



Mold Basics for Primary Care Clinicians: A Case Study and Review For Physicians

12/2009

Purpose:

- To explain the relationship between indoor mold exposure and illness
- To assist clinicians with the diagnosis of mold-related illness
- To summarize current recommendations for clinical and environmental testing

Case Study:

A 50-year-old male presented to a community medicine clinic with complaints of progressive fatigue, headaches and nausea. The patient noticed that his symptoms have worsened since spending more of his waking hours at home, due to losing his job six months ago. He reported not having seen a doctor in “at least 10 years”. He believes that his symptoms are due to mold that he sees on his bathroom ceiling, and wants the clinic physician to help him convince the apartment complex property manager to have the air tested in his apartment.

The patient required much reassurance and validation that he his symptom of illness were “real”. However, it was necessary to explain that his symptoms were not typical of mold allergy, and that he needed a thorough internal medicine work-up, as he had not seen a doctor in at least ten years. He was successfully referred to a local internal medicine clinic.

The patient was given the phone number for his local health department and was able to get assistance in working with the apartment complex’s property manager. The source of leaking water in his home was identified during a walk through assessment, and was subsequently addressed. He was advised that air tests at his apartment were not recommended.

A. Introduction

Fungi (molds) are ubiquitous in our environment. People are constantly exposed to mold in both indoor and outdoor environments and pinpointing one source of exposure can be difficult to impossible. In fact, exposure may come from multiple sources. The general public and some health care providers who are less familiar with the subject have attributed a burden of disease to mold that is disproportionate with symptoms. This has been documented in peer-reviewed literature. Making a correct diagnosis is an on-going challenge for busy health care providers with limited time. Clinicians must tease apart complex symptoms to diagnose the true condition, while validating patient’s concerns and educating them with accurate information.

This document will attempt to give the practicing clinician a synopsis of the state of the art thinking about indoor mold, damp spaces, and health effects. This information will enable you to better educate and treat patients who may be worried by mold (the worried well) and those with symptoms that can be attributed to exposure to indoor mold and damp spaces.

Please note that this document will focus the general population’s exposure to indoor mold in residential, school, and office building settings. Invasive or disseminated fungal disease in immunocompromised

patients, and short-term, heavy occupational fungal exposures such as those experienced by farmers and compost workers are beyond the scope of this document.

B. Institute of Medicine Reports

The difference between causality and association can be a difficult concept for patients to grasp, especially when it comes to mold and perceived illness. The Institute of Medicine (IOM) published two landmark reports that form a basis for critical thinking about mold and related health effects. The authors of both reports performed comprehensive reviews of the scientific literature. *Clearing the Air: Asthma and Indoor Air Exposures*¹ examines how indoor pollutants like mold contribute to the causation, prevalence, triggering, and severity of asthma. *Damp Indoor Spaces and Health*² looks at laboratory, clinical, and epidemiologic studies on how damp indoor environments and mold influence the health of occupants.

Here is a summary of the IOM findings. Tabular summaries of the two IOM reports regarding asthma, indoor air quality, damp indoor spaces, and mold are attached to the end of this document.

- ◆ No causal relationship was found between indoor mold and respiratory problems like asthma symptoms in asthmatics who are sensitive to mold, upper respiratory tract symptoms, coughing, and wheezing in otherwise healthy people, *however*,
- ◆ Positive association was found between indoor mold/indoor dampness and asthma symptoms in asthmatics who are sensitive to mold, as well as upper respiratory tract symptoms, coughing, and wheezing in otherwise healthy people; increase found in the prevalence of these health effects among occupants of buildings that have dampness problems or visible mold.
- ◆ No association was found between indoor mold, indoor dampness and other health problems, such as fatigue, difficulty in concentrating, cancer, and other neurologic effects
- ◆ Suggestive evidence was found that excessive indoor dampness might be associated with the development of asthma; evidence was limited because alternative explanations for the association could not be ruled out with confidence.
- ◆ Limited evidence was found for the association between excessive indoor dampness and episodes of shortness of breath and lower respiratory illness in children.

C. What Does This Mean For The Practicing Clinician?

You can assure your patients that indoor mold does not cause new onset asthma, airflow obstruction in healthy people, skin symptoms, mucous membrane irritation, GI problems, COPD, fatigue, cancer, neuropsychiatric symptoms, rheumatologic & other immune disease, reproductive effects, or acute idiopathic pulmonary hemorrhage in infants. If they are seeing you for any of these problems, you will continue to work with them to treat those conditions.

If a respiratory illness associated with mold exposure is suspected, a key step is to find and eliminate indoor sources of moisture and/or mold. It may be ultimately helpful to explain how source identification and avoidance are tightly integrated with the diagnosis of mold-induced respiratory disease and corresponding treatment. If your patient is an asthmatic living in a damp or moldy environment, their indoor environment may exacerbate their symptoms. You can work with them to clinically manage their symptoms, but they should also take action to dry out their living/working space and remove visible mold. You might advise them that air testing is generally not useful – source reduction is the key.

For otherwise healthy patients presenting with upper respiratory tract symptoms, coughing, and wheezing, explain that there could be a number of things causing or aggravating these symptoms. Damp/moldy indoor environments might be one of many contributing factors. As stated above, reassure patients that you will medically assess them and develop a treatment plan if warranted. Patients should be encouraged to take action to ensure that their living/working space is dry and there is no visible mold.

D. Patient Assessment Considerations

Assessing the patient to develop a working diagnosis and treatment plan requires the clinician to ask probing questions about health status and exposure history.

1. Personal Health Status

It is important to find out whether the patient is immunocompetent or immunocompromised (HIV, cancer, autoimmune disease, long term steroid use, transplant status, etc.) The IOM reports found no causal or associative evidence of developing new-onset asthma in immunocompetent individuals exposed to mold or damp indoor spaces. There was sufficient associative evidence linking exacerbation of asthma and development of hypersensitivity

pneumonitis to mold or to damp indoor exposures in sensitive individuals.

2. Environmental Exposure History (Focusing On Mold)

Diagnosis of environmental illness requires asking the patient exposure history questions related to work, home, and recreational environments. It is useful to ask open-ended questions. The National Environmental Education Foundation (NEEF) and EPA have environmental and occupational history primers and forms that clinicians may use when treating pediatric and adult patients^{3,4}.

3. Assessment Challenge

Patients may provide compelling histories for possible mold-induced illness with reports of worsening symptoms during the week while working in a damp environment, and resolution of symptoms during the weekend. Conversely, a patient complaining of non-specific symptoms such as fatigue, nausea, and body aches may need reassurance that the clinician is committed to looking for a diagnosis, and that his/her symptoms are not related to mold, even if mold is visible in the patient's home.

4. Referral and Testing

Managing patients with symptoms of unclear etiology can be challenging. In some cases, referral to a pulmonologist, allergist, or occupational medicine physician can be of great assistance. Contact information for the occupational and environmental medicine clinics at Yale and University of Connecticut Health Center (UCHC) are listed in the resource section at the end of this document.

Some Typical Environmental Exposure History Questions^{3,4,5}

- ◆ What does your job entail?
- ◆ Do you have any known environmental exposures at work?
- ◆ What activities do you participate in when you are not working?
- ◆ Is there moisture in the building where you work, or in your home?
- ◆ Do you notice an association of your symptoms with a specific activity, time of day, or day of the week?
- ◆ Do your symptoms become worse or better in a particular setting?
- ◆ In your home/school/workplace:
 - ◆ Is there carpeting?
 - ◆ Is there forced hot air heating?
 - ◆ Is there central air conditioning?
 - ◆ How would you rate general cleanliness?(i.e., is dust present on surfaces)

E. Understanding Mold-Related Symptoms

Most exposures to indoor mold produce either a hypersensitivity (Type I) or delayed hypersensitivity (Type IV) reaction. Even though patients may credit a wide variety of symptoms to mold exposure, the majority of what is seen clinically is upper respiratory and/or irritant in nature. The most commonly diagnosed illnesses attributable to mold are asthma and allergic rhinitis. See attachment for IOM table of illnesses and associations with indoor mold and damp spaces.

Patients may want to discuss exposure to “toxic mold” with you. You may wish to explain that this is not a scientific term, but one created by the media. It is true that certain species can produce mycotoxins, but production may be intermittent and varied in quantity and concentration. It is important to note that most of what we know about mycotoxins exposure and disease comes from ingestion of contaminated foodstuffs. Very little is known about the effects of mycotoxins via inhalation. Practically speaking, the Connecticut Department of Public Health (CT DPH) recommends eliminating the exposure to indoor mold via source removal instead of spending resources to speciate molds and trying to figure out if they are producing mycotoxins in a given environment.

Most Commonly Diagnosed Mold-Related Symptoms

- ◆ Asthma
- ◆ Allergic Rhinitis
- ◆ Rhinorrhea
- ◆ Nasal Congestion
- ◆ Sneezing
- ◆ Post Nasal Drip with Sore Throat
- ◆ Coughing
- ◆ Hoarseness

F. Patient Requests for “Doctor’s Note” For Air Testing

Some patients ask physicians for a note to “have the air tested” in their home/school/office. This is an especially common request from parents of school age children who attribute many of their children’s ills to mold exposure in school. A skilled physician can both validate a patient’s concerns, and explain that monitoring air in the home, school, or workplace for mold is not a recommended practice for many reasons. First, due to the ubiquitous nature of mold, it is present in every environment. Normal diurnal fluctuation patterns result in different species releasing spores at different times throughout the day. Second, there are no standards for air monitoring for mold. Third, there is great variation in mold virulence and in individuals’ susceptibility.

G. Patient Requests for Allergy Testing

Some patients insist that they need allergy testing to “prove” that they work in a “sick building”. Clinical judgment and judicious allergen testing can be useful tools for a physician in decreasing patient symptoms when combined with source reduction and/or remediation. Some patients with positive skin tests for mold allergies use these results as a basis for a myriad of health complaints, including intolerance to their workplace/school. It is important to explain to these patients that positive skin test results indicate exposure at some time. These results cannot identify where and when the exposure occurred. It is worth mentioning to patients that if they are highly allergic to mold, eliminating sources of water and mold can be beneficial, but they should avoid performing mold clean-up themselves. Resources for mold clean-up guidance may be found at the end of this document.

H. Environmental Assessment and Remediation

Before recommending any type of environmental testing, some important questions physicians should ask are, how will the results be used; will they change what I plan to do next; if a patient’s symptoms are clinically related to mold, will environmental testing add any additional information? Resources are often limited, and rather than spending money on environmental testing, funds may be better used to remove the contaminant source (e.g., eliminating water leaks, abating the mold) and improve ventilation in the home/school/office.

Instead of environmental testing, you may advise your patient that performing a visual environmental assessment / walk-through evaluation to look for mold and moisture can be very useful, because source identification and reduction usually results in decreased symptoms in affected individuals. The source of mold and moisture is not always readily apparent. An independent environmental professional/ industrial hygienist may be hired to provide a more in-depth investigation. However, their investigation does not automatically mean that testing should be performed. Visual assessment and other qualitative tools are often the most appropriate way to gather data to characterize the environment.

I. Decreasing Mold In The Patient's Environment

There are a number of information sources available to assist people in dealing with indoor mold. Renters should first contact landlords to discuss abatement of chronic moisture and removal of mold. Parents who think that there may be a mold problem in their children's schools should first contact the school administration. If they need further assistance, local health departments are an excellent resource for patients who need help assessing moisture and mold in their homes and schools. The CT DPH can be a great resource for physicians who have questions related to mold induced illness and environmental assessments (phone # 860-509-7740). Homeowners can contact their local health dept or CT DPH for technical information, but may have to hire a consultant to help investigate (but not test!) the cause of more severe mold/moisture problems.

If a location is identified where a patient's symptoms are most noticeable, there are a number of suggestions a physician can make to empower the patient. CT DPH has a fact sheet, *Get The Mold Out: Mold Clean-Up Guidance for Residences*, which helps the general public understand basic concepts so that they can make an informed decision regarding mold abatement. Resources and contact information are provided at the end of the document. The EPA *Tools for Schools* program is an excellent resource that provides educational and training tools that parents and school administrators can use to identify and manage environmental contaminants in schools, including moisture and mold. The University of Connecticut Division of Occupational and Environmental Medicine has prepared a detailed document for clinicians entitled, *Guidance for Clinicians In The Recognition of Health Effects Related to Mold Exposure and Moisture Indoors*. This guide includes home environmental survey forms, which you may copy for your patients (table C, page D-4).⁶



Patients should be encouraged to take action to ensure that their living/working space is dry and there is no visible mold.

Take Home Message

One of the many important roles of the PCP is to educate patients that fungi are present in nearly all settings. For symptoms that are documented to be attributable to mold, PCPs should aim to teach patients that the goal of treatment is to minimize the offending exposure, as it may be unrealistic to remove all mold from an environment. Additionally, air testing for homes, schools, and workplaces is not normally recommended. Finally, the goal of treatment may be management and reduction of symptoms, rather than cure.

Check Your Knowledge

1. Which of the following statements about sampling for mold is true?

- A. Air sampling for mold is rarely indicated when mold contamination is suspected in a home.
- B. Indoor and outdoor mold concentrations in the air are constant throughout the year.
- C. When mold is visible in a home, environmental testing for mold usually adds useful information.
- D. There are standards for mold concentrations in air in homes.

2. Which of the following is true about resources for mold-related illness?

- A. EPA's *Tools for Schools* is only useful for occupational exposure to mold.
- B. A landlord should never be of assistance to a tenant with a suspected moisture problem.
- C. The CT DPH can be an excellent resource for physicians when suspecting an environmental illness.
- D. Occupational medicine specialists, pulmonologists, and allergists are of no help in making a correct diagnosis for mold related respiratory illnesses.

3. A basic environmental history should include which of the following?

- A. What does your specific job entail, including known exposures?
- B. What do you usually do when not at work (what are your hobbies)?
- C. Is there a moisture problem at home or work?
- D. All of the above

Answers To Knowledge Check

1. A

Explanation: If mold and/or evidence of water damage is visible in the home and a patient has physician-documented symptoms related to mold exposure, testing the home adds little to no additional value in treating the patient.

2. C

Explanation: The CT DPH is an excellent resource for physicians; however the local health department can best facilitate mold assessment for an individual patient.

3. D

Explanation: Understanding your patient's physical environment can often give clinicians clues about triggers and exposures that may be diagnostically significant, and can aid healthcare professionals in designing a treatment plan.

Resources

Taking An Occupational/Environmental History

- ◆ **Agency for Toxic Substances and Disease Registry:** Case Studies in Environmental Medicine Series: Taking an Exposure History. <http://www.atsdr.cdc.gov/csem/csem.html>
This educational case study document is one in a series of self-instructional courses designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation and care of potentially exposed patients.
- ◆ **U.S Environmental Protection Agency:** Chapter 3. Environmental and Occupational History. In: Recognition And Management of Pesticide Poisonings. EPA 375-R-98-003. March 1999.
- ◆ **National Environmental Education Foundation:**
Pediatric History Primer: <http://www.neefusa.org/pdf/primer.pdf>

Occupational and Environmental Medicine Clinics

- ◆ **University of Connecticut Occupational and Environmental Medicine Clinic:** 860-679-2893
Farmington, CT
- ◆ **Yale Occupational and Environmental Medicine Clinic:** 203-785-4197 New Haven, CT

General Mold Information for Patients

- ◆ **Indoor Air Quality Testing Should Not Be The First Move**
http://www.dph.state.ct.us/EOHA/Documents/ieq_testing.pdf
- ◆ **CT DPH Fact Sheet: *Mold in the Home:***
<http://www.dph.state.ct.us/EOHA/Documents/mold.pdf>
- ◆ **EPA's *Brief Guide to Mold, Moisture and Your Home***
<http://www.epa.gov/iaq/molds/images/moldguide.pdf>
- ◆ **Mold Web Resources**
http://www.ct.gov/dph/lib/dph/environmental_health/eoha/pdf/mold_web_resources.pdf
- ◆ **US Environmental Protection Agency Mold Resources**
<http://www.epa.gov/mold/index.html>

Mold Removal

- ◆ **Connecticut Guidelines for Mold Abatement Contractors**
http://www.dph.state.ct.us/EOHA/Documents/CT_Guidelines_for_Mold_Remediation_Contractors_Final.pdf
- ◆ **Get The Mold Out: Mold Clean-Up Guidance for Residences**
CT Department of Public Health Fact Sheet
http://www.dph.state.ct.us/EOHA/Documents/Get_The_Mold_Out.pdf
- ◆ **NYC Dept of Health & Mental Hygiene's *Guidelines on Assessment and Remediation of Fungi in Indoor Environments***
<http://www.ci.nyc.ny.us/html/doh/html/epi/moldrpt1.shtml>

References

¹Institute of Medicine. Clearing the air: asthma and Indoor exposures. Washington, DC: National Academies Press, 2000.

²Institute of Medicine. Damp indoor spaces and health. Washington, DC: National Academies Press, 2004.

³Environmental and Occupational History. Chapter 3. In: Recognition And Management of Pesticide Poisonings. U.S Environmental Protection Agency. EPA 375-R-98-003. March 1999. <http://www.epa.gov/opp00001/safety/healthcare/handbook/handbook.htm>

⁴National Environmental Education Foundation
Pediatric Environmental History Initiative: <http://www.neefusa.org/health/PEHI/index.htm>
Pediatric Environmental History Primer <http://www.neefusa.org/pdf/primer.pdf>
Pediatric Environmental History Forms <http://www.neefusa.org/health/PEHI/HistoryForm.htm>

⁵Frank A and Balk S. ATSDR Case Studies in Environmental Medicine # 26, Taking an Exposure History. Atlanta: Agency for Toxic Substances and Disease Registry, Oct 1992.

⁶Storey E, Dangman KH, et al. Guidance for clinicians on the recognition and management of health effects related to mold exposure and moisture indoors. Farmington, CT: University of Connecticut Health Center, Division of Occupational and Environmental Medicine, Center for Indoor Environments and Health, 2004.
<http://oehc.uhc.edu/clinser/MOLD%20GUIDE.pdf>

Summary of Two Key Institute of Medicine Reports Regarding Asthma, Indoor Air Quality, Damp Indoor Spaces, and Mold

Prepared by National Center for Healthy Housing – www.nchh.org Page 1 of 2

Source: **National Academies Press, 2000. Clearing the Air: Asthma and Indoor Air Exposures. Executive Summary**
Institute of Medicine. ISBN 0-309-06496-1 See www.nap.edu/books/0309064961/html/.

Association Between Biological and Chemical Exposures in the Home and:			
Development of Asthma in Sensitive Individuals		Exacerbation of Asthma in Sensitive Individuals	
Biological Agents	Chemical Agents	Biological Agents	Chemical Agents
Sufficient Evidence of a Causal Relationship			
House dust mite	<i>No agents met this definition</i>	<ul style="list-style-type: none"> • Cat • Cockroach • House dust mite 	ETS (in preschoolaged children)
Sufficient Evidence of an Association			
<i>No agents met this definition</i>	ETS (in preschoolaged children)	<ul style="list-style-type: none"> • Dog • Fungi or molds • Rhinovirus 	Nitrogen oxides (high-level exposures)*
Limited or Suggestive Evidence of an Association			
<ul style="list-style-type: none"> • Cockroach (in preschool aged children) • Respiratory Syncytial Virus 	<i>No agents met this definition</i>	<ul style="list-style-type: none"> • Domestic birds • <i>Chlamydia pneumoniae</i> • <i>Mycoplasma pneumoniae</i> • Respiratory Syncytial Virus 	<ul style="list-style-type: none"> • ETS (in school aged and older children, & adults) • Formaldehyde • Fragrances
Inadequate or Insufficient Evidence to Determine Whether or Not an Association Exists			
<ul style="list-style-type: none"> • Cat, Dog, Domestic Birds • Rodents • Cockroaches (except for preschool-aged children) • Endotoxins • Fungi or molds • <i>Chlamydia pneumoniae</i> • <i>Mycoplasma pneumoniae</i> • <i>Chlamydia trachomatis</i> • Houseplants • Pollen 	<ul style="list-style-type: none"> • Nitrogen oxides • Pesticides • Plasticizers • Volatile organic compounds (VOCs) • Formaldehyde • Fragrances • ETS (in older children and adults) 	<ul style="list-style-type: none"> • Rodents (as pets or feral animals) • <i>Chlamydia trachomatis</i> • Endotoxins • Houseplants • Pollen exposure in indoor environments • Insects other than • Cockroaches 	<ul style="list-style-type: none"> • Pesticides • Plasticizers • Volatile organic compounds (VOCs)
Limited or Suggestive Evidence of No Association			
• Rhinovirus (adults)	<i>No agents met this definition</i>	<i>No agents met this definition</i>	<i>No agents met this definition</i>

*At concentrations that may occur only when gas appliances are used in poorly ventilated kitchens.

- **Sufficient Evidence of a Causal Relationship:** Evidence fulfills association criteria and in addition satisfies criteria regarding the strength of association, biologic gradient (dose-response effect), consistency of association, biologic plausibility and coherence, and temporality used to assess causality.
- **Sufficient Evidence of an Association:** Association has been observed in studies in which chance, bias, and confounding factors can be ruled out with reasonable confidence (e.g. several small bias free studies showing an association that is consistent in magnitude and direction)
- **Limited or Suggestive Evidence of an Association:** Evidence is suggestive of an association but is limited because chance, bias, and confounding cannot be ruled out with confidence (e.g. one high quality study shows association, but results of other studies are inconsistent)
- **Inadequate or Insufficient Evidence to Determine Whether or Not an Association Exists:** Available studies are of insufficient quality, consistency, or statistical power to permit a conclusion; or no studies exist
- **Limited or Suggestive Evidence of No Association:** Several adequate studies are mutually consistent in not showing an association (but limited to the conditions, level of exposure, and length of observation covered in the study).

Summary of Two Key Institute of Medicine Reports Regarding Asthma, Indoor Air Quality, Damp Indoor Spaces, and Mold

Prepared by National Center for Healthy Housing – www.nchh.org Page 2 of 2

Source: *National Academies Press, 2004. Damp Indoor Spaces and Health. Tables ES-1 and ES-2*

Summary of Findings Regarding Association Between Health Outcomes and:	
<u>Exposure to Damp Indoor Environments</u>	<u>Presence of Mold or Other Agents in Damp Indoor Environments</u>
<i>Sufficient Evidence of a Causal Relationship</i>	
_____	_____
<i>Sufficient Evidence of an Association</i>	
<ul style="list-style-type: none"> • Upper respiratory (nasal and throat) tract symptoms • Cough • Wheeze • Asthma symptoms in sensitized persons 	<ul style="list-style-type: none"> Upper respiratory (nasal and throat) tract symptoms • Cough • Hypersensitivity pneumonitis in susceptible persons • Wheeze • Asthma symptoms in sensitized persons
<i>Limited or Suggestive Evidence of an Association</i>	
<ul style="list-style-type: none"> • Dyspnea (shortness of breath) • Lower respiratory illness in otherwise healthy children • Asthma development 	<ul style="list-style-type: none"> • Lower respiratory illness in otherwise healthy children
<i>Inadequate or Insufficient Evidence to Determine Whether or Not an Association Exists</i>	
<ul style="list-style-type: none"> • Airflow obstruction (in otherwise healthy persons) • Skin symptoms • Mucous membrane irritation syndrome • Gastrointestinal tract problems • Chronic obstructive pulmonary disease • Fatigue • Inhalation fevers (nonoccupational exposures) • Neuropsychiatric symptoms • Lower respiratory illness in otherwise healthy adults • Cancer • Acute idiopathic pulmonary hemorrhage in infants • Reproductive effects • Rheumatologic and other immune diseases 	<ul style="list-style-type: none"> • Dyspnea (shortness of breath) • Skin symptoms • Asthma development • Gastrointestinal tract problems • Airflow obstruction (in otherwise healthy persons) • Fatigue • Mucous membrane irritation syndrome • Neuropsychiatric symptoms • Chronic obstructive pulmonary disease • Cancer • Inhalation fevers (nonoccupational exposures) • Reproductive effects • Lower respiratory illness in otherwise healthy adults • Rheumatologic and other immune diseases • Acute idiopathic pulmonary hemorrhage in infants

Institute of Medicine of the National Academies, ISBN 0-309-09246-9.

See www.nap.edu/books/0309091934/html/.

- **Sufficient Evidence of a Causal Relationship:** Evidence is sufficient to conclude that a causal relationship exists between the agent and the outcome. That is, the evidence fulfills the criteria for “sufficient evidence of an association” and, in addition, satisfies the following criteria: strength of association, biologic gradient, consistency of association, biologic plausibility and coherence, and temporally correct association.
- **Sufficient Evidence of an Association:** Evidence is sufficient to conclude that there is an association. That is, an association between the agent and the outcome has been observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence.
- **Limited or Suggestive Evidence of an Association:** Evidence is suggestive of an association between the agent and the outcome but is limited because chance, bias, and confounding cannot be ruled out with confidence.
- **Inadequate or Insufficient Evidence to Determine Whether an Association Exists:** The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence of an association. Alternatively, no studies exist that examine the relationship.