CHEST®

Occupational and Environmental Contributions to Chronic Cough in Adults
Chest Expert Panel Report

Susan M. Tarlo, MBBS, FCCP; Kenneth W. Altman, MD, PhD; John Oppenheimer, MD; Kaiser Lim, MD; Anne Vertigan, PhD; David Prezant, MD; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel

BACKGROUND: In response to occupational and environmental exposures, cough can be an isolated symptom reflecting exposure to an irritant with little physiological consequence, or it can be a manifestation of more significant disease. This document reviews occupational and environmental contributions to chronic cough in adults, focusing on aspects not previously covered in the 2006 ACCP Cough Guideline or our more recent systematic review, and suggests an approach to investigation of these factors when suspected.

METHODS: MEDLINE and TOXLINE literature searches were supplemented by articles identified by the cough panel occupational and environmental subgroup members, to identify occupational and environmental aspects of chronic cough not previously covered in the 2006 ACCP Cough Guideline. Based on the literature reviews and the Delphi methodology, the cough panel occupational and environmental subgroup developed guideline suggestions that were approved after review and voting by the full cough panel.

RESULTS: The literature review identified relevant articles regarding: mechanisms; allergic environmental causes; chronic cough and the recreational and involuntary inhalation of tobacco and marijuana smoke; nonallergic environmental triggers; laryngeal syndromes; and occupational diseases and exposures. Consensus-based statements were developed for the approach to diagnosis due to a lack of strong evidence from published literature.

CONCLUSIONS: Despite increased understanding of cough related to occupational and environmental triggers, there remains a gap between the recommended assessment of occupational and environmental causes of cough and the reported systematic assessment of these factors. There is a need for further documentation of occupational and environmental causes of cough in the future. CHEST 2016; 150(4):894-907

KEY WORDS: allergy; cough; environmental; occupational; smoking

---

CORRESPONDENCE TO: Susan M. Tarlo, MBBS, FCCP, Toronto Western Hospital EW7-449, 399 Bathurst St, Toronto, ON M5T 2S8, Canada; e-mail: susan.tarlo@utoronto.ca

---

Summary of Suggestions

1. **For every adult patient with chronic cough, we suggest that occupational and environmental causes be routinely elicited in the history.**
   a. **The duration, severity, and temporal relationship of the exposure to the onset or exacerbation of the patient's cough should be noted.**
   b. **Smoking history and atopic history should be elicited.**
   c. **Material Safety Data Sheets and/or occupational hygiene reviews of the workplace may be helpful in the overall assessment of symptoms including cough.**
   d. **The time period between last exposure and medical evaluation should be noted because results of objective testing may be influenced by this** (Ungraded, Consensus Based Statement).

2. **For adult patients with chronic cough, if the history is suggestive of an occupational or environmental association, we suggest that it be confirmed when possible by objective testing, in order to maximize favorable patient outcomes and determine the incidence of occupational and environmental causes of chronic cough. This may include pulmonary function testing and rhinolaryngoscopy** (Ungraded, Consensus Based Statement).

3. **For adult patients with chronic cough with an occupational or environmental exposure history, we suggest that appropriate objective tests should be performed to elucidate potential mechanistic associations between cough and the suspected exposure. These include the following:**
   i. **Methacholine challenge for cough associated with work-related asthma/eosinophilic bronchitis**
   ii. **Sputum/induced sputum cytology for eosinophilia**
   iii. **Before and after exposure tests to demonstrate potential causality (eg, perform both at the end of a regular working week and, if positive, repeat at the end of a period off work such as the end of vacation, to document any work-related changes)**
   iv. **Immunologic tests for hypersensitivity guided by specific exposure history including:**
      1. **Skin tests**
      2. **Specific serum IgE antibodies**
      3. **Specific serum IgG antibodies for suspected hypersensitivity pneumonitis**

   4. **Beryllium lymphocyte proliferation tests for chronic beryllium disease** (Ungraded, Consensus Based Statement)

4. **For adult patients with chronic cough and a high suspicion of cough due to environmental and/or occupational exposures, we suggest that these patients be managed according to evidence-based guidelines for these exposures and/or be referred to specialists with expertise in environmental and occupational disease** (Ungraded, Consensus Based Statement).

The upper and lower respiratory tracts are uniquely exposed to the environment, including irritants, allergens, and noxious chemicals that can cause acute or chronic cough. However, in our recent systematic review of studies where a cough algorithm was employed, we demonstrated a common lack of detailed documentation of potential occupational and environmental contributions to chronic cough.[1] This absence of documentation occurred despite the inclusion in the methods sections of previous recommendations to address occupational and environmental factors, especially in cough guidelines, algorithms, and consensus statements published since 2006. This failure to follow through on a plan of investigation qualifies as intervention infidelity.[2]

In response to occupational and environmental exposures, cough can be an isolated symptom reflecting exposure to an irritant with little physiological consequence, or it can be a manifestation of more significant disease. Consequently, it should be considered as an indicator of a potentially adverse stimulus or underlying disease.

The purpose of this article was to review occupational and environmental contributions to chronic cough with a focus on aspects not previously covered in the 2006 ACCP Cough Guideline[3] or our more recent systematic review,[1] and to provide suggestions for the appropriate investigation and management of these factors when suspected. In our background section, we provide an account of occupational and environmental aspects important to consider in all patients with chronic cough that includes: allergic/hypersensitivity causes, smoke, other nonallergic environmental triggers, occupational causes, and indirect effects of the environment or occupation such as irritable larynx syndromes. However, it is not possible to be fully comprehensive in the scope of causes and mechanisms covered in this consensus document.

Methods

Using the methodology recently reported,[1] a systematic review was initially performed to determine: (1) whether published algorithms and consensus statements on chronic cough included recommendations to address occupational and environmental causative factors in chronic cough; and (2) the extent to which studies that used those algorithms and pathways in patient series with chronic cough used a systematic approach to identify and report occupational and environmental causative factors.

Second, a literature search was performed by using MEDLINE and TOXLINE, supplemented by articles identified by the cough panel occupational and environmental subgroup members, to identify occupational and environmental contributions to chronic cough with a main focus on aspects not previously covered in the previous ACCP Cough Guideline in 2006.[3]

Based on the literature reviews and the Delphi methodology as previously described, the cough panel occupational and environmental subgroup developed guideline recommendations or suggestions. These then underwent review and voting by the full cough panel. For a recommendation or suggestion to be accepted, it had to be voted on by 75% of the eligible Cough Panelists and achieve ratings of "strongly agree" or "agree" by 80% of the voting panelists.

Results

As recently reported,[1] among the 10 general chronic cough guidelines and protocols identified, only the three published since 2006 included advice on detailed occupational and environmental assessments. One additional cough statement focused entirely on occupational cough. However, of the 28 cohort studies of patients with chronic cough that specifically noted that they followed guidelines or protocols, none provided details regarding occupational and environmental assessments, suggesting a gap between recommended guidelines and clinical practice. e-Appendix 1 presents the authors' suggested approach to diagnosis and management of occupational and environmental components to chronic cough.

The literature review as summarized below identified articles relevant to chronic cough and occupational/environmental factors that are categorized as: mechanisms; allergic environmental causes; chronic cough and the recreational and involuntary inhalation of tobacco and marijuana smoke; nonallergic environmental triggers; laryngeal syndromes; and occupational diseases and exposure aspects. Although this is not a comprehensive review, this document is aimed at illustrating the diversity of occupational and environmental factors that should be considered in patients with chronic cough.

Background Information

Mechanisms

There are many examples and potential mechanisms by which occupational and environmental factors may cause or exacerbate an acute or chronic cough, as summarized in Table 1. *Direct effects* of particulates or gas may be to stimulate cough receptors or directly induce asthma,[4-6] and it is possible that direct effects of noxious chemicals such as ammonia, through trigeminal nerve stimulation, may increase awareness of the

TABLE 1] Possible Mechanisms of Occupational and Environmental-Induced Cough

Example	Proximity of Exposure	Stimuli	Effector	References
Construction dust, particulate allergen	Direct	Particulate	Receptor, CN X	4
Asthma	Direct	Particulate		5,6
Ammonia	Direct	Gaseous	Trigeminal nerve, CN V	7[a]
Allergic inflammation, Sinusitis, bronchitis	Indirect	Inflammatory/infectious mediators	Sensory receptor	8,9
Cough-variant asthma	Indirect and direct	Inflammatory mediators		10
Increased receptor sensitivity, altered brainstem pathway, and airway reactivity after removal of caustic agent	Secondary physiology ± psychogenic or conditioned reflex response	All	Threshold shift, neurokinins, decreased inhibition	11-15[a]
Emotional/habit response to familiar triggers	Cortical	All	Central neurologic	16,17

CN V= cranial nerve V; CN X = cranial nerve X.
[a]Anecdotal report with no proven effect on proposed mechanism of cough in humans.

sensation (although this relation specifically to cough has not been substantiated).[7] *Indirect* effects of occupational dust and allergens are strongly associated with secondary infectious or noninfectious sinusitis, bronchitis, and cough-variant asthma, with stimulation of the cough triggered by inflammatory mediators or by direct neurogenic stimulation.[8-10] Secondary physiological changes may similarly result from remodeling of the receptor and neural circuitry, increasing cough sensitivity to subsequent exposures even upon removal of the original trigger.[11-15] In addition, behavioral modifications may result from acute or chronic exposures, perhaps manifesting as somatic cough syndrome.[16,17] The larynx also has a potential role in the mechanism of occupational cough. Phonation can be a significant trigger of cough in patients with chronic cough no matter what the cause of the cough, occurring in approximately 33% of patients.[18,19] Although it is not necessarily linked to the amount of vocal load (ie, cough is not necessarily worse in people who report extensive voice use),[20] it is hard to ignore that trauma from the act of coughing itself may be partly or entirely responsible. For example, a wide spectrum of respiratory complications due to the physical events that can occur during coughing have been reported that includes lower and upper airway trauma associated with severe compression of airways and violent undulations of laryngeal structures.[21-24]

When patients appreciate that speaking provokes coughing, they try to avoid the use of their voice. There is also a high prevalence of voice problems in patients with chronic cough. For example, 40% of patients with chronic cough have clinically significant deviations in auditory perceptual voice quality[25] otherwise known as *hoarseness*. Instrumental assessment of vocal quality, including acoustic voice assessment and electroglottography, shows greater impairment in patients with chronic cough than healthy control subjects.[26] This phenomenon is likely to be exacerbated in those working in professions with high vocal demands such as teachers,[27,28] sports instructors,[29] call center operators,[30] and singers.[31,32] Dysphonia and cough can be exacerbated, particularly when there has been a change in vocal requirements during the course of one's employment. Because overuse of one's voice can trigger cough receptors in the irritated vocal folds,[33] among those who are professional singers, cough could be contributed to by singing and thus qualify as a cough with an occupational component. This phenomenon may be exacerbated in singers with poor vocal technique such as insufficient respiratory support, poor resonance, or excess

laryngeal strain when attempting to reach notes in the upper pitch range.

It has been hypothesized that there could be reduced vocal fold closure during phonation in patients with chronic cough.[34] The high prevalence of breathy vocal quality, abnormal harmonic to noise ratio, and reduced closed phase of vocal fold vibration during electroglottography is consistent with reduced vocal fold closure during phonation. It is unclear whether this is due to increased tension in the posterior cricoarytenoid region, a subconscious effort to avoid vocal fold closure and thus trigger further coughing. Alternatively, it may be due to coughing-induced edema of the vocal folds[35] or laryngeal structures from the previously mentioned violent undulations of laryngeal structures or inflammation from high expiratory velocities that can exert frictional stress on mucosal walls.[23] This physiology may account for some of the aforementioned behavioral modifications.

Further study examining basic science mechanisms and consequences of occupational and environmental exposures on cough is warranted to substantiate causality and help determine safe levels of exposure of potentially noxious materials in the workplace.

Allergy and Chronic Cough

When one considers the potential causes of chronic cough, it is important to remember that two of the most common causes may both have an allergic nidus: upper airway cough syndrome due to a variety of rhinosinus conditions, previously referred to as postnasal drip syndrome, and asthma. In a study by Irwin et al[36] that prospectively examined the prevalence of the causes of cough in a group of 122 consecutive patients in a tertiary care center, it was found that 41% were diagnosed with postnasal drip syndrome and 24% were due to asthma, thus reinforcing the potential of an allergic trigger. Furthermore, when Irwin et al stratified causes of upper airway cough syndrome, they found that 23% were due to allergic rhinitis.

Symptoms associated with allergic rhinitis include nasal obstruction, clear to yellow rhinorrhea, postnasal drip, and nasal pruritus, with paroxysms of sneeze. Conjunctival pruritus and clear discharge may be associated with allergic rhinitis. Pertinent findings on physical examination may include pale, boggy nasal mucosa with clear to yellow rhinorrhea.[37] Symptoms of allergic rhinitis may occur only seasonally or may occur perennially. Generally, allergenic triggers in the spring

include tree and grass pollen, while fall allergens include weeds and molds. Perennial allergens include dust mites, animal dander, cockroach, and indoor molds such as aspergillus and penicillium.

Although asthma generally is associated with wheeze, chest tightness and shortness of breath with auscultatory wheeze, and a prolonged expiratory phase, in some patients the only symptom and finding is cough (ie, cough-variant asthma).[38] Prospective studies have demonstrated that asthma is among the most common etiologies of chronic cough (24%-29%) in adult nonsmokers.[36,38-40] The diagnosis of this illness is made through performance of spirometry, which may demonstrate expiratory obstruction with significant β_2-adrenergic response or normal baseline spirometry with increased airway responsiveness to methacholine. Asthma may have an allergic diathesis and, as noted earlier, allergenic triggers can be stratified into seasonal or perennial causes.

Although upper airway cough syndrome as well as asthma are more common causes of chronic cough, nonasthmatic eosinophilic bronchitis (NAEB) was identified in 13.2% of those with chronic cough in a prospective study by Brightling et al.[41] NAEB was first identified as a cause of chronic cough in 1989 by Gibson et al.[42] As seen in patients with asthma, these patients demonstrate corticosteroid responsiveness; however, they lack spirometric obstructive patterns and bronchial hyperresponsiveness.[43] The diagnosis is made via proof of airway eosinophilia (determined by sputum induction or bronchial wash fluid obtained by bronchoscopy).[43] Not surprisingly, these patients demonstrate atopic tendencies, with elevated sputum eosinophils and increased IL-5 gene expression, as well as an increase in eicosanoid production.[44] Like asthma, the cause of this Th2 milieu upregulation can be uncertain; however, triggers such as allergens[45] and occupational exposures[46] have been reported as the cause of cough due to NAEB.

Thus, because several of the common causes of chronic cough may be mediated by an allergic mechanism, clinicians caring for such patients must be familiar with allergy diagnostic testing to aid in the implementation of environmental control measures, when considering allergy immunotherapy or to aid in titration of pharmacotherapy. When contemplating an allergic etiology to cough, a careful history is of paramount importance. This is important, as results of diagnostic tests (both skin and serum-specific IgE testing) can be positive in the absence of clinical relevance.[47] This is often not equivalent to clinical allergy: these tests prove sensitivity, but results must be interpreted in the context of clinical history.

Chronic Cough and the Recreational and Involuntary Inhalation of Tobacco and Marijuana Smoke

Chronic cough algorithms begin with the premise that if the patient is actively smoking, then smoking cessation should be initiated. Repeated inhalation of biomass smoke directly through consumption of tobacco and marijuana smoke[48] can cause chronic cough and phlegm production.[49] The exposure to secondhand smoke, especially from maternal smoking, has been linked to lower respiratory tract illness in infants and young children, and to cough and asthma in school-aged children.[50] In this section, we briefly review chronic cough in smokers of cigarettes and marijuana as well as exposure to secondhand smoke.

Although animal studies suggest that nicotine can stimulate C fibers,[51] cigarette smoking in humans actually decreases cough sensitivity as measured by capsaicin inhalation.[52] Capsaicin sensitivity recovers within 2 weeks after smoking cessation.[53] Cigarette smoke affects the respiratory tract from the larynx to the alveoli. Laryngeal inflammation and Reinke's edema of the vocal cords are common findings in smokers.[54] Reinke's edema occurs when there is edema of the superficial layer of the lamina propria in the vocal folds, and it is characterized by loosely arranged and fragmented collagen fibers that are intermixed with myxoid stroma.[55]

Close to 60% of inhaled particulates are deposited in the lung. Unprotonated or free-based nicotine in the smoke dissolves easily in lung fluid and passes into the blood. The amount of unprotonated nicotine also correlates with the harshness or smoothness of the cigarette. In addition to mutagenicity, tobacco smoke is disruptive and even cytotoxic to epithelial cells lining the respiratory tract. Tobacco smoke generated by drawing a breath through the butt of a lighted cigarette, cigar, or pipe is called mainstream smoke.[49] Mainstream smoke has a vapor phase and a particulate/tar phase. Both phases contain high concentrations of free radicals. This has been estimated to be as much as 10^{14} free radicals per puff of cigarette.[56] The vapor phase contains cadmium, hydrogen cyanide, acetaldehyde, acrolein, hydrogen sulfide, and volatile organic compounds. Table 2 illustrates the components and the effects of

TABLE 2] Tobacco and Marijuana Smoke Components and Effects

	Mainstream Smoke[a]	Sidestream Smoke[a]
Definition	• The smoke released at the mouth end of the cigarette rod during puffing. • These particles have an average mass median diameter of 0.35-0.40 μm.	• Secondhand or environmental tobacco smoke is an air-diluted mixture of sidestream smoke and exhaled mainstream smoke. • Exhaled mainstream smoke constitutes 1%-43% of secondhand smoke. • There is rapid dilution and dispersion into the indoor environment. • The particulate component decreases more than the vapor phase of the smoke. • The median particle size of secondhand tobacco smoke is smaller than that of the particles of mainstream smoke.
Combustive property	• Mainstream smoke is generated by combustion of the cigarette with temperatures that reach 900°C during a puff and 400°C between puffs. • During a puff, the fire cone at the tip burns the tobacco at the periphery of the cigarette rod.	• Sidestream smoke is generated at 400°C. • It is the tobacco in the core that burns between puffs. • Combustion occurs at a lower temperature and with less available oxygen. • It has more ammonia, resulting in higher alkalinity and more water content than those for mainstream smoke.
Vapor phase[b]	The gas phase of cigarette smoke includes nitrogen, oxygen, carbon dioxide, carbon monoxide, acetaldehyde, methane, hydrogen cyanide, nitric acid, acetone, acrolein, ammonia, methanol, hydrogen sulfide, hydrocarbons, gas phase nitrosamines, and carbonyl compounds. Many heavy metals found in the leaves are volatilized by the heat into the gas phase but are found in the particulate phase of both mainstream smoke and secondhand smoke.	
Particulate phase[b]	The particulate phase includes carboxylic acids, phenols, water, humectants, nicotine, terpenoids, paraffin waxes, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, and catechols.	

Clinical correlates
  1,3 butadiene: carcinogen
  Acrolein: cilia toxic
  Formaldehyde: cilia toxic; irritant
  Nitrogen oxides: oxidant activity
  Cadmium: oxidative injury
  Hydrogen cyanide: cellular oxidative poison
	Sufficient evidence exists to infer a causal conclusion between smoking and the following:
	• Acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease
	• Impaired lung growth during childhood and adolescence
	• Early onset of decline in lung function
	• A premature onset of and an accelerated age-related decline in respiratory symptoms related to lung function in children and adolescents, including coughing, phlegm, wheezing, and dyspnea
	• Asthma-related symptoms in childhood and adolescence
	• All major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea
	• Poor asthma control
	• COPD morbidity and mortality
	• A reduction of lung function in infants of mothers who smoked during pregnancy
		Sufficient evidence exists to infer a causal conclusion between secondhand smoke exposure from parental smoking and the following:
		• Lower respiratory tract illnesses in infants and children
		• Middle ear disease in children, including acute and recurrent otitis media and chronic middle ear effusion
		• Cough, phlegm, wheeze, and breathlessness among children of school age
		• Ever having asthma among children of school age
		• Onset of wheeze illnesses in early childhood from maternal smoking during pregnancy
		• Persistent adverse effects on lung function across childhood
		• Lower level of lung function during childhood
		• Odor annoyance
		• Nasal irritation

The amount, type, blend, and preparation of the tobacco, physical dimensions, paper (porosity), presence and type of filter and smoking habits (puff volume and puff interval) can alter the relative levels of chemical components in mainstream and sidestream smoke.
[a]Data from US Centers for Disease Control and Prevention.[49]
[b]Data from Moir et al.[57]

tobacco and marijuana smoke.[49,57] Acrolein is toxic to ciliated cells. The resulting smoke-induced airway inflammation is a complex cascade of inflammatory cell recruitment, especially of neutrophils, activation, and mediator release.[49,58] The outcome is apoptosis and necrosis of respiratory epithelial cells with mucus plugging and bacterial colonization described in bronchitis.

Secondhand smoke is the air around an active smoker.[49] It is a combination of sidestream smoke coming from the burning tip of a smoldering cigarette and exhaled mainstream smoke. Combustion in sidestream smoke occurs at a lower temperature than mainstream smoke at 400°C. Smoldering burns the core of the cigarette rod in contrast to puffing, which burns the periphery. The composition of sidestream smoke is different from mainstream smoke (Table 2).[57] Current data indicate that secondhand smoke may cause respiratory illness such as chronic obstructive lung disease and lung cancer in exposed adults.[50,59-61] In addition, there is sufficient evidence of a causal relationship between parental smoking and lower respiratory tract illness in young children, and chronic cough and asthma in school-aged children.[50] There are insufficient data at present to draw conclusions as to effects of e-cigarettes, vaping, and hookah use.[62]

Marijuana smoking is associated with chronic cough and sputum production.[63] Current commercially manufactured filtered cigarettes have approximately 1 g of tobacco, while a hand-rolled "joint" typically contains one-half a gram of marijuana and is often mixed with tobacco in a 50/50 combination (so-called spliffs).[64] The tar content differs depending on whether a joint is filtered, unfiltered, smoked as a blunt (ie, hollowed out cigar stuffed with marijuana), or smoked through a waterpipe. There are also lot-to-lot differences with the emergence of so-called designer preparations.[65] Although marijuana smokers typically do not and cannot consume as many joints as cigarette smokers consume cigarettes each day and remain functional, they inhale deeper and hold their breath longer, resulting in four times the tar deposited in their lungs per joint versus each cigarette.[63] Using a standard cigarette manufacturing criteria, marijuana mainstream smoke was compared with cigarette smoke and was found to have a similar amount of tar but significantly higher levels of nitric oxide, ammonia, hydrogen cyanide, and aromatic amines compared with a cigarette.[57] A review by

Tashkin[48] summarized the effects of smoking marijuana on the respiratory system and found an increase in prevalence of chronic cough, phlegm production, wheezing, and dyspnea in habitual smokers of marijuana. He also found significant airway inflammation with squamous cell hyperplasia, loss of ciliated cells, vascular proliferation, submucosal edema, and goblet cell hyperplasia in the endobronchial biopsy specimens of marijuana smokers similar to tobacco smokers.[66,67] Airway inflammation induced by marijuana smoking is indistinguishable from tobacco-induced changes, but there are no data available on effects of sidestream or secondhand smoke from marijuana.

It is important for the clinician who is evaluating a patient with chronic cough to inquire not only about tobacco but also marijuana smoking. Secondhand exposure to tobacco smoke is especially important in the evaluation of children with chronic cough.

Other Non-IgE Antibody Environmental Triggers: Mechanisms, Identification, Diagnosis, and Management

Environmental exposures that cause or exacerbate chronic cough may produce these effects through a mechanism that is not mediated by specific IgE antibodies. Respiratory irritants include vapors, gases, dusts, and fumes. These can cause simple chronic bronchitis (chronic cough and sputum), or COPD,[68,69] and can cause or increase risks of asthma.[70] Effects can be magnified among smokers.[71] Among those who already have airway disease and cough, these exposures can also exacerbate cough. Rhinitis and laryngeal syndromes can also be caused or exacerbated in a similar manner. These exposures can occur in the workplace but also in homes or in outdoor environments. A few examples outside workplace settings are exposures to emissions from biomass fuel[72] or wood stoves for cooking or heating,[73] air pollution,[74] and natural disasters such as volcano ash,[75] and wildfires,[76] as well as man-made disasters such as the World Trade Center collapse.[77] The cough that occurred in those exposed to the highly alkaline inhaled dust following the World Trade Center collapse was likely multifactorial[78] and in different people may have resulted from new onset or exacerbation of asthma, bronchitis,[79] rhinitis, laryngeal syndromes, and possibly also gastroesophageal reflux disease resulting from swallowed dust.[80,81] An additional later effect that also may have caused cough was bronchiolitis.[82]

Within the home environment, hobbies and avocations may also result in irritant exposures to vapors, gases, dusts, and fumes such as glues for making models, paints, solvents, cleaning products, exposures from home renovations leading to exposures to insulation and other dusts, fungal components, and other potential irritant agents or antigens. As another example, exposure to birds or to feathers in down duvets or clothing can lead to hypersensitivity pneumonitis.

Fungal contamination of homes (or in work buildings including classrooms) may cause exposure to volatile organic emissions that may be associated with an upper airway cough in the absence of specific IgE antibodies, through a presumed irritant mechanism. There also has been an association between such exposure and increased respiratory symptoms in children living in damp/moldy homes.[83,84] Mold exposure can also be a cause of cough in association with hypersensitivity pneumonitis.[3]

Diagnosis of the environmental contribution relies on the documentation of the underlying disease (pulmonary function tests/chest/sinus imaging/induced sputum/ears, nose, and throat assessment), and the history of exposure in relation to the timing of cough. For those who have had an accidental exposure and have developed a chronic cough following this exposure, it is useful to review previous health records to identify preceding disease, and to assess possible atopic disease as discussed earlier. The development of similar symptoms in others who were exposed adds to the probability of an association. Occasionally a home visit or formal environmental assessment may be useful, for example, to document fungal contamination. If hypersensitivity pneumonitis is suspected, accepted diagnostic pathways should be followed.[85,86]

Management of an environmental non-IgE antibody contribution to chronic cough includes pharmacologic management as for other causes of cough but also includes avoidance of further exposure to the relevant agents as reasonable.

Occupational and Environmental Aspects of Cough From Laryngeal Syndromes, and Cough Hypersensitivity Syndrome

The concept of occupational cough can include cough associated with conditions such as laryngeal syndromes (eg, muscle tension dysphonia or paradoxical vocal fold movement).

There is a degree of overlap between occupational cough and other descriptions of cough in the literature such as cough hypersensitivity syndrome,[87] unexplained cough, and irritant-induced vocal cord dysfunction that requires further elaboration. The clinical presentation between these conditions is similar, and environmental exposures such as temperature changes, mechanical irritation, or chemical exposures may trigger cough in an already hypersensitive system.

Clinical Approach to Diagnosis and Management of Laryngeal Disorders

The high prevalence of laryngeal symptoms in patients with chronic cough[25] suggests that screening for laryngeal disorders should occur as part of the initial assessment. Screening tools for laryngeal disorders have not been developed specifically for patients with occupational cough. Screening can involve assessment for potential laryngeal disorders that could include laryngeal symptoms such as inspiratory dyspnea, laryngeal irritation, dysphonia, tightness in the throat, or cough triggered by talking. Alternatively, screening for specific laryngeal symptoms could be performed as part of the initial speech-language pathology assessment.

Suggested indicators for referral for evaluation of laryngeal dysfunction include history of dysphonia or episodic voice loss, significant laryngeal irritation, and co-existing symptoms of paradoxical vocal fold movement. These factors are more likely to be important in patients in vocally demanding professions such as teachers and singers.

Although noxious triggers such as exposure to smoke and fumes can be easily modified, it can be more difficult to modify many of the innocuous or nontussive cough triggers that continue to exacerbate the condition. For example, exposure to cold air and talking are common everyday occurrences and difficult to modify without incurring significant lifestyle restrictions.[19]

Occupational Diseases and Exposure Aspects

Occupational exposures can cause a cough by the same mechanisms detailed above for environmental allergic/hypersensitivity responses, including asthma, hypersensitivity pneumonitis, or nonallergic rhinitis and bronchitis. In addition, a cough caused by work may be due to an occupational cause of lung cancer or respiratory diseases such as chronic beryllium disease. The previous ACCP Cough Guidelines[3] included a review of these causes as has the more recent European Academy of Allergy Asthma and Clinical Immunology Task Force Statement on Occupational Causes of Cough.[88]

The occupational contribution to the burden of asthma is estimated to be about 18% and to COPD approximately 15%,[69,89,90] but there is little evidence for the population-attributable risk of work-related cough. One estimate has been 4% to 18%, but a distinction between personal causes of cough and occupational causes in published articles has not been clear, and the estimate range is wide.[91] Following the World Trade Center collapse, 10% of those highly exposed to the alkaline dust developed a chronic cough.[92,93]

Since the occupational and environmental component of the 2006 ACCP Consensus Statement on chronic cough[3] appeared in print, several additional publications have reported chronic cough to be associated with work exposures. Examples showing the range and frequency include mild steel welding with metal and gas exposure such as manganese and ozone (in 24% of workers),[94] sea-fish processing,[95] compost workers and garbage collectors.[96,97] Among Egyptian textile workers, chronic cough was reported in 33% compared with 6% of control subjects,[98] and among brick kiln workers in Pakistan, 22% had a chronic cough.[99] There has also been an occupational association made between gastroesophageal reflux disease and cough[100] in choristers and in first responders following exposure to World Trade Center irritants.[80,82,92] For most epidemiologic studies, the mechanism of cough has not been explored in detail and may occur from several mechanisms within the same population, including upper airway irritation, irritant bronchitis, smoking-related bronchitis, upper airway cough syndrome, and, in some cases asthma, COPD, or hypersensitivity pneumonitis.

For patients with an occupational cause of cough, the diagnosis has additional implications beyond identifying the specific causes of cough, notably including: (1) the potential need to modify work conditions or even to change a job and/or leave a workplace; (2) the need to provide objective support for a workers' compensation claim; and (3) the need to consider possible similar effects on co-workers and to introduce appropriate protective measures to reduce risks. As with environmental allergic or irritant causes of cough, control or avoidance of exposure is often a key component of management. Use of respiratory protective equipment at work may be effective for transient exposures, but it is not a substitute for appropriate control of air concentrations in the workplace by substitution of hazardous products when possible, use of robotics, containment and optimum ventilation as well as other occupational hygiene measures.

In a similar manner to the identification of allergy as a cause of symptoms, the identification of an occupational cause of chronic cough relies primarily on the history. If the cough is a component of other respiratory disease with long latency such as asbestosis or chronic beryllium disease, a full occupational history is then needed to identify possible causative exposures and occupations that potentially may have occurred many years before the onset of symptoms. Conversely, if the cough is due to diseases such as allergic rhinitis, asthma, NAEB, or hypersensitivity pneumonitis, the occupational history should then focus on exposures within hours of the onset of symptoms. Similarly, there are several nonallergic causes of cough with rapid onset of symptoms such as irritant laryngitis or bronchitis, and other conditions with onset of symptoms several hours after exposure such as organic dust toxic syndrome, metal fume fever, and humidifier fever. In addition, for occupational diseases with relatively short latency, it is important to inquire as to a history of worsening symptoms at work or after work and improvement during periods away from work.

Further investigations, in addition to chest imaging, will depend on the suspected occupational disease, as have been detailed in previous guidelines and consensus statements.[3,88,101,102] When possible, an objective confirmation of the diagnosis and the occupational contribution is important to prevent unnecessary changes in work and to allow appropriate workers' compensation decisions. This is most readily achieved for patients with work-related asthma or acute hypersensitivity pneumonitis in whom monitoring of pulmonary function tests during periods at work and off work can show the work relationship. Immunologic tests can support the diagnosis for those with an occupational allergic cause and for those with work-related hypersensitivity pneumonitis, but there are only limited available extracts for occupational allergens and antigens to use in testing. Specific inhalational challenges may be performed to identify the causative agent in rhinitis, asthma, and hypersensitivity pneumonitis but need expertise in performing these tests, and carry potential risk, so are seldom performed in North America.

Management and prevention have also been discussed in previous statements but include potential changes to the workplace exposure, both for the patient and to prevent similar effects in co-workers.

Suggestions

1. **For every adult patient with chronic cough, we suggest that occupational and environmental causes be routinely elicited in the history.**
    a. **The duration, severity, and temporal relationship of the exposure to the onset or exacerbation of the patient's cough should be noted.**
    b. **Smoking history and atopic history should be elicited.**
    c. **Material Safety Data Sheets and/or occupational hygiene reviews of the workplace may be helpful in the overall assessment of symptoms including cough.**
    d. **The time period between last exposure and medical evaluation should be noted because results of objective testing may be influenced by this** (Ungraded, Consensus Based Statement).

2. **For adult patients with chronic cough, if the history is suggestive of an occupational or environmental association, we suggest that it be confirmed when possible by objective testing, in order to maximize favorable patient outcomes and determine the incidence of occupational and environmental causes of chronic cough. This may include pulmonary function testing and rhinolaryngoscopy** (Ungraded, Consensus Based Statement).

3. **For adult patients with chronic cough with an occupational or environmental exposure history, we suggest that appropriate objective tests should be performed to elucidate potential mechanistic associations between cough and the suspected exposure. These include the following:**
    i. **Methacholine challenge for cough associated with work-related asthma/eosinophilic bronchitis**
    ii. **Sputum/induced sputum cytology for eosinophilia**
    iii. **Before and after exposure tests to demonstrate potential causality (eg, perform both at the end of a regular working week and, if positive, repeat at the end of a period off work such as the end of vacation, to document any work-related changes)**
    iv. **Immunologic tests for hypersensitivity guided by specific exposure history including:**
        1. **Skin tests**
        2. **Specific serum IgE antibodies**
        3. **Specific serum IgG antibodies for suspected hypersensitivity pneumonitis**
        4. **Beryllium lymphocyte proliferation tests for chronic beryllium disease** (Ungraded, Consensus Based Statement)

4. **For adult patients with chronic cough and a high suspicion of cough due to environmental and/or occupational exposures, we suggest that these patients be managed according to evidence-based guidelines for these exposures and/or be referred to specialists with expertise in environmental and occupational disease** (Ungraded, Consensus Based Statement).

Future Studies Needed to Address Gaps in Evidence or Knowledge

- Development of additional diagnostic tests to allow objective evidence of the relationship between chronic cough and occupational or environmental triggers (currently the association with common environmental allergens can be inferred in patients with an appropriate history, from allergy skin tests, and in vitro serologic tests, but there are very limited extracts available for identifying allergic responses to many fungi and to many occupational allergens and chemical sensitizers).
- Simpler practical tests need to be available to clinicians to diagnose cough from eosinophilic bronchitis due to occupational and environmental causes (induced sputum cytology is of limited availability and induced sputum cannot be obtained in all patients with this suspected condition). The role of exhaled nitric oxide as a possible alternative diagnostic test for occupational/environmental eosinophilic bronchitis causing cough should be evaluated.
- The mechanism(s) of occupational and environmental triggers to laryngeal syndromes causing chronic cough should be further identified and management strategies identified in clinical trials using questionnaires with well-documented cough scales.
- The occupational contribution to the burden of chronic cough should be assessed in large population studies.
- Prospective studies of populations with chronic cough should identify the relative frequency of occupational and environmental causes of cough and effects following modification of these factors.

Conclusions

Since the previous ACCP cough statement in 2006, there has been an increased understanding of the mechanisms of cough related to environmental triggers. There have also been several studies that have clarified laryngeal

disorders leading to chronic cough, and the role of occupational and environmental triggers for laryngeal causes of cough. Evidence-based consensus documents have been developed for occupational asthma and for occupational causes of cough. Despite this, there remains a gap between the recommended assessment of occupational and environmental causes of cough, and the reported systematic assessment of these factors in published clinical case series, and there is a need for further documentation of occupational and environmental contributions to cough in the future. Identification of occupational and environmental causes of chronic cough can affect symptom management and offers opportunity for exposure control and prevention.

Acknowledgments

References

1. Tarlo SM, Altman KW, French CT, Diekemper RL, Irwin RS. Evaluation of occupational and environmental factors in the assessment of chronic cough in adults: a systematic review. *Chest.* 2016;149(1):143-160.

2. French CT, Diekemper RL, Irwin RS. Assessment of intervention fidelity and recommendations for researchers conducting studies on the diagnosis and treatment of chronic cough in the adult: CHEST Guideline and Expert Panel Report. *Chest.* 2015;148(1):32-54.

3. Tarlo SM. Cough: occupational and environmental considerations: ACCP evidence-based clinical practice guidelines. *Chest.* 2006;129(suppl 1):186s-196s.

4. Maier KL, Alessandrini F, Beck-Speier I, et al. Health effects of ambient particulate matter—biological mechanisms and inflammatory responses to in vitro and in vivo particle exposures. *Inhal Toxicol.* 2008;20(3):319-337.

5. Deering-Rice CE, Shapiro D, Romero EG, et al. Activation of transient receptor potential ankyrin-1 by insoluble particulate material and association with asthma. *Am J Respir Cell Mol Biol.* 2015;53(6):893-901.

6. He M, Ichinose T, Liu B, et al. Silica-carrying particulate matter enhances Bjerkandera adusta-induced murine lung eosinophilia. *Environ Toxicol.* 2016;31(1):93-105.

7. Petrova M, Diamond J, Schuster B, Dalton P. Evaluation of trigeminal sensitivity to ammonia in asthmatics and healthy human volunteers. *Inhal Toxicol.* 2008;20(12):1085-1092.

8. Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. *Am J Respir Crit Care Med*. 2004;169(1):15-19.

9. Grace M, Birrell MA, Dubuis E, Maher SA, Belvisi MG. Transient receptor potential channels mediate the tussive response to prostaglandin E2 and bradykinin. *Thorax*. 2012;67(10):891-900.

10. Liu M, Liu K, Zhu N, Xia J, Chen X. Inflammatory mediators in induced sputum and airway hyperresponsiveness in cough variant asthma during long-term inhaled corticosteroid treatment. *Mediators Inflamm*. 2012;2012:403868.

11. Mazzone SB, McGovern AE. Na+-K+-2Cl- cotransporters and Cl- channels regulate citric acid cough in guinea pigs. *J Appl Physiol (1985)*. 2006;101(2):635-643.

12. Canning BJ. Afferent nerves regulating the cough reflex: mechanisms and mediators of cough in disease. *Otolaryngol Clin North Am*. 2010;43(1):15-25, vii.

13. Barnes PJ. Neurogenic inflammation in the airways. *Respir Physiol*. 2001;125(1-2):145-154.

14. Paton JF. Pattern of cardiorespiratory afferent convergence to solitary tract neurons driven by pulmonary vagal C-fiber stimulation in the mouse. *J Neurophysiol*. 1998;79(5):2365-2373.

15. Altman KW, Noordzij JP, Rosen CA, Cohen S, Sulica L. Neurogenic cough. *Laryngoscope*. 2015;125(7):1675-1681.

16. Vertigan AE, Murad MH, Pringsheim T, et al. Somatic cough syndrome (previously referred to as psychogenic cough) and tic cough (previously referred to as habit cough) in adults and children: CHEST Guideline and Expert Panel Report. *Chest*. 2015;148(1):24-31.

17. Haydour Q, Alahdab F, Farah M, et al. Management and diagnosis of psychogenic cough, habit cough, and tic cough: a systematic review. *Chest*. 2014;146(2):355-372.

18. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Voice and upper airway symptoms in people with chronic cough and paradoxical vocal fold movement. *J Voice*. 2007;21(3):361-383.

19. Vertigan A, Gibson P. Chronic refractory cough as a laryngeal sensory neuropathy: evidence from a reinterpretation of cough triggers. *J Voice*. 2011;25(5):596-601.

20. Vertigan AE, Bone SL, Gibson PG. Laryngeal sensory dysfunction in laryngeal hypersensitivity syndrome. *Respirology*. 2013;18(6):948-956.

21. Irwin RS. Complications of cough: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(suppl 1):54S-58S.

22. Irwin RS, Ownbey R, Cagle PT, Baker S, Fraire AE. Interpreting the histopathology of chronic cough: a prospective, controlled, comparative study. *Chest*. 2006;130(2):362-370.

23. Singh V, Chowdhary R, Chowdhary N. The role of cough and hyperventilation in perpetuating airway inflammation in asthma. *J Assoc Physicians India*. 2000;48(3):343-345.

24. Von Leden H, Isshiki N. An analysis of cough at the level of the larynx. *Arch Otolaryngol*. 1965;81:616-625.

25. Vertigan AE, Theodoros DG, Winkworth AL, Gibson PG. Perceptual voice characteristics in chronic cough and paradoxical vocal fold movement. *Folia Phoniatr Logop*. 2007;59(5):256-267.

26. Vertigan AE, Theodoros DG, Winkworth AL, Gibson PG. Acoustic and electroglottographic voice characteristics in chronic cough and paradoxical vocal fold movement. *Folia Phoniatr Logop*. 2008;60(4):210-216.

27. Lin FC, Chen SH, Chen SC, Wang CT, Kuo YC. Correlation between acoustic measurements and self-reported voice disorders among female teachers. *J Voice*. 2015;18(15). 00109-00105.

28. Pereira ER, Tavares EL, Martins RH. Voice disorders in teachers: clinical, videolaryngoscopical, and vocal aspects. *J Voice*. 2015;29(5):564-571.

29. Rumbach AF. Voice problems of group fitness instructors: diagnosis, treatment, perceived and experienced attitudes and expectations of the industry. *J Voice*. 2013;27(6):19.

30. Hazlett DE, Duffy OM, Moorhead SA. Occupational voice demands and their impact on the call-centre industry. *BMC Public Health*. 2009;9(108):1471-2458.

31. Phyland DJ, Oates J, Greenwood KM. Self-reported voice problems among three groups of professional singers. *J Voice*. 1999;13(4):602-611.

32. Guss J, Sadoughi B, Benson B, Sulica L. Dysphonia in performers: toward a clinical definition of laryngology of the performing voice. *J Voice*. 2014;28(3):349-355.

33. Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. *Chest*. 2014;146(6):1633-1648.

34. Murry T, Tabaee A, Aviv J. Respiratory retraining of refractory cough and laryngopharyngeal reflux in patients with paradoxical vocal fold movement disorder. *Laryngoscope*. 2004;114(8):1341-1345.

35. Irwin RS, Pratter MR, Holland PS, Corwin RW, Hughes JP. Postnasal drip causes cough and is associated with reversible upper airway obstruction. *Chest*. 1984;85(3):346-352.

36. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis*. 1990;141(3):640-647.

37. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol*. 2008;122(suppl 2):S1-S84.

38. Dicpinigaitis PV. Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(suppl 1):75S-79S.

39. McGarvey LP, Heaney LG, Lawson JT, et al. Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. *Thorax*. 1998;53(9):738-743.

40. Yacoub MR, Malo JL, Labrecque M, Cartier A, Lemiere C. Occupational eosinophilic bronchitis. *Allergy*. 2005;60(12):1542-1544.

41. Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med*. 1999;160(2):406-410.

42. Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave FE. Chronic cough: eosinophilic bronchitis without asthma. *Lancet*. 1989;1(8651):1346-1348.

43. Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest*. 2006;129(suppl 1):116S-121S.

44. Brightling CE, Ward R, Woltmann G, et al. Induced sputum inflammatory mediator concentrations in eosinophilic bronchitis and asthma. *Am J Respir Crit Care Med*. 2000;162(3 pt 1):878-882.

45. Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin Exp Allergy*. 2000;30(1):41-47.

46. Quirce S. Eosinophilic bronchitis in the workplace. *Curr Opin Allergy Clin Immunol*. 2004;4(2):87-91.

47. Cox L, Williams B, Sicherer S, et al. Pearls and pitfalls of allergy diagnostic testing: report from the American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunology Specific IgE Test Task Force. *Ann Allergy Asthma Immunol*. 2008;101(6):580-592.

48. Tashkin DP. Effects of marijuana smoking on the lung. *Ann Am Thorac Soc*. 2013;10(3):239-247.

49. US Centers for Disease Control and Prevention. Chapter 3. Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm. In: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. In: National Center for Chronic Disease Prevention and Health Promotion (US), ed. Atlanta, GA: US Department of Health and Human Services; 2010.

50. US Centers for Disease Control and Prevention. Chapter 6. Respiratory effects in children from exposure to secondhand smoke. In: *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, GA: National Center for Biotechnology Information; 2006.

51. Lee LY, Burki NK, Gerhardstein DC, Gu Q, Kou YR, Xu J. Airway irritation and cough evoked by inhaled cigarette smoke: role of neuronal nicotinic acetylcholine receptors. *Pulm Pharmacol Ther.* 2007;20(4):355-364.

52. Dicpinigaitis PV. Cough reflex sensitivity in cigarette smokers. *Chest.* 2003;123(3):685-688.

53. Dicpinigaitis PV, Sitkauskiene B, Stravinskaite K, Appel DW, Negassa A, Sakalauskas R. Effect of smoking cessation on cough reflex sensitivity. *Eur Respir J.* 2006;28(4):786-790.

54. Marcotullio D, Magliulo G, Pezone T. Reinke's edema and risk factors: clinical and histopathologic aspects. *Am J Otolaryngol.* 2002;23(2):81-84.

55. Sakae FA, Imamura R, Sennes LU, Mauad T, Saldiva PH, Tsuji DH. Disarrangement of collagen fibers in Reinke's edema. *Laryngoscope.* 2008;118(8):1500-1503.

56. Pryor WA, Prier DG, Church DF. Electron-spin resonance study of mainstream and sidestream cigarette smoke: nature of the free radicals in gas-phase smoke and in cigarette tar. *Environ Health Perspect.* 1983;47:345-355.

57. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol.* 2008;21(2):494-502.

58. van der Vaart H, Postma D, Timens W, Ten Hacken N. Acute effects of cigarette smoke on inflammation and oxidative stress: a review. *Thorax.* 2004;59(8):713-721.

59. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet.* 2009;374(9691):733-743.

60. Yin P, Jiang CQ, Cheng KK, et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet.* 2007;370(9589):751-757.

61. Stayner L, Bena J, Sasco AJ, et al. Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health.* 2007;97(3):545-551.

62. Rowell TR, Tarran R. Will chronic e-cigarette use cause lung disease? *Am J Physiol Lung Cell Mol Physiol.* 2015;309(12):L1398-L1409.

63. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med.* 1988;318(6):347-351.

64. National Institute of Health National Institute on Drug Abuse. Facts about marijuana and marijuana abuse. NIDA Notes, Volume 11, Number 2, 1996. National Institute on Drug Abuse website. http://archives.drugabuse.gov/NIDA_Notes/NNVol11N2/MarijuanaTearoff.html. Accessed November 3, 2016.

65. Sifaneck SJ, Ream GL, Johnson BD, Dunlap E. Retail marijuana purchases in designer and commercial markets in New York City: sales units, weights, and prices per gram. *Drug Alcohol Depend.* 2007;90(suppl 1):S40-S51.

66. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest.* 1997;112(2):319-326.

67. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young marijuana and tobacco smokers. *Am J Respir Crit Care Med.* 1998;157(3):928-937.

68. Waked M, Salame J, Khayat G, Salameh P. Correlates of COPD and chronic bronchitis in nonsmokers: data from a cross-sectional study. *Int J Chron Obstruct Pulmon Dis.* 2012;7:577-585.

69. Balmes J, Becklake M, Blanc P, et al. American Thoracic Society Statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med.* 2003;167(5):787-797.

70. Vandenplas O, Wiszniewska M, Raulf M, et al. EAACI position paper: irritant-induced asthma. *Allergy.* 2014;69(9):1141-1153.

71. Blanc PD, Iribarren C, Trupin L, et al. Occupational exposures and the risk of COPD: dusty trades revisited. *Thorax.* 2009;64(1):6-12.

72. Kim YJ, Jung CY, Shin HW, Lee BK. Biomass smoke induced bronchial anthracofibrosis: presenting features and clinical course. *Respir Med.* 2009;103(5):757-765.

73. Sood A, Petersen H, Blanchette CM, et al. Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers. *Am J Respir Crit Care Med.* 2010;182(9):1098-1104.

74. Cai Y, Schikowski T, Adam M, et al. Cross-sectional associations between air pollution and chronic bronchitis: an ESCAPE meta-analysis across five cohorts. *Thorax.* 2014;69(11):1005-1014.

75. Longo BM, Yang W, Green JB, Crosby FL, Crosby VL. Acute health effects associated with exposure to volcanic air pollution (vog) from increased activity at Kilauea Volcano in 2008. *J Toxicol Environ Health A.* 2010;73(20):1370-1381.

76. Mirabelli MC, Kunzli N, Avol E, et al. Respiratory symptoms following wildfire smoke exposure: airway size as a susceptibility factor. *Epidemiology.* 2009;20(3):451-459.

77. Rom WN, Reibman J, Rogers L, et al. Emerging exposures and respiratory health: World Trade Center dust. *Proc Am Thorac Soc.* 2010;7(2):142-145.

78. Guidotti TL, Prezant D, de la Hoz RE, Miller A. The evolving spectrum of pulmonary disease in responders to the World Trade Center tragedy. *Am J Ind Med.* 2011;54(9):649-660.

79. Mauer MP, Cummings KR, Hoen R. Long-term respiratory symptoms in World Trade Center responders. *Occup Med (Lond).* 2010;60(2):145-151.

80. de la Hoz RE, Christie J, Teamer JA, et al. Reflux symptoms and disorders and pulmonary disease in former World Trade Center rescue and recovery workers and volunteers. *J Occup Environ Med.* 2008;50(12):1351-1354.

81. McCabe D, Altman KW. Laryngeal hypersensitivity in the World Trade Center-exposed population: the role for respiratory retraining. *Am J Respir Crit Care Med.* 2012;186(5):402-403.

82. Mann JM, Sha KK, Kline G, Breuer FU, Miller A. World Trade Center dyspnea: bronchiolitis obliterans with functional improvement: a case report. *Am J Ind Med.* 2005;48(3):225-229.

83. Yang CY, Lin MC, Hwang KC. Childhood asthma and the indoor environment in a subtropical area. *Chest.* 1998;114(2):393-397.

84. Institute of Medicine of the National Academies, Committee on Damp Indoor Spaces and Health Board on Health Promotion and Disease Prevention. *Damp Indoor Spaces and Health, Chapter 5. Human health effects associated with damp indoor environments, Respiratory Symptoms.* Washington, DC: The National Academies Press; 2004.

85. Schuyler M, Cormier Y. The diagnosis of hypersensitivity pneumonitis. *Chest.* 1997;111(3):534-536.

86. Lacasse Y, Selman M, Costabel U, et al. Clinical diagnosis of hypersensitivity pneumonitis. *Am J Respir Crit Care Med.* 2003;168(8):952-958.

87. Chung KF. Approach to chronic cough: the neuropathic basis for cough hypersensitivity syndrome. *J Thorac Dis.* 2014;6(suppl 7):S699-S707.

88. Moscato G, Pala G, Cullinan P, et al. EAACI position paper on assessment of cough in the workplace. *Allergy.* 2014;69(3):292-304.

89. Blanc PD. Occupation and COPD: a brief review. *J Asthma.* 2012;49(1):2-4.

90. Toren K, Blanc PD. Asthma caused by occupational exposures is common—a systematic analysis of estimates of the population-attributable fraction. *BMC Pulm Med.* 2009;9:7.

91. Groneberg DA, Nowak D, Wussow A, Fischer A. Chronic cough due to occupational factors. *J Occup Med Toxicol.* 2006;1:3.

92. Prezant DJ, Weiden M, Banauch GI, et al. Cough and bronchial responsiveness in firefighters at the World Trade Center site. *N Engl J Med.* 2002;347(11):806-815.

93. Weakley J, Webber MP, Gustave J, et al. Trends in respiratory diagnoses and symptoms of firefighters exposed to the World Trade Center disaster: 2005-2010. *Prev Med.* 2011;53(6):364-369.

94. Hedmer M, Karlsson JE, Andersson U, Jacobsson H, Nielsen J, Tinnerberg H. Exposure to respirable dust and manganese and prevalence of airways symptoms, among Swedish mild steel welders in the manufacturing industry. *Int Arch Occup Environ Health.* 2014;87(6):623-634.

95. Shiryaeva O, Aasmoe L, Straume B, Bang BE. Respiratory symptoms, lung functions, and exhaled nitric oxide (FENO) in two types of fish processing workers: Russian trawler fishermen and Norwegian salmon industry workers. *Int J Occup Environ Health*. 2015;21(1):53-60.

96. Hoffmeyer F, van Kampen V, Taeger D, et al. Prevalence of and relationship between rhinoconjunctivitis and lower airway diseases in compost workers with current or former exposure to organic dust. *Ann Agric Environ Med*. 2014;21(4):705-711.

97. Schantora AL, Casjens S, Deckert A, et al. Prevalence of work-related rhino-conjunctivitis and respiratory symptoms among domestic waste collectors. *Adv Exp Med Biol*. 2015;834:53-61.

98. Beshir S, Mahdy-Abdallah H, Saad-Hussein A. Ventilatory functions in cotton textile workers and the role of some inflammatory cytokines. *Toxicol Ind Health*. 2013;29(2):114-120.

99. Shaikh S, Nafees AA, Khetpal V, Jamali AA, Arain AM, Yousuf A. Respiratory symptoms and illnesses among brick kiln workers: a cross sectional study from rural districts of Pakistan. *BMC Public Health*. 2012;12:999.

100. Cammarota G, Masala G, Cianci R, et al. Reflux symptoms in professional opera choristers. *Gastroenterology*. 2007;132(3):890-898.

101. Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. *Chest*. 2008;134(suppl 3):1S-41S.

102. Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med*. 2005;62(5):290-299.