. Med Mycol. 2009
  – Moulds responsible for infection, allergy, and toxicity.
  – Other conditions attributed to indoor airborne mycotoxin are unproven.

- Toxicological and exposure data for 15 MVOCs most often analyzed and reported WDB
- MVOC exposure can cause eye and upper-airway irritation.
- However, in exposure studies, symptoms don’t appear until MVOC concentrations are several orders of magnitude higher than those measured indoors
  - single MVOC levels in indoor environments have ranged from a few ng/m³ up to 1 mg/m³.
- This is also supported by dose-dependent sensory-irritation response, as determined by ASTM mouse bioassay.
- Toxicological database is poor even for the 15 examined MVOCs.
Barbeau DN, Grimsley LF, White LE, El-Dahr JM, Lichtveld M. Mold exposure and health effects following hurricanes Katrina and Rita. *Annu Rev Public Health.* 2010 Apr 21;31:165-78

- Flooding after Hurricanes Katrina and Rita created conditions ideal for indoor mold growth
- High levels of indoor and outdoor molds in the months following the hurricanes were found.
  - Homes with greater flood damage, esp. with >3 feet of indoor flooding, had higher levels of mold compared to those without flooding.
  - Water intrusion through roof was also associated with mold growth.
- No increase in the occurrence of adverse health outcomes has been observed in published reports to date.
Scientific Evidence of Mycotoxins causing SBS: Conclusion

• Scientific evidence is lacking
• Disease defined as presence of occupant symptoms, i.e., no objective findings or tests
  – In fact, most studies alleging SBS effects often consider increased #’s of subjective vague complaints as having more “disease”
• Studies uniformly lack a control non-complaint building
• Almost all lack control non-symptomatic subjects from same buildings
• Litigation seems to be fueling the debate
Scientific Organizations with Mold Statements

- Five major scientific / medical organizations reviewed evidence on health effects of indoor mold
- All statements conclude that exposure to mold in indoor environments is:
  - Known to exacerbate allergies
  - Not known to cause infection
  - Not known to cause toxic responses
IOM Report
National Academy Of Science

• Institute of Medicine report: *Damp Indoor Spaces and Health* (2004)
• Concluded that damp conditions contributed risk of respiratory symptoms independent of mold growth
• Did not support “toxic mold” hypothesis
AAAII Position Statement

• State-of-the-art review of known mold-related illnesses:
  – asthma, allergic rhinitis, allergic bronchopulmonary aspergillosis, sinusitis, and hypersensitivity pneumonitis.

• Purported mold-related illnesses occurrence of mold-related toxicity (mycotoxicosis) from exposure to inhaled mycotoxins in non-occupational settings is not supported by the current data, and its occurrence is improbable.

• Exposure to molds and their products does not induce a state of immune dysregulation (eg, immunodeficiency or autoimmunity).

• The practice of performing large numbers of nonspecific immune-based tests as an indication of mold exposure or mold-related illness is not evidence based and is to be discouraged.
2009 WHO guidelines for indoor air quality: dampness and mould

- Comprehensive review of the scientific evidence on health problems associated with building moisture and biological agents.
- Epidemiological evidence occupants of damp or mouldy buildings are at increased risk of respiratory symptoms, respiratory infections and exacerbation of asthma.
- No evidence that nervous system symptoms are caused by mold exposures or that damp buildings have levels of mycotoxins that would cause disease.
- There data showing that autoimmune responses are caused by microorganisms or microbial substances found in damp buildings.
- Remediation of dampness can reduce adverse health outcomes.
ACOEM Position Statement

• Adverse Human Health Effects Associated with Molds in the Indoor Environment- 2/24/2011
  – Update of 2002 Mold Statement
• Indoor mold exposures can be a cause of certain allergic and hypersensitivity reactions.
• A causal relationship has not been established between building-related symptoms and indoor mold exposures
• Delivery by the inhalation route of a toxic dose of mycotoxins in the indoor environment is highly unlikely, even for the most vulnerable subpopulations
• Current scientific evidence does not support the existence of a causal relationship between inhaled mycotoxins in home, school, or office environments and adverse human health effects
Conclusions

Five learned organizations basically conclude the same thing:
Indoor mold exposures are associated with allergy, asthma exacerbations, Hypersensitivity reactions But not with neurotoxic diseases
Information Resources for Health Professionals and Consumers

  – Health effects, clean-up, indoor air quality regulations, schools and mold

• CDC: [http://www.cdc.gov/mold/default.htm](http://www.cdc.gov/mold/default.htm)
  – Fact sheets, health effects, mold clean-up guidelines

• Most state health departments