CHAPTER 3

Lung Disease in Flavoring and Food Production: Learning from Butter Flavoring

Nancy Sahakian* and **Kathleen Kreiss***

Contents

*Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Division of Respiratory Disease Studies, Morgantown, West Virginia 26505

Advances in Food and Nutrition Research, Volume 55
ISSN 1043-4526, DOI: 10.1016/S1043-4526(08)00403-8

Abstract Workers in the food industry are exposed to multiple respiratory hazards that include irritants, allergens, and substances capable of causing destruction and scarring of the lungs. Cases of constrictive bronchiolitis obliterans, a severe potentially disabling lung disease, have been identified in workers exposed to flavorings. Workplace engineering controls, work practices, and respiratory protection can minimize potential exposures. Medical surveillance of workers exposed to known respiratory hazards will help to identify disease early, facilitate the prompt removal of workers from the causative exposure(s), and prevent further worsening and/or permanence of disease. When companies or employees suspect occupational respiratory disease, they can involve public health agencies to investigate any excess risk of lung disease, risk factors among processes and exposures, and effectiveness of interventions, if needed.

I. INTRODUCTION

In 2000, the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) became aware of eight former workers of a microwave popcorn facility who had been diagnosed with a rare lung disease, bronchiolitis obliterans (BO). Further investigation determined that exposure to artificial butter flavoring was the causative agent. Additional cases of flavoring-related BO were subsequently identified in workers in the microwave popcorn-, flavor-, and diacetyl-[1] manufacturing industries. Worksite interventions helped to prevent BO in other workers exposed to flavoring chemicals. In this chapter, we describe the anatomy and defense mechanisms of the respiratory tract, medical tests used to diagnose respiratory diseases, occupational respiratory diseases, specific respiratory hazards in the food industry, how exposures can be reduced, and how workers can be monitored through medical surveillance to allow early identification and protection of affected workers. Finally, we outline the discovery that occurred as a result of the public health response to cases of BO in workers in the microwave popcorn and flavoring industries.

This information can assist in future identification of other occupationally related respiratory diseases in the food industry.

[1] Diacetyl is a major component of butter flavoring.

II. RESPIRATORY TRACT ANATOMY AND DEFENSE MECHANISMS

The upper respiratory tract includes the nasal passages, sinuses, pharynx (mouth and throat), and larynx (voice box). The lower respiratory tract includes the trachea, bronchial tree (bronchi, bronchioles, terminal bronchioles, and respiratory bronchioles), air sacs (alveoli), and supporting tissue (interstitium). The internal caliber of the airways decreases with sequential branching of the bronchial tree. Bronchioles have a diameter of about 1 mm. Terminal bronchioles have a diameter of about 0.3–0.5 mm. Compared to the larger airways, smaller airways are composed of proportionately less cartilage and more smooth muscle; at the level of the terminal bronchioles, smooth muscle totally circumscribes the airways. Rapid exchange of gases between the air in the air sacs and the blood in the capillaries is facilitated by the thin air sac wall that is only several cells thick and by the proximity of capillaries (the smallest blood vessels).

Large inhaled particles are entrapped by hairs in the nasal passages. Many of the smaller inhaled particles are entrapped in the mucus layer that coats the respiratory tract. Small particles that reach the air sacs are engulfed and ingested by immune cells called macrophage cells. Particles that contain irritating chemical substances can damage the site in the respiratory tract where they impact; however, even inert particles can damage the respiratory tract at high enough concentrations. The mucus layer also absorbs highly water-soluble chemicals, such as ammonia and formaldehyde, and prevents these chemicals from penetrating deeper into the lung. Mucous glands within the respiratory tract, as well as goblet cells on the internal surface of the respiratory tract, create the mucus. Additionally, cells with hair-like projections, called cilia located alongside goblet cells, propel the mucus layer with its entrapped particles and chemical contaminants upward where the mucus is either swallowed or coughed out. The lungs are able to repair minor injuries by replacing damaged cells with normal lung cells. Repetitive or excessive injury may result in permanent loss of lung tissue or repair with scar tissue. Scarring can occur within the air sacs, the airways, or the supporting tissue of the lung.

III. MEDICAL TESTS USED TO DIAGNOSE LUNG DISEASE

A spirometry test is a breathing test in which a person takes as deep a breath as possible and blows out quickly and completely into a tube connected to a spirometry machine (Table 3.1). Lung measurements obtained from this test include forced expiratory volume in one second (FEV_1), the amount of air blown out in one second; forced vital capacity (FVC), the total amount of air blown out; the FEV_1/FVC ratio; and the

TABLE 3.1 Pulmonary tests

Pulmonary test	Description	Results
Spirometry	After inhaling as much air as possible, the patient blows out as quickly and completely as possible into a tube connected to a spirometry machine	Airways obstruction (asthma, emphysema, BO). Restrictive pattern (HP)
Bronchodilator trial	When a spirometry test shows airways obstruction, an inhalable medication that relaxes the muscles in the small airways is administered and the spirometry test is repeated	Reversible airways obstruction suggests the presence of asthma
Serial spirometry or serial peak expiratory flow rate (PEFR) measurements	Spirometry tests or PEFR measurements are repeated five or more times each day during the waking hours over a 3- to 4-week period	Lower FEV_1 or lower PEFR measurements on workdays compared to non-workdays are suggestive of work-related asthma
Bronchoprovocation test	The baseline FEV_1 is compared to FEV_1 following a simulated occupational exposure or a controlled exposure to an occupational agent[a]	A drop in FEV_1 suggests work-related asthma
Methacholine challenge test	The baseline FEV_1 is compared to FEV_1 following administration of	A drop in FEV_1 following a low dose of methacholine

(*continued*)

TABLE 3.1 (*continued*)

Pulmonary test	Description	Results
	methacholine, an inhalable drug that can cause the muscles in the small airways to contract	suggests the presence of asthma
Antibody test	Blood tests that detect antibodies to an allergen; reactions to skin pricking with antigen imply allergic sensitization	A positive test indicates antibody sensitization, which is associated with allergic rhinitis, allergic conjunctivitis, and allergic asthma
Diffusing capacity of the lung for carbon monoxide (DL_{CO})	A test dose of carbon monoxide is inhaled and measurements are obtained to determine how much of this is absorbed. This measurement is used to estimate how well other gases are exchanged by the lungs	A low DL_{CO} may be caused by: (1) scarring of the lung tissue in HP; (2) obliteration of the small airways in severe BO; and (3) destruction of the air sacs in emphysema
High-resolution-computed tomography (HRCT) of the chest	Detailed radiological images that provide a three-dimensional picture of the lungs	HRCT can detect: (1) scarring of the lung tissue in HP; (2) air trapping in the air sacs during expiration in BO; and (3) destruction of the air sacs in emphysema

[a] Bronchoprovocation tests using an occupational agent are infrequently performed because only a few medical facilities in the United States are equipped to perform this test.

peak expiratory flow rate (PEFR), the fastest rate at which air can be exhaled. FEV_1, FVC, and PEFR are compared to average values for a person of the same height, age, gender, and race to yield percent predicted values; for example, a test result that is 80% of the average value

would be 80% of predicted value. Additionally, there are normal ranges with lower limit of normal values for lung measurements of a person of a specific height, age, gender, and race. A pattern of airways obstruction is identified if the FEV_1 and FEV_1/FVC are below the lower limit of normal and the FVC is normal. In this case, the individual has an adequate lung capacity but is unable to blow the inhaled air out quickly due to resistance in the airways. Symptoms associated with this type of lung abnormality are wheezing and chest tightness. A restrictive pattern is identified if the FEV_1/FVC ratio is normal and the FVC is below the lower limit of normal. An individual with a restrictive pattern is unable to take in a full breath; however, he or she is able to quickly exhale the inhaled air. Symptoms associated with this type of lung abnormality include shortness of breath on exertion.

An inhalable medication that relaxes the muscles in the airways (bronchodilator) is frequently administered when airways obstruction is identified. In this bronchodilator trial test, the spirometry test is subsequently repeated and compared to the results from the initial spirometry test. If there is substantial improvement in lung function with the administration of the bronchodilator, the airways obstruction is reversible. An example of a lung disease with reversible airways obstruction is asthma, in which symptoms occur episodically when airways obstruction occurs. If there is little or no improvement after the administration of the bronchodilator, the airways obstruction is fixed. An example of a lung disease with fixed airways obstruction is BO, where there is scarring of the airways.

In the methacholine challenge test, subjects inhale a drug that can cause the muscles in the small airways to contract. People with asthma will have a reduction in their FEV_1 after inhaling a low dose of this drug, reflecting increased ''irritability'' or bronchial hyperreactivity.

To make an association between occupational exposures and asthma, serial spirometry, serial measurements of PEFR, provocation with a simulated occupational exposure or an occupational agent, and antibody tests are frequently conducted. In work-related asthma, repeat spirometry and/or PEFR measurements five or more times daily during the waking hours over a 3- to 4-week period may show lower FEV_1 or PEFR measurements on workdays compared to non-workdays. A drop in FEV_1 with a simulated occupational exposure and/or with exposure to an occupational agent is also suggestive of work-related asthma. If there is exposure to a known occupational allergen, then antibody sensitization may be tested with a blood test (radioallergosorbent test) that detects antibodies specific to the allergen or with a skin prick test.

The ability of the lungs to exchange gases is measured by the diffusing capacity of the lung for carbon monoxide (DL_{CO}). In this test, ability of the lungs to absorb a test dose of carbon monoxide is measured and is used to approximate their ability to exchange oxygen and carbon dioxide.

Inflamed lung tissue (hypersensitivity pneumonitis, HP), complete obliteration of a large proportion of the airways (severe BO), and damage to the air sacs (emphysema) will reduce the DL_{CO} measurement.

High-resolution computed tomography (HRCT) of the chest is able to detect inflammation and scarring of the supporting lung tissue, air trapping in the air sacs during expiration, and extensive destruction of air sacs; findings that are present in HP, BO, and emphysema, respectively.

IV. TYPES OF OCCUPATIONAL RESPIRATORY DISEASE

Respiratory disease may occur as a result of one of three mechanisms: immunological sensitization and response, irritation, and injury followed by destruction and/or scarring. In most immunological respiratory diseases, a period of time is required for a person's immune cells to become sensitized; subsequent exposure results in respiratory symptoms. The period of time from first exposure to onset of symptoms is referred to as the latency period. Immunological diseases that are antibody mediated consistently have latency periods. These include anaphylaxis, allergic conjunctivitis/rhinitis, and allergic asthma. HP is a cell-mediated immunological disease that may result in symptoms in sensitized individuals within hours after a high-intensity exposure or after months of low-intensity exposures. In diseases due to irritation, there is generally injury to the lining of the respiratory tract, resulting in mucus production and possibly permanent damage of the respiratory tract. Irritating chemicals and particles may also cause irritant-induced asthma, especially in the case of an overwhelming exposure. BO is an example of a respiratory disease due to injury followed by scarring. Emphysema is a respiratory disease characterized by injury followed by permanent destruction of the air sacs.

Shortness of breath, cough, and wheeze are common symptoms of respiratory diseases (Table 3.2). These shared symptoms make misdiagnosis by physicians common if the diagnosis is based solely on reported symptoms. Medical tests help to distinguish the respiratory diseases from each other (Table 3.3). Other pitfalls in medical diagnosis include diagnosing common diseases (such as asthma, emphysema, and chronic bronchitis) instead of the actual rarer diseases (such as BO); and not considering occupational exposures as the cause.

A. Anaphylaxis, allergic conjunctivitis/rhinitis, and allergic asthma

An allergen is a chemical or substance that results in an immunoglobulin E-mediated (antibody) allergic response. Allergens are usually high molecular weight organic compounds. The production of antibodies

TABLE 3.2 Symptoms of occupational lung diseases

Respiratory disease	Predominant symptoms
Allergic asthma Irritant-induced asthma Work-aggravated asthma	Episodic wheeze, chest tightness, shortness of breath, and cough
Chronic bronchitis	Daily cough that produces phlegm for three or more consecutive months out of a year
Hypersensitivity pneumonitis	Progressive shortness of breath, cough, and weight loss (low-intensity exposures); shortness of breath, cough, muscle achiness, chills, sweating, and fatigue on workdays (high-intensity exposures)
Emphysema	Progressive shortness of breath and cough
Constrictive BO	Progressive shortness of breath and cough

(sensitization) may occur following inhalation, ingestion, or contact with the eyes or skin. Subsequent exposure results in symptoms of hives, anaphylaxis (see the following paragraph), conjunctivitis/rhinitis, and/or asthma. The route of sensitization may differ from the route of exposure responsible for symptoms: for example, an individual sensitized by airborne exposures at work may develop allergic respiratory symptoms following ingestion of the same allergen in a food (Acero *et al.*, 1998). Sensitization can be detected by a blood test (such as the radioallergosorbent test) or a skin prick test for specific allergens. Because of the risk of provoking a life-threatening event, a skin prick test is not performed on individuals with a history of anaphylaxis.

Anaphylaxis is a severe systemic allergic reaction, which can be fatal. Frequently the first symptom is itchy hives (welts) within minutes of exposure. Swelling of the larynx, with constriction of the air passage and a rapid drop in blood pressure quickly follow. Treatment includes immediate removal from exposure, administration of epinephrine, and strict avoidance of reexposure.

Symptoms of allergic conjunctivitis and rhinitis include red, itchy, watery eyes, watery nasal discharge, nasal congestion, and sneezing. Asthma is characterized by episodic airways obstruction and symptoms of wheeze, chest tightness, shortness of breath, and cough. Asthma symptoms are due to contraction of the smooth muscles, swelling of the lining, and mucus in large and small airways (Table 3.4). Symptoms generally appear or worsen within several hours after exposure. Once an exposure association is made, early removal from exposures may result in cure with

TABLE 3.3 Medical test results for occupational lung diseases

Test	Occupational asthma or work-aggravated asthma	Hypersensitivity pneumonitis	Emphysema	Constrictive BO
Lung examination	Wheeze during an asthma attack	Crackles (rales), occasionally wheeze	Decreased breath sounds	Crackles (rales), wheeze
Spirometry	May show airways obstruction	May be normal, or may show airways obstruction or a restrictive pattern	Airways obstruction	Airways obstruction
Bronchodilator trial	Airways obstruction improves	Airways obstruction may minimally improve	Airways obstruction does not improve	Airways obstruction does not improve
Methacholine challenge	Increased reactivity	May show increased reactivity	Normal reactivity	Normal reactivity
Diffusing lung capacity for carbon monoxide (DL_{CO})	Normal	Decreased	Decreased	Normal or decreased
High-resolution-computed tomography (HRCT) of the chest	Normal	Inflammation of the interstitium, scarring of the lung tissue, and/or small nodules	Large holes in the lungs (bullae)	Air trapping during exhalation

TABLE 3.4 Description and causes of occupational lung diseases in the food industry

Respiratory disease	Site of disease	Description	Known causes in the food industry
Allergic asthma	Bronchi, bronchioles, terminal bronchioles	Antibody-mediated response to inhaled allergens with contraction of the smooth muscles in the walls of the airways, swelling of the airways, and mucus secretion in the airways	Cereal flour, buckwheat flour, soy flour, seafood allergens, pork, sesame seeds, sunflower seeds, lupin, spinach, sarsaparilla root dust, cocoa, coffee dusts, green tea, egg protein, lactalbumin, milk powder, casein, honey, α-amylase, glucoamylase, pectinase, gluconase, pepsin, pectin, spices, carmine, flavorings
Irritant-induced asthma	Bronchi, bronchioles, terminal bronchioles	Contraction of the smooth muscles in the walls of the airways, swelling of the airways, and mucus secretion in the airways due to inhaled irritants	A single high-intensity or multiple low-intensity exposures to chlorine gas, bleaching agents, cleaning agents, and fumigants
Work-aggravated asthma	Bronchi, bronchioles, terminal bronchioles	Contraction of the smooth muscles in the walls of the airways, swelling of the airways, and mucus secretion in the airways due to nonspecific occupational exposures or occupational allergens to which the worker was previously sensitized	Cold air, dusts, aerosol sprays, smoke, fumes, occupational allergens to which the worker was previously sensitized

Chronic bronchitis	Bronchi, bronchioles	Enlarged mucous glands and an increased number of goblet cells produce an excessive amount of mucus	Bakery and food-processing exposures
Constrictive BO	Terminal and respiratory bronchioles	Injury of the airways results in scarring and in some cases complete obliteration of the air passages	Diacetyl, butter flavoring, overheated cooking oil
Emphysema	Alveoli, respiratory bronchioles	Destruction of the walls of the air sacs and scarring of and weakening of the walls of the small airways	–
Hypersensitivity pneumonitis	Interstitium	Cell-mediated response to substances results in the formation of scar tissue in the supporting tissue of the lung	*Penicillium* in cheese or cheese casings, green coffee dust, *Botrytis cinerea* on grapes, *Aspergillus oryzae* in soy sauce, grain weevils, carmine

the disappearance of episodic asthma symptoms. Continued exposure may result in an increased likelihood of: (1) persistent asthma with asthma symptoms even when no longer exposed, with symptoms at nighttime, after exercise, with respiratory infections, and with exposure to cold air or irritants; and (2) scarring of the airways resulting in fixed airways obstruction. Smokers and individuals with a history of asthma, hay fever, or eczema are at greater risk for developing occupational allergic asthma.

Occupational allergens in the food industry include mammalian and avian proteins, and allergens from plants, mold, bacteria, spices, and seafood (Bernstein *et al.*, 1999). Enzymes, which have multiple applications within the food industry, are frequently allergens. α-Amylase derived from *Aspergillus oryzae* is used to stimulate the growth of yeast and facilitate the rising of bread. Glucoamylase derived from *A. niger* is used in the production of high-fructose corn syrup. Pectinases are used to assist in the removal of the pith from fruit and to clarify fruit juices. Rennet, proteases, and lipases are used in cheese production.

Spirometry and bronchodilator trial tests that indicate reversible airways obstruction and/or airways reactivity when challenged with methacholine are used to diagnose asthma. Occupational allergic asthma is subsequently diagnosed when respiratory symptoms have begun after hire and after a latency period of several weeks to several years, and there is an indication that asthma symptoms or the status of asthma are worse on workdays. Changes in asthma status suggestive of occupational asthma include serial spirometry tests or PEFR measurements that show lower FEV_1 or PEFR measurements on workdays compared to non-workdays; and improvement in the methacholine challenge test after the worker has been removed from work exposures for several months. Although largely unavailable, provocation tests with allergens cause a decline in FEV_1.

Allergic rhinitis and asthma commonly occur in bakers and fish and seafood processing workers (Bernstein *et al.*, 1999). Occupational asthma has additionally been reported in egg-processing workers (Smith *et al.*, 1987); coffee workers (Osterman *et al.*, 1985; Zuskin *et al.*, 1981); green tea factory workers (Shirai *et al.*, 2003), spice factory workers and workers who handle spices (Añíbarro *et al.*, 1997; Falleroni *et al.*, 1981; Fraj *et al.*, 1996; Lemière *et al.*, 1996; Sastre *et al.*, 1996; Seuri *et al.*, 1993; Zuskin *et al.*, 1988); cocoa-processing workers and workers who handle cocoa (Perfetti *et al.*, 1997; Zuskin *et al.*, 1998); and natural food dye (carmine) production workers (Lizaso *et al.*, 2000; Rodriguez *et al.*, 1990; Tabar-Purroy *et al.*, 2003).

Case reports of occupational asthma include a candy worker exposed to lactalbumin (Bernaola *et al.*, 1994) and a bakery worker exposed to milk powder (Toskala *et al.*, 2004), a candy worker and a jam-manufacturing worker exposed to pectin (Cohen *et al.*, 1993; Kraut *et al.*, 1992), a worker in

a meat tenderizer manufacturing plant exposed to papain (Novey *et al.*, 1979), a meat kneader exposed to casein (Rossi *et al.*, 1994), a meat processor exposed to pork meat (Labrecque *et al.*, 2004), bakery workers exposed to sesame and sunflower seeds (Alday *et al.*, 1996; Keskinen *et al.*, 1991; Vandenplas *et al.*, 1998), a worker who handled lupin powder (Campbell *et al.*, 2007), a pasta factory worker exposed to spinach powder (Schuller *et al.*, 2005), a herbal tea worker exposed to sarsaparilla root dust (Vandenplas *et al.*, 1996), a cereal maker exposed to honey (Johnson *et al.*, 1999), fruit-processing workers exposed to pectinase and gluconase (Sen *et al.*, 1998), and a cheese maker exposed to pepsin (Añíbarro and Fontela, 1996). Asthma associated with occupational exposure to flavorings has also been reported (CDC, 2007a). The impact of occupational asthma in food industry workers was quantified in a random population survey of workers in New Zealand that found food processors (other than bakers) to be about 2.5 times more likely to report wheeze than office workers (Fishwick *et al.*, 1997a).

Bakers' asthma and allergic rhinitis are the most common forms of occupational respiratory disease in the food industry. Among bakery workers, the prevalence of occupational asthma and allergic rhinitis ranges from 5% to 7% and 15% to 20%, respectively (Houba *et al.*, 1996). Bakers' asthma is most often due to cereal flours (such as wheat, rye, and barley flour) and less frequently due to buckwheat flour, soy flour, fungal α-amylase, fungal glucoamylase, proteases, cellulases, xylanase, molds, and storage mites (Bauer *et al.*, 1986; Merget *et al.*, 2001; Quirce *et al.*, 1992, 2002; Tarvainen *et al.*, 1991). Antibody sensitization rates for wheat flour and α-amylase among bakers range from 5% to 25% and 2% to 15%, respectively. Estimated wheat flour-related incidence rates among bakers are 10 cases of antibody sensitization per 1000 workers per year, and 3–4 cases of respiratory allergy per 1000 workers per year (Heederik and Newman Taylor, 1999).

The diagnosis of respiratory allergy in bakery workers is made by the presence of nasal and/or airways symptoms after an initial symptom-free period (latency period) of months to several years. Rhinitis often occurs first, followed by the development of asthma; however, asthma in the absence of rhinitis is not uncommon. Asthma symptoms develop within minutes to hours of exposure at work and may persist for 24 h or more. A temporal relationship with work may only be discovered during 1- or 2-week vacations. Supporting medical tests include: (1) positive radioallergosorbent blood test or skin prick test specific to flour proteins and/or α-amylase allergen; (2) reversibility of airways obstruction when a bronchodilator is administered and/or airways reactivity when challenged with methacholine; and (3) serial lung function tests that improve away from work. Once sensitized, workers will become symptomatic with exposure to very low concentrations of airborne allergen. Because of this, the only

effective solution is a change in their work. As an interim measure until a change in work is feasible, the worker may wear a respirator with a particulate filter to minimize exposures.

The amounts of flour allergen and α-amylase per gram of dust vary considerably, making airborne dust concentration a poor measure of allergen exposure in bakeries. Use of environmental allergen levels to assess health risk is challenging due to the lack of standardization of immunoassays among analytical laboratories. As yet, there are no recognized occupational exposure limits for flour dust, flour allergens, or α-amylase. The absence of regulation, however, does not imply safety for this classic example of occupational asthma.

Prevention measures include eliminating activities that generate high levels of dust, such as emptying bags, compressing empty paper bags that previously contained flour or dough improvers, dusting dough, dry sweeping, and use of pressurized air. Potential solutions include use of divider oil to prevent dough adhesion to surfaces instead of dusting with flour, automated forming instead of dough-braking, closed transfer of flour, exhaust ventilation that circumscribes the dough mixer, use of flow table exhaust systems if dusting dough is unavoidable, covering dough mixers during the dough-making process, and the use of encapsulated or dissolved enzyme formulations (Burstyn *et al.*, 1997; Heederik and Newman Taylor, 1999).

Medical surveillance of food industry workers is suggested for workers exposed to allergenic materials. A typical program includes: (1) baseline and periodic skin prick or radioallergosorbent tests for specific antibodies (antibody sensitization); and (2) instruction of workers to promptly report new upper or lower respiratory symptoms (or worsening of prehire symptoms) to the facility director of safety. Workers who develop antibody sensitization or symptoms are medically evaluated by a pulmonologist or allergist. Workers subsequently diagnosed with occupational rhinitis or asthma are relocated away from further exposure. There is no standard recommended interval for antibody sensitization testing. In the detergent-manufacturing industry where workers are exposed to proteases, amylases, lipases, and cellulases, it has been suggested to test workers every 6 months for the first 2 years, and thereafter every 2 years. This decision was based on studies that have shown that the risk of antibody sensitization is highest during the first 2 years of exposure (Nicholson *et al.*, 2001).

B. Irritant-induced asthma, work-aggravated asthma, and chronic bronchitis

Irritant-induced asthma usually occurs following a single or multiple accidental high-intensity exposures. Repetitive lower intensity exposures to irritants may also cause asthma (Balmes, 2002). Once asthma develops,

its symptoms may occur with exposure to nonspecific stimuli, such as cold air, dusts, aerosol sprays, smoke, and fumes. Chlorine gas, bleaching agents, cleaning agents, anhydrous ammonia, and fumigants are exposures in the food industry known to cause irritant-induced asthma. Exposure to endotoxin, a cell wall component of gram-negative bacteria, has been associated with respiratory symptoms and a reversible work-related change in lung function among potato processors (Zock *et al.*, 1998).

In work-aggravated asthma, a worker with preexisting asthma has worsening of asthma symptoms due to exposures in the workplace. These exposures may be irritant chemicals, cold air, or allergens to which the worker was sensitized prior to hire. The diagnosis is made if the asthma was not active within 2 years before the hire date and there is: (1) worsening of asthma symptoms on workdays; and (2) serial spirometry tests and/or repeat PEFR measurements suggesting a work-related pattern.

Chronic bronchitis is defined as a daily cough that produces phlegm for three consecutive months out of a year. It is due to enlarged mucous glands and an increased number of goblet cells that result in an excessive amount of mucus. Involvement of goblet cells is particularly important due to their location in smaller airways where the mucus can interrupt airflow. Chronic bronchitis is most commonly caused from cigarette smoking. However, a random population-based study of 20- to 44-year-old workers demonstrated that current and former smokers in the food industry were two to three times more likely to report phlegm production compared to office workers who also were current or former smokers (Zock *et al.*, 2001). Another study found chronic bronchitis to be 3 times more likely in food processors and chronic bronchitis with airways obstruction to be 26 times more likely in bakers, compared to office workers (Fishwick *et al.*, 1997b).

C. Hypersensitivity pneumonitis

HP is an uncommon lung disease caused by cell-mediated sensitization to organic dusts or chemicals. With high-intensity exposures, symptoms can include shortness of breath, cough, muscle achiness, chills, sweating, and fatigue that occur on workdays. Complete normalization of symptoms and lung function can occur with early removal of workers from exposure. If exposure continues, permanent lung damage from scarring can occur. Symptoms associated with low-intensity exposure include progressive shortness of breath and cough, as well as weight loss. The slow progression of symptoms and the persistence of symptoms away from work that occur with low-intensity exposure may result in delayed recognition of the disease by both workers and physicians. Medical evaluation often includes a restrictive spirometry pattern and may reveal crackles

(rales) on chest examination, decreased ability of the lungs to exchange gases, and immunoglobulin G antibodies specific to the causative agent. Workers in the food industry at risk for developing HP include cheese workers exposed to *Penicillium* in cheese or cheese casings, coffee workers exposed to green coffee dust, wine growers exposed to *Botrytis cinerea* on grapes, soy sauce brewers exposed to *A. oryzae*, millers exposed to grain weevils in wheat flour, and natural dye production workers exposed to carmine (Christiansen *et al.*, 1981; Schuyler, 1998).

D. Emphysema

In emphysema there is destruction of the walls of the air sacs. Lung function tests demonstrate fixed airways obstruction due to collapse of airways during exhalation and a decreased ability of the lungs to exchange gases. Physical examination of the lungs usually reveals decreased breath sounds. Approximately 20% of cases of emphysema are due to occupational causes and the remaining 80% are mostly due to smoking. Smokers with emphysema should not be assumed to have smoking-related emphysema, particularly young smokers. This is because only about 15% of smokers will ever develop emphysema and most individuals with smoking-related emphysema will become symptomatic in their fifties after having smoked 20 or more pack-years (ATS, 1995). Risk of emphysema is increased among food industry workers: a large US health survey found airways obstruction to be 2.1 times more prevalent in food products manufacturing workers than in office workers after adjusting for smoking and other factors (Hnizdo *et al.*, 2002). The causes have not been investigated.

E. Bronchiolitis obliterans

BO is a rare lung disease. In constrictive BO, there is inflammation and injury of the small airways that lead to the air sacs (terminal and respiratory bronchioles). Subsequent repair mechanisms result in scarring and narrowing or complete obliteration of the affected airways. The disease is patchy in distribution so that all sections of the lung are not equally affected. Symptoms consist of cough and shortness of breath with exertion, which typically do not improve away from the causative exposure. With continued exposure, the scarring involves increasingly greater amounts of the lung and workers become increasingly short of breath. Scarring and breathlessness are permanent, resulting in the consideration for lung transplants in some workers. Spirometry tests reveal fixed airways obstruction. HRCT of the chest with inspiratory and expiratory images may show air trapping in the expiratory images. Unlike emphysema, the lungs ability to exchange gases is unaffected until late in the

disease. Lung biopsy typically shows inflammation and scarring of the small airways. However in individuals with BO, lung biopsies frequently fail to make the diagnosis. Characteristics of flavoring-related constrictive BO are described in the literature (Akpinar-Elci *et al.*, 2004); a lung biopsy is usually not required to make this diagnosis. In addition to diacetyl and butter flavorings, overheated cooking oil has also been reported as a cause of constrictive BO (Simpson *et al.*, 1985).

V. FLAVORING-RELATED BO

A. NIOSH investigation of flavoring-related BO

In 2000, eight cases of BO among former workers of a microwave popcorn plant resulted in an investigation that identified a new occupational hazard in the food industry. BO is a rare lung disease, so the occurrence of eight cases in a small rural community was unusual. The fact that they had all worked at the same plant gave rise to suspicion of a common cause. The persistence of symptoms away from work (typical in this disease) in these eight workers delayed recognition of a work-related illness by physicians. One pulmonologist caring for these workers called the US Occupational Safety and Health Administration (OSHA); however, the compliance officer who visited the plant could not find any known pulmonary hazard. Ultimately, an occupational medicine physician who reviewed medical records on the eight workers for a workers' compensation attorney reported the cases to the Missouri Department of Health and Social Services, which, in turn, requested assistance from NIOSH. All eight workers had become ill while employed at the microwave popcorn plant with the earliest case starting in 1993. Four of the eight workers had worked in the flavor-mixing room and four had worked in the microwave popcorn packaging area. Six of the eight workers had FEV_1 measurements less than 40% of predicted (criterion of the Social Security Administration for total disability from respiratory disease); four were on lung transplant waiting lists.

NIOSH conducted a medical survey of current workers and an environmental survey of the facility in November 2000 (Kreiss *et al.*, 2002a). Workers added salt, heated butter flavoring, and coloring agents to heated soybean oil (130 °F) in large mixing tanks. The flavoring mixture was pumped into heated holding tanks on an open mezzanine level and then added to popcorn in microwavable bags in the microwave popcorn packaging lines below (Fig. 3.1). There was no physical barrier between the flavor-mixing tanks, holding tanks, and microwave popcorn packaging lines. Heating of the flavors and of the flavored soybean oil resulted in volatilization of the flavoring ingredients. Chemical vapors from the

FIGURE 3.1 Sentinel microwave popcorn plant with holding tanks in the mezzanine above microwave popcorn packaging line.

mixing tanks on the main floor and holding tanks on the mezzanine level exposed microwave popcorn packaging workers on the main floor of the plant. Quality control workers popped the microwave popcorn and opened popped bags to assess the quality of the popcorn. Workers did not use respiratory protection. A thermal desorption tube air sample from the mixing room demonstrated a complex spectra of over 100 volatile organic compounds, with ketones predominating. Using diacetyl as a marker of exposure, NIOSH measured diacetyl air concentrations based on 8-h time-weighted averages (8-h TWA). The mean diacetyl air concentrations based on work area air samples collected over multiple days were 37.8 parts per million (ppm) for the mixing tank room, 2.0 ppm for the microwave popcorn packaging line, and 0.5 ppm for the quality control room.

The prevalence of airways obstruction in this workforce was 3.3 times greater than expected when compared to national data. Nineteen of the 21 workers identified with airways obstruction had fixed airways obstruction. Cumulative worker exposures were calculated in parts per million diacetyl-years and workers were placed in equally sized worker categories of least, minimally, moderately, and most exposed. When successive categories of least to greatest exposed workers were compared, it was found that the proportion of workers with airways obstruction increased and average-percent-predicted FEV_1 decreased, demonstrating an exposure–response relationship with diacetyl. Five of

six quality control workers had airways obstruction despite relatively low diacetyl air concentrations in this work area (Kreiss *et al.*, 2002a). Potential hazards in these quality control workers may have been caused by peak exposures to a combination of volatile organic compounds unique to this work area. Quality control workers are exposed to momentary bursts of volatile organic compounds when they open freshly popped bags of popcorn. The high temperatures associated with popping microwave popcorn generated different proportions of volatile organic chemicals than present in the mixing and microwave popcorn packaging areas.

NIOSH subsequently evaluated five other microwave popcorn plants and analyzed aggregated data from all six plants. In five of the six plants, mixers and/or microwave popcorn packaging workers had medical findings consistent with BO. Mixers had a lower mean-percent-predicted FEV_1 compared to other workers. Microwave popcorn packaging workers in plants where mixing tanks were located in proximity to the packaging lines had a higher prevalence of airways obstruction compared to microwave popcorn packaging workers in plants where the tanks were isolated in a separate room with the door closed. The mean work area 8-h TWA diacetyl air concentrations in plants where cases of BO occurred were 0.2–37.8 ppm in mixing rooms and 0.3–1.9 ppm in microwave popcorn packaging areas (Kanwal *et al.*, 2006). (*The NIOSH sampling method #2557 for diacetyl was subsequently found to underestimate diacetyl air concentrations in samples collected in high-humidity conditions; development of an alternate sampling method is currently in progress*.)

In 2006 and 2007, NIOSH investigated two flavor-manufacturing plants. Medical testing of 29 production workers identified 7 workers with fixed airways obstruction who had worked in plated-powder and/or liquid flavoring work areas; 4 of these workers had severe fixed airways obstruction (CDC, 2007b,c). Mean work area diacetyl air concentrations (*using NIOSH method #2557*) for plated-powder production and liquid production in one of these plants were 0.25 and 0.02 ppm, respectively (CDC, 2007b).

Animal inhalation studies were conducted at NIOSH in which rats were exposed to vapors from a butter flavoring used at the sentinel microwave popcorn plant. Rats were exposed for 6 h to vapors with diacetyl concentrations of 203, 285, 352, or 371 ppm. Exposure to butter-flavoring vapors of 285 or more ppm diacetyl resulted in damage to the bronchi; nasal damage was seen in all the exposed rats (Hubbs *et al.*, 2002). Studies using pure diacetyl vapors demonstrated nasal damage in rats exposed for 6 h to 198 or more ppm diacetyl (Hubbs *et al.*, 2008). The degree of inflammation and damage to the nose, larynx, trachea, and bronchi in exposed rats is concentration dependent (Hubbs *et al.*, 2008). Due to the absence of mouth breathing, the larger surface area of the nose in rodents compared to humans, and the high water solubility of diacetyl,

much of the observed injury in rodent studies is in the upper airways. In order to demonstrate animal findings more comparable to health effects experienced by humans, a study conducted at the National Institute of Environmental Health Sciences placed liquid diacetyl in the oropharynx of mice. The liquid that was subsequently inhaled resulted in scarring at the level of the smallest airways. Diacetyl inhalation studies demonstrated inflammation of the nose, larynx, and bronchi when mice inhaled 100 or more ppm of diacetyl for 1 h/day, 5 days/week for 4 weeks (Morgan *et al.*, 2006).

Butter flavoring is implicated in BO among microwave popcorn workers. Diacetyl, a major component of butter flavoring, causes BO based on cases of BO among chemical manufacturing workers who made diacetyl (van Rooy *et al.*, 2007) and animal studies that showed respiratory effects from diacetyl alone. Other chemicals in flavorings are also likely to cause or contribute to BO based on: (1) reports of BO in flavor-manufacturing workers thought to be due to acetaldehyde (Lockey *et al.*, 2002); (2) lung disease in flavored popcorn-manufacturing workers for whom diacetyl was not detected in the air (CDC, 2007a); and (3) rat butter-flavoring experiments demonstrating respiratory damage in excess of that attributable to diacetyl alone (Kreiss *et al.*, 2002b).

B. Recommended interventions

Over 2000 different chemicals are used to formulate artificial flavors (FEMA, 2004). Flavoring chemicals are generally volatile. Flavored powders produced by flavor-plating or spray dried processes may be inhaled if these powders become airborne. Implementation of engineering controls in flavor-manufacturing plants and food production plants can minimize workers' exposure to flavoring chemicals. Of special concern are processes that involve heat (as heat will increase the volatilization of flavoring chemicals) and processes that agitate powders. High-exposure processes are best enclosed in a separate room under negative pressure and venting of the exhaust air to the outdoors distant from the air intake vents for the facility. Effective use of local exhaust ventilation will reduce exposures in mixing, blending, and spray-drying operations, as well as exposures produced during the pouring and measuring of ingredients; respective applications include use within mixing tanks, around the perimeter of blenders and spray dryers, and at the point of operation of pouring and measuring activities. Mixing vessels should remain lidded during mixing processes. The process of adding ingredients to vessels should be converted to an automated closed process. Respirators with particulate filters and organic vapor cartridges should be used as an interim measure until engineering controls successfully eliminate worker exposures.

Safe exposure levels to diacetyl and other flavor ingredients are not known. It is likely that both peak and average exposures of diacetyl and other chemicals are important. Exposure monitoring for diacetyl is recommended with the intention of keeping diacetyl peak and 8-h TWA concentrations as low as possible. Eight-hour TWA and peak diacetyl exposures for workers diagnosed with flavoring-related BO illustrate how greatly these measurements may differ. The mean 8-h TWA for the mixing room of the sentinel microwave popcorn plant where workers with flavoring-related BO had worked was 37.8 ppm diacetyl (range: 2.3–97.9); months later, using a direct-reading instrument (Fourier transform infrared spectroscopy, FTIR), the diacetyl level inside the headspace of the holding tank was measured as high as 1230 ppm (CDC, 2006). The mean 8-h TWA for the powder production work area in a flavor-manufacturing plant where other workers with flavoring-related BO had worked was 0.2 ppm diacetyl (range: 0.002–0.790) (*using NIOSH method #2557*), and the peak diacetyl level using FTIR was 210 ppm (CDC, 2007b).

Some exposed workers in the flavor-manufacturing and food production industries who have developed severe respiratory disease experienced symptoms within months of exposure to flavoring chemicals. Other exposed workers with fixed airways obstruction did not have any obvious symptoms. Many workers with flavoring-related BO were initially misdiagnosed by their physicians as having asthma, emphysema, or chronic bronchitis. Because of the severity, permanency, short latency, and the possibility of misdiagnosis of this disease, exposed workers should be part of a medical surveillance program that includes spirometry testing. If airways obstruction is identified, a bronchodilator should be administered and spirometry repeated to establish the presence of fixed airways obstruction. Spirometry should be initially conducted at time of hire (baseline test) and should be repeated every 6 months. Newly hired workers with preexisting lung disease should be medically evaluated to determine whether work exposures place them at increased risk for progression of their lung disease. Workers with posthire onset of fixed airways obstruction or a 15% or greater drop in FEV_1 from the baseline value should be: (1) referred to a pulmonologist for medical evaluation; (2) relocated to prevent further exposures; and (3) allowed to return to their previous job only if their physician does not find fixed airways obstruction or 15% or greater decline in FEV_1, or engineering controls are implemented at the worksite to control exposures and there is physician oversight. In workplaces with a case of work-related fixed airways obstruction, coworkers should have spirometry testing more frequently, such as every 3 months.

Quality spirometry is required both to minimize the number of workers who are inappropriately referred to pulmonologists for evaluation and to identify workers who may have decreased lung function compared to their baseline spirometry test. Poor coaching by the spirometry technician may

result in a poor effort by the worker being tested, which may be reflected by inaccurately low lung volume results. If there is poor effort for an interval spirometry test, the worker may be needlessly referred to a pulmonologist for a medical evaluation; if there is poor effort for a baseline test, a subsequent interval spirometry test may not detect a large drop in FEV_1 when it exists. If a large decline in FEV_1 is detected, prompt removal of affected workers may help maintain their lung function tests within the normal range and prevent disability. Spirometry tests from on-site and off-site testing locations frequently are of poor quality and do not meet quality criteria of the American Thoracic Society (Miller *et al.*, 2005). Initial and refresher training of spirometry technicians, periodic quality assurance evaluation of spirometry tests completed by individual spirometry technicians, and quality spirometry testing equipment help to insure good quality tests.

C. Timeline of the emergence of flavoring-related BO and the industry and regulatory agency response

BO in microwave popcorn workers established a newly identified cause of occupational lung disease. However, the problem had been present several decades earlier when two workers in a company that made flavored cornstarch and flour mixes were reported to have BO (CDC, 1986). The workers were nonsmokers in their twenties who developed progressive shortness of breath and severe fixed airways obstruction within 5–8 months of hire. Two former mixers in the same company aged 36 and 38 who were exsmokers (22 and 10–15 pack-years, respectively) and who did not have symptoms were identified to have moderate airways obstruction, likely due to exposure to flavorings, given their age and smoking histories. At the time, an association between butter-flavoring exposures and BO was not made, although one of the workers had attributed the symptoms to Cinna Butter, and diacetyl was one of the common ingredients used in the plant.

Other workers with flavoring-related BO were not appropriately diagnosed, even after reports of flavoring-related BO were published in the scientific literature (Kreiss *et al.*, 2002a; Lockey *et al.*, 2002; Parmet and von Essen, 2002), public health communications (CDC, 2002), and the press. Frequent misdiagnoses by physicians included asthma, bronchitis, and emphysema due to a presumptive diagnosis, an incomplete medical evaluation, and/or failure to make a connection with occupational exposures.

In 2002, 14 cases of flavoring-related BO among microwave popcorn workers and flavor-manufacturing workers were reported (CDC, 2002; Kreiss *et al.*, 2002a; Lockey *et al.*, 2002; Parmet and von Essen, 2002). The NIOSH Alert on flavoring-related lung disease was disseminated in 2004 to flavor and food manufacturers and regional OSHA offices (CDC, 2004).

In that same year, the Flavor and Extract Manufacturers Association (FEMA) disseminated to its member companies a list of 34 high-priority chemicals and 49 low-priority chemicals used in the flavoring industry that were suspected to be respiratory hazards (FEMA, 2004). Exposure control and medical surveillance of workers with spirometry testing were recommended in both the NIOSH and FEMA communications. From 2006 to 2007 additional cases of flavoring-related lung disease were reported in microwave popcorn-manufacturing workers (Kanwal *et al.*, 2006), flavor-manufacturing workers (CDC, 2007d), diacetyl-manufacturing workers (van Rooy *et al.*, 2007), and workers who popped corn and coated the hot popcorn with powdered cheese and jalapeno flavorings (CDC, 2007a).

In July 2006, labor unions petitioned OSHA for an emergency temporary standard for diacetyl. In July 2007, OSHA began a National Emphasis Program to address the hazards and control measures associated with working in the microwave popcorn industry. Under this program, OSHA prioritized inspections to this industry. In September 2007, due to congressional input and renewed pressure by labor unions, OSHA began formal rulemaking for occupational exposure to diacetyl and food flavorings containing diacetyl. Formal rulemaking usually requires several years to allow for a thorough review of the scientific literature, assessment of the economic impact of a regulation, and stakeholder input. Frequently, OSHA decides that no regulation should be established.

Consumer concerns about food product safety increased in September 2007 when information of a possible case of flavoring-related BO in a patient who had daily consumed two or more bags of extra-butter-flavored microwave popcorn for 10 years was released to the press (Harris, 2007). A single case of disease is insufficient to make a causal association between disease and exposure if the association cannot be tested by other means. Because no other cases of BO among microwave popcorn consumers have been reported in the medical literature or to government agencies, the risk to consumers is unclear. However, the perceived risk by consumers motivated flavor-manufacturing companies to reformulate artificial butter flavoring used in microwave popcorn. Two possible substitutes for diacetyl are starter distillate and diacetyl trimer. Starter distillate is a diacetyl-containing product of a fermentation process. Diacetyl trimer is a molecule that contains three diacetyl molecules. The inclusion of these alternative substances neither eliminates diacetyl nor assures safety for workers.

D. Liability

Workers' compensation benefits pay workers for medical expenses and lost wages due to occupational injury or illness. In exchange for carrying workers' compensation insurance, companies are protected against legal

suits by their employees. Workers with flavoring-related BO have pursued workers' compensation from their employers and have been involved in third-party litigation against flavor-manufacturing companies (frequently in the form of class action suits).

VI. RECOGNITION OF EMERGING OCCUPATIONAL RESPIRATORY DISEASE IN THE FOOD INDUSTRY

There are a number of barriers to the recognition of currently unknown causes of occupational respiratory disease in the food industry. Food additives, including diacetyl, are classified by the US Food and Drug Administration as ''generally recognized as safe'' (GRAS). This classification is based on published studies of safety by consumption or on a substantial history of consumption by a significant number of consumers. The GRAS classification does not address safety of inhalation exposures to workers in the food industry and may give employers and workers a false assurance of safety. Physicians frequently do not explore potential causative agents when evaluating individual patients suffering from a common lung disease, such as asthma. Rarer lung diseases, such as BO, may be misdiagnosed as a common disease, such as asthma. The lack of work-related symptoms in some occupational respiratory diseases (such as HP due to low-intensity exposures, emphysema, and BO) can delay recognition of an occupational cause. Additionally, physicians may attribute lung disease in smokers to smoking even at ages younger than middle age when smoking-related obstruction is improbable.

If a new cause of occupational respiratory disease is suspected, the most appropriate action for employers, employees, or physicians is to contact public health agencies, such as local or state health departments or NIOSH. Public health agencies can utilize teams of medical staff, industrial hygienists, and epidemiologists to investigate the potential problem. Such multidisciplinary investigations can assess exposure, test for health effects, describe process-related risk factors, define exposure–response relationships, and make recommendations to control exposures. Referral to OSHA is generally not productive as this is a regulatory agency, and compliance officers address exposure levels of known regulated chemicals and substances. Biological plausibility of potential causative agents can be established through animal models in industry-funded investigations, research institutions, or federal agencies. Effectiveness of control interventions can be evaluated through longitudinal follow-up of exposed worker populations.

The extent of flavoring-related lung disease in food production is an emerging endeavor outside of microwave popcorn- and flavoring-manufacture industries. Butter flavorings are used in snack foods, baked goods, candies, and dairy products. In December 2007, the media raised concern about diacetyl risks in food service workers using butter-flavored fats on grills (Schneider, 2007). Much more work needs to be done to characterize the exposures and risks associated with working in these food production and food service industries.

VII. PREVENTION OF KNOWN OCCUPATIONAL RESPIRATORY DISEASES IN THE FOOD INDUSTRY

Exposure to hazardous agents can be minimized through enclosure of work processes, use of lids on containers of mixing vessels, use of local exhaust ventilation, mandatory use of respirators, and eyes and skin protection. Emphasis should be placed on engineering controls to reduce exposure rather than reliance on respiratory protection. Multiple problems are inherent with respirator use. These include inadequate fit, respirator malfunction, inappropriate use, and failure of workers to consistently use respirators whenever exposed. For volatile exposures, a NIOSH-certified full-facepiece, negative-pressure respirator with organic vapor cartridges is the minimum level of respiratory protection recommended. If there are also particulate exposures, as is the case in powder flavor manufacturing, then particulate filters should be used in tandem with the organic vapor cartridges. A comprehensive respiratory protection program (OSHA, 2007) includes a written program, a program director, initial medical clearance and annual fit-testing, filter and cartridge change-out schedules, training, and seal checks whenever the respirator is used.

Prehire and periodic spirometry testing with bronchodilator trial may help to identify new-onset reversible airways obstruction (asthma), as well as fixed airways obstruction and excessive fixed FEV_1 decrements (emphysema, BO). Many workers in the food industry are exposed to occupational allergens. For these workers, prehire and periodic testing for antibody sensitization will identify workers who may go on to develop allergic respiratory diseases, including asthma. Periodic symptom questionnaires and reporting of respiratory symptoms to the director of safety will target individuals who would benefit from further medical evaluation. For workers with occupational allergic rhinitis, decreased exposures and frequent medical follow-up may have utility in preventing progression to allergic asthma. Finally, if an occupational respiratory disease is diagnosed, avoidance of further exposure is prudent.

REFERENCES

Acero, S., Tabar, A. I., Alvarez, M. J., Garcia, B. E., Olaguibel, J. M., and Moneo, I. (1998). Occupational asthma and food allergy due to carmine. *Allergy* **53**, 897–901.

Akpinar-Elci, M., Travis, W., Lynch, D., and Kreiss, K. (2004). Bronchiolitis obliterans syndrome in popcorn plant workers. *Eur. Respir. J.* **24**, 298–302.

Alday, E., Curiel, G., Lopez-Gil, M. J., and Carreno, D. (1996). Occupational hypersensitivity to sesame seeds. *Allergy* **51**, 69–70.

American Thoracic Society (1995). Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **152**, S77–S120.

Añíbarro, B., and Fontela, J. L. (1996). Occupational asthma in a cheese worker. *Allergy* **51**, 960–961.

Añíbarro, B., Fontela, J. L., and De La Hoz, F. (1997). Occupational asthma induced by garlic dust. *J. Allergy Clin. Immunol.* **100**, 734–738.

Balmes, J. (2002). Occupational airways diseases from chronic low-level exposures to irritants. *Clin. Chest Med.* **23**, 727–735.

Bauer, X., Fruhmann, G., Haug, B., Rasche, B., Reiher, W., and Weiss, W. (1986). Role of Aspergillus amylase in bakers' asthma. *Lancet* **1**, 43.

Bernaola, G., Echechipia, S., Urrutia, I., Fernández, E., Audícana, M., and Fernández de Corres, L. (1994). Occupational asthma and rhinoconjunctivitis from inhalation of dried cow's milk caused by sensitization to alpha-lactalbumin. *Allergy* **49**, 189–191.

Bernstein, I. L., Chan-Yeung, M., Malo, J. L., and Bernstein, E. I. (1999). ''Asthma in the Workplace,'' 2nd ed. Marcel Dekker, Inc, New York.

Burstyn, I., Teschke, K., and Kennedy, S. (1997). Exposure levels and determinants of inhalable dust exposure in bakeries. *Ann. Occup. Hyg.* **41**, 609–624.

Campbell, C. P., Jackson, A. S., Johnson, A. R., Thomas, P. S., and Yates, D. H. (2007). Occupational sensitization to lupin in the workplace: Occupational asthma, rhinitis, and work-aggravated asthma. *Allergy Clin. Immunol.* **119**, 1133–1139.

Centers for Disease Control and Prevention (CDC) (1986). ''Health Hazard Evaluation Report: International Bakers Services, Inc., South Bend, Indiana.'' US Department of Health and Human Services, CDC, National Institute for Occupational Safety and Health, Cincinnati, OH. (DHHS [NIOSH] publication no. 85-171-1710.).

Centers for Disease Control and Prevention (CDC) (2002). Fixed obstructive lung disease in workers at a microwave popcorn factory—Missouri, 2000–2002. *MMWR. Morb. Mortal. Wkly. Rep.* **51**, 345–347.

Centers for Disease Control and Prevention (CDC) (2004). ''NIOSH Alert: Preventing Lung Disease in Workers that Use or Make Flavorings.'' US Department of Health and Human Services, CDC, National Institute for Occupational Safety and Health, Cincinnati, OH. (DHHS [NIOSH] publication no. 2004-110.) Available at http://www.cdc.gov/niosh/docs/2004-100.

Centers for Disease Control and Prevention (CDC) (2006). ''Hazard Evaluation and Technical Assistance Report: Gilster-Mary Lee Corporation, Jasper, Missouri.'' US Department of Health and Human Services, CDC, National Institute for Occupational Safety and Health, Cincinnati, OH. (DHHS [NIOSH] publication no. 2000-0401-2291.)

Centers for Disease Control and Prevention (CDC) (2007a). ''Hazard Evaluation and Technical Assistance Report: Yatkso's Popcorn, Sand Coulee, Montana.'' US Department of Health and Human Services, CDC, National Institute for Occupational Safety and Health, Cincinnati, OH. (DHHS [NIOSH] publication no. 2006-0195-3044.)

Centers for Disease Control and Prevention (CDC) (2007b). ''Hazard Evaluation and Technical Assistance Report: Report on Severe Fixed Obstructive Lung Disease in Workers at a Flavoring Plant.'' US Department of Health and Human Services, CDC, National Institute

for Occupational Safety and Health, Cincinnati, OH. (DHHS [NIOSH] publication no. 2006-0303-3043.)

Centers for Disease Control and Prevention (CDC) (2007c). Hazard Evaluation and Technical Assistance: Gold Coast Ingredients, Inc., Commerce, California.'' US Department of Health and Human Services, CDC, National Institute for Occupational Safety and Health. Interim Letter I, March 29, 2007.

Centers for Disease Control and Prevention (CDC) (2007d). Fixed obstructive lung disease among workers in the flavor-manufacturing industry—California, 2004–2007. *Morb. Mortal. Wkly. Rep.* **56**, 389–393.

Christiansen, M. L., Ahlbom, G., Frank, W., Jersild, C., Sølvsteen, P., and Schwartz, B. (1981). Extrinsic allergic alveolitis caused by occupational inhalation of carmine. *Eur. J. Respir. Dis.* **113**(Suppl. 62), 82–83.

Cohen, A. J., Forse, M. S., and Tario, S. M. (1993). Occupational asthma caused by pectin inhalation during the manufacture of jam. *Chest* **103**, 309–311.

Falleroni, A. E., Zeiss, C. R., and Levitz, D. (1981). Occupational asthma secondary to inhalation of garlic dust. *J. Allergy Clin. Immunol.* **68**, 156–160.

Fishwick, D., Pearce, N., D'Souza, W., Lewis, S., Town, I., Armstrong, R., Kogevinas, M., and Crane, J. (1997a). Occupational asthma in New Zealanders: A population based study. *Occup. Environ. Med.* **54**, 301–306.

Fishwick, D., Bradshaw, L. M., D'Souza, W., Town, I., Armstrong, R., Pearce, N., and Crane, J. (1997b). Chronic bronchitis, shortness of breath, and airway obstruction by occupation in New Zealand. *Am. J. Respir. Crit. Care Med.* **156**, 1440–1446.

Flavor and Extract Manufacturers Association of the United States (2004). ''Respiratory Health and Safety in the Flavor Manufacturing Workplace.''. Flavor and Extract Manufacturers Association of the United States, Washington, DC. Available at http://www.femaflavor.org/html/public/Respiratory Rpt.pdf.

Fraj, J., Lezaun, A., Colás, C., Duce, F., Domínguez, M. A., and Alonso, M. D. (1996). Occupational asthma induced by aniseed. *Allergy* **51**, 337–339.

Harris, G. (2007). Doctor links a man's illness to a microwave popcorn habit. *N.Y. Times.* September 5, 2007.

Heederik, D., and Newman Taylor, A. J. (1999). Occupational asthma in the baking industry. *In* ''Asthma in the Workplace'' (I. L. Bernstein, M. Chan-Yeung, J.-L. Maol, and D. I. Bernstein, eds). Marcel Dekker, Inc, New York.

Hnizdo, E., Sullivan, P. A., Bang, K. I., and Wagner, G. (2002). Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: A study of data from the third National Health and Nutrition Examination Survey. *Am. J. Epidemiol.* **156**, 738–746.

Houba, R., van Run, P., Heederik, D., and Doekes, G. (1996). Wheat antigen exposure assessment for epidemiological studies in bakeries using personal dust sampling and inhibition ELISA. *Clin. Exp. Allergy* **26**, 164–163.

Hubbs, A. F., Battelli, L. A., Goldsmith, W. T., Porter, D. W., Frazer, D., Friend, S., Schwegler-Berry, D., Mercer, R. R., Reynolds, J. S., Grote, A., Castranova, V., Kullman, G., *et al.* (2002). Necrosis of nasal and airway epithelium in rats inhaling vapors of artificial butter flavoring. *Toxicol. Appl. Pharmacol.* **185**, 128–135.

Hubbs, A. F., Goldsmith, W. T., Kashon, M. L., Frazer, D., Mercer, R. R., Battelli, L. A., Kullman, G. J., Schwegler-Berry, D., Friend, S., and Castranova, V. (2008). Respiratory toxicologic pathology of inhaled diacetyl in Sprague-Dawley rats. *Toxicol. Pathol.* **36,** 330–344.

Johnson, A., Dittrick, M., and Chan-Yeung, M. (1999). Occupational asthma caused by honey. *Allergy* **54**, 189–190.

Kanwal, R., Kullman, G., Piacitelli, C., Boylstein, R., Sahakian, N., Martin, S., Fedan, K., and Kreiss, K. (2006). Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. *J. Occup. Environ. Med.* **48**, 149–157.

Keskinen, H., Ostman, P., Vaheri, E., Tarvainen, K., Grenquist-Norden, G., Karppinen, O., and Nordman, H. (1991). A case of occupational asthma, rhinitis and urticaria due to sesame seed. *Clin. Exp. Allergy* **21**, 623–624.

Kraut, A., Peng, Z., Becker, A. B., and Warren, C. P. (1992). Christmas candy maker's asthma. IgG4-mediated pectin allergy. *Chest* **102**, 1605–1607.

Kreiss, K., Gomaa, A., Kullman, G., Fedan, K., Simoes, E., and Enright, P. L. (2002a). Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N. Engl. J. Med.* **347**, 330–338.

Kreiss, K., Hubbs, A., and Kullman, G. (2002b). Correspondence: Bronchiolitis in popcorn-factory workers. *N. Eng. J. Med.* **347**, 1981–1982.

Labrecque, M., Coté, J., Cartier, A., Lemière, C., and Malo, J. L. (2004). Occupational asthma due to pork antigens. *Allergy* **59**, 893–894.

Lemière, C., Cartier, A., Lehrer, S. B., and Malo, J. L. (1996). Occupational asthma casued by aromatic herbs. *Allergy* **51**, 647–649.

Lizaso, M. T., Moneo, I., García, B. E., Acero, S., Quince, S., and Tabar, A. I. (2000). Identification of allergens involved in occupational asthma due to carmine dye. *Ann. Allergy Asthma Immunol.* **84**, 549–552.

Lockey, J., McKay, R., Barth, E., Dahlsten, J., and Baughman, R. (2002). Bronchiolitis obliterans in the food flavoring manufacturing industry. *Am. J. Respir. Crit. Care Med.* **165**(Suppl. 1), 438–439.

Merget, R., Sander, I., Raulf-Heimsoth, M., and Baur, X. (2001). Baker's asthma due to xylanase and cellulase without sensitization to alpha-amylase and only weak sensitization to flour. *Int. Arch. Allergy Immunol.* **124**, 502–505.

Miller, M. R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C. P. M., Gustafsson, P., Jensen, R., Johnson, D. C., *et al.* (2005). Standardization of spirometry. *Eur. Respir. J.* **26**, 319–338. URL: http://www.thoracic.org/sections/publications/statements/pages/pfet/pft2.html.

Morgan, D. I., Flake, G., Kirby, P. J., Burka, L. T., Kleeberger, S. R., Garantziotis, S., Germolec, D. R., and Palmer, S. M. (2006). Respiratory tract toxicity of diacetyl in C57BL/6 mice. *Toxicol. Sci.* **90**(Suppl. 1), 210.

Nicholson, P. J., Newman Taylor, A. J., Oliver, P., and Cathcart, M. (2001). Current best practice for the health surveillance of enzyme workers in the soap and detergent industry. *Occup. Med.* **51**, 81–92.

Novey, H. S., Marchioli, L. E., Sokol, W. N., and Wells, I. D. (1979). Papain-induced asthma—physiological and immunological features. *J. Allergy Clin. Immunol.* **63**, 98–103.

Occupational Safety and Health Administration (2007). (accessed 2007). Respiratory Protection Standard. 29 Code of Federal Regulations: 1910.134. URL: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=12716.

Osterman, K., Johansson, S. G. O., and Zetterstrom, O. (1985). Diagnostic tests in allergy to green coffee. *Allergy* **40**, 336–343.

Parmet, A., and von Essen, S. (2002). Rapidly progressive, fixed airway obstructive disease in popcorn workers: A new occupational pulmonary illness? *J. Occup. Environ. Med.* **44**, 216–218.

Perfetti, L., Lehrer, S. B., McCants, M., and Malo, J. L. (1997). Occupational asthma caused by cacao. *Allergy* **52**, 778–780.

Quirce, S., Cuevas, M., Díez-Gómez, M. L., Fernández-Rivas, M., Hinojosa, M., González, R., and Losada, E. (1992). Respiratory allergy to *Aspergillus*-derived enzymes in bakers' asthma. *J. Allergy Clin. Immunol.* **90**, 970–978.

Quirce, S., Fernández-Nieto, M., Bartolomé, B., Bombín, C., Cuevas, M., and Sastre, J. (2002). Glucoamylase: Another fungal enzyme associated with baker's asthma. *Ann. Allergy Asthma Immunol.* **89**, 197–202.

Rodriguez, A., de la Cuesta, C. G., Olaguibel, M. J., Tabar, A., and Santos, F. (1990). Occupational asthma due to inhaled carminic acid dye: Case report. *Clin. Exp. Allergy* **20**(Suppl. 1), 43.

Rossi, G. L., Corsico, A., and Moscato, G. (1994). Occupational asthma cause by milk proteins: Report on a case. *J. Allergy Clin. Immunol.* **93**, 799–801.

Sastre, J., Olmo, M., Novalvos, A., Ibañez, D., and Lahoz, C. (1996). Occupational asthma due to different spices. *Allergy* **51**, 117–120.

Schneider, A. (2007). Flavoring additive puts professional cooks at risk. *Seattle Post-Intelligencer.* December 21, 2007.

Schuller, A., Morisset, M., Maadi, F., Kolopp Sarda, M. N., Fremont, S., Parisot, L., Kanny, G., and Moneret-Vautrin, D. A. (2005). Occupational asthma due to allergy to spinach powder in a pasta factory. *Allergy* **60**, 408–409.

Schuyler, M. (1998). Hypersensitivity pneumonitis. *In* ''Fishman's Pulmonary Diseases and Disorders'' (A. P. Fishman, J. A. Elias, J. A. Fishman, M. A. Grippi, L. R. Kaiser, and R. M. Senior, eds), 3rd ed., pp. 1085–1097. McGraw-Hill, New York.

Sen, D., Wiley, K., and Williams, J. G. (1998). Occupational asthma in fruit salad processing. *Clin. Exp. Allergy* **28**, 363–367.

Seuri, M., Taivanen, A., Ruoppi, P., and Tukiainen, H. (1993). Three cases of occupational asthma and rhinitis caused by garlic. *Clin. Exp. Allergy* **23**, 1011–1014.

Shirai, T., Reshad, K., Yoshitomi, A., Chida, K., Nakamura, H., and Taniguchi, M. (2003). Green tea-induced asthma: Relationship between immunological reactivity, specific and non-specific bronchial responsiveness. *Clin. Exp. Allergy* **33**, 1252–1255.

Simpson, E. G., Belfield, P. W., and Cooke, N. J. (1985). Chronic airflow limitation after inhalation of overheated cooking oil fumes. *Postgrad. Med. J.* **61**, 1001–1002.

Smith, A. B., Bernstein, D. I., Tar-Ching, A. W., Gallagher, J. S., London, M., Koff, S., and Carson, G. A. (1987). Occupational asthma from inhaled egg protein. *Am. J. Ind. Med.* **12**, 205–218.

Tabar-Purroy, A. I., Alcarez-Puebla, M. J., Acero-Sainz, S., Garcia-Figueroa, B. E., Echechipia-Madoz, S., Olaguibel-Rivera, J. M., and Quirce-Gancedo, S. (2003). Carmine (E-120)-induced occupational asthma revisited. *J. Allergy Clin. Immunol.* **111**, 415–419.

Tarvainen, K., Kanerva, L., Tupasela, O., Grenquist-Nordén, B., Jolanki, R., Estlander, T., and Keskinen, H. (1991). Allergy from cellulose and xylanase enzymes. *Clin. Exp. Allergy* **21**, 609–615.

Toskala, E., Piipari, R., Aalto-Korte, K., Tuppurainen, M., Kuuliala, O., and Keskinen, H. (2004). Occupational asthma and rhinitis cause by milk proteins. *J. Occup. Environ. Med.* **46**, 1100–1101.

van Rooy, F. G. B. J., Rooyackers, J. M., Prokop, M., Houba, R., Smit, L. A. M., and Heederik, D. J. J. (2007). Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am. J. Respir. Crit. Care Med.* **176**, 498–504.

Vandenplas, O., Depelchin, S., Toussaint, G., Delwiche, J. P., Vande Weyer, R., and Saint-Remy, J. M. (1996). Occupational asthma caused by sarsaparilla root dust. *J. Allergy Clin. Immunol.* **97**, 1416–1418.

Vandenplas, O., Vander Borght, T., and Delwiche, J. P. (1998). Occupational asthma caused by sunflower-seed dust. *Allergy* **53**, 907–908.

Zock, J. P., Hollander, A., Heederik, D., and Douwes, J. (1998). Acute lung function changes and low endotoxin exposures in the potato processing industry. *Am. J. Ind. Med.* **33**, 384–391.

Zock, J. P., Sunyer, J., Kogevinas, M., Kromhout, H., Burney, P., Antó, J. M., and E.C.R.H.S. study group (2001). Occupation, chronic bronchitis, and lung function in young adults. *Am. J. Respir. Crit. Care Med.* **163**, 1572–1577.

Zuskin, E., Valic, F., and Kanceljak, B. (1981). Immunological and respiratory changes in coffee workers. *Thorax* **36**, 9–13.

Zuskin, E., Kanceljak, B., Skuric, Z., Pokrajac, D., Schachter, E. N., Witek, T. J., and Maayani, S. (1988). Immunological and respiratory findings in spice-factory workers. *Environ. Res.* **47**, 95–108.

Zuskin, E., Kanceljak, B., Schachter, E. N., Dognic-Cvar, J., Mustajbegovic, J., and Budak, A. (1998). Respiratory function and immunological status in cocoa and flour processing workers. *Am. J. Ind. Med.* **33**, 24–32.