

# Agricultural Dust– induced Lung Disease

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The practice of agriculture has changed substantially over the past 4 decades in response to economic, technologic, and societal factors. Consequently, the agricultural worker faces a new set of health risks in today's agricultural environment (Table 36.1). In the United States during the latter part of the 20th century, there was a shift from the historical pattern of a large number of traditional family-owned and -operated farms to the current condition, in which there are fewer but larger farms that rely on workers who most often do not live on the farm, including seasonal and migrant workers (1). In the United States, apart from seasonal and migrant workers, between 2 million and 3.5 million individuals work in farming (2). However, in developing countries, the numbers are much higher in both absolute terms and as a percentage of the population. In Asia, 50% to 70% of the workforce is directly involved in agriculture, and in Africa it is 70% to 90%; thus, farming is the most common industry worldwide (1). On the 2.1 million farms in the United States (3) there are approximately 700,000 animal confinement workers, including 80,000 poultry farm workers (4).

Changes in the business of agriculture and the agricultural infrastructure have led to the practice of housing large numbers of animals inside buildings, often referred to as *concentrated animal feeding operations* (CAFOs). This has in turn led to a decrease in the number of swine farms in the United States; in the 1960s, there were over 1.1 million swine farms, but by 1999, there were only about 100,000 (5). Interestingly, the total number of swine raised on these farms has remained stable or increased, accounted for by increasingly concentrated

animal populations: there were about 61 million swine in 1915 and 59 million in 2000 (5). In fact, from 1993 to 1999, the number of swine increased by 250% (5). In CAFOs, animals are kept in enclosed buildings where the air becomes filled with animal-related debris and dust (5). The increased use of CAFOs has created a variety of new potential health problems, many of which are related to inhalation of animal and other organic dusts. The inhalational health effects of exposure to the agricultural environment are related to several factors: dusts, animal secretions, skin, and feces, as well as bacteria and fungi and their products, including endotoxin (6). Even though there are fewer farms overall, the Occupational Safety and Health Administration (OSHA) only infrequently evaluates larger operations, and it exempts agricultural operations with ten or fewer employees.

As a group, farm workers are the second most likely among all occupations to have never smoked; only members of the clergy are more likely to have never smoked (7,8). Epidemiologic studies have shown farmers and other agricultural workers, and perhaps those merely living near agricultural lands and facilities, to be at increased risk of developing lung disease. The increase may be threefold relative to non-farm workers and is independent of smoking. Agricultural workers are exposed to a variety of both plant- and animal-derived dusts in the fields and farmyards; they may even inadvertently expose their family members through transfer of dusts into the house via contaminated clothing. This chapter will examine the airway diseases as well as the lung parenchymal diseases commonly associated with agricultural dust exposure.

**Table 36.1****Categories of Exposure and Selected Agents Known to Cause Asthma Related to Agricultural Exposures**

Category	Occupations	Causative Agents
Organic dusts	Grain and cotton industries, farmers, and lumber industry	Endotoxin, tannins, plant proteins and pollens, mycotoxins, and insect parts
Animal-derived material	Farmers and animal handlers	Antigenic proteins
Irritants	Farmers and pesticide manufacturers	Pesticides, herbicides, and fertilizers
Fumes	Farmers	Ammonia, oxides of nitrogen, and welding fumes

## EXPOSURE TO DUSTS IN THE FARMING ENVIRONMENT

The concentration of animals in confined spaces, such as in CAFOs, has led to greater exposure to animal- and plant-related dusts among farm workers. The dust itself is heterogeneous, and its characteristics vary depending on the type of farming from which it came. Measurements of the levels of dusts in swine confinement buildings may exceed American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) for nuisance dust; in addition, the dust contains biologically active agents including endotoxin, microbes, and proteins (9).

Certain routine activities in daily farm work result in the creation and dispersal of dusts; even activities of the animals themselves are major producers of dust particles. Periods of high dust concentration occur when animals are fed, when they rub against one another, or when their feed is distributed. However, it is possible to reduce the dust production in some circumstances. For example, when pigs are given access to feed throughout the day, they are less likely to stir up dusts (10).

Residents of rural areas are at risk for the same types of exposure as agricultural workers if they live near animal confinement facilities. Only a few relatively small studies of people living near CAFOs are available, and one of these (11) involving 18 subjects and 18 controls indicated that people living within 2 miles of a swine confinement operation had higher rates of coughing, wheezing, sputum production, and dyspnea. These same symptoms were also seen in the CAFO workers. Among 155 people living near large livestock operations, even nonsmokers reported increased respiratory symptoms and other symptoms (runny nose, burning eyes, headache) similar to those experienced by workers inside the operation (12). Some have pointed out that the results of these small studies cannot be extrapolated to all members of populations living near a CAFO (13). Furthermore, studies using measurement of the levels of dusts and endotoxin in ambient air revealed that dust,

endotoxin, and H<sub>2</sub>S gas were not detectable at distances greater than 300 m from farms, even in cases where local residents had complained of dust-related symptoms (6). Other studies have shown that odors alone are associated with increased health problems among those living near CAFOs, though it has been postulated that the odor is merely a marker for the presence of an actual disease-causing agent (5).

### Bioaerosols

Airborne mixtures of plant and animal parts or microbial entities are known as *bioaerosols* (14). In the agricultural setting, it is known that several of the components of bioaerosols have adverse human health effects, the most important of these including endotoxin and certain microorganisms. Endotoxin is present in Gram-negative bacterial cell walls and is ubiquitous in ambient air in the agricultural environment. Gram-negative bacteria are commonly found on the leaves of crops, and endotoxin becomes aerosolized when the crops are manipulated. Both acute and chronic human airway and lung disease can result after inhalation of endotoxin (14). Fungi and their spores are also ubiquitous in the environment, and exposure may lead to a number of inhalational and systemic diseases. Fungal-derived toxins may also cause disease; *Aspergillus*-derived aflatoxin is carcinogenic, and it is known that other mycotoxins from common fungi, such as *Penicillium* and *Fusarium* species are found in cotton and grain dust (14).

### Dust Composition

Light microscopy of air samples from confinement buildings shows that dust consists primarily of feed particles (starch granules, grain meal, and corn silk) and swine feces; in addition, animal dander, mold spores and hyphae, pollens, grains, insect parts, mineral ash, antibiotics, animal growth promoting agents, and pesticides are also found in the dust (9,15). The dust particles are heterogeneous, ranging in size from <0.01 to 100 μm, (although

40% are  $<4 \mu\text{m}$  in diameter) (16) and are frequently contaminated with adsorbed proteins and ammonia gas (9). The dust also contains microbes such as Gram-positive bacteria and a lesser number of Gram-negative bacteria, fungi, and thermophilic actinomycetes (9). In addition, because the dust is made up of many types of particles and substances, it is difficult to study the possible health effect of any one component in isolation (17).

### Inorganic Components

Inorganic components of the dust, such as silica, are present even in grain-derived dusts, comprising up to 43% of the total dust (16), and vary depending on factors such as the composition of the soil and the climate (17). The exposure to inorganic dusts is highest in dry climates (17). Air sampling has found silica particles in the ambient air inhaled by farm workers during routine farming activities at concentrations that exceed the ACGIH-recommended TLVs (18). Silica, one of the most abundant elements in the earth's crust, is released from the ground when rock or soil is mechanically disturbed through practices such as plowing soils and harvesting crops, especially in dry climates. Modern farm implements with their enclosed, climate-controlled cabs play a role in reducing worker exposure to dust. In open-cab tractors, the median total particle exposures are 2 to 20 mg per  $\text{m}^3$  (17) and in closed-cab tractors using air filtration, the total dust is typically reduced to 0.1 to 1 mg per  $\text{m}^3$  (19). Exposure to the elements weathers the silica particles, making them less likely to cause lung disease; this may be related to the decrease in particle surface-based free radicals (19). Fresh-fractured silica released during mining or sandblasting is more likely to be pathogenic (16,17), producing more cellular toxicity and free radicals (20,21) compared with aged and weathered particles that have been exposed to the elements (19). Dusts including silica previously deposited on the leaves of growing plants become secondarily aerosolized as plants are manipulated during harvest.

### Organic Components

Endotoxin from Gram-negative bacterial cell walls is almost invariably present in agricultural dusts; exposure levels thus depend on the total concentration of dust, degree of endotoxin contamination of the dust, and the minute ventilation of the workers (22). Both the airways and lung parenchyma are susceptible to developing dust-related disease. Airway diseases such as chronic bronchitis and asthma are most common, but interstitial lung disease also occurs after dust exposure; in addition, there are a few infectious diseases closely related to farm dust exposure. There are well-defined work-related decreases in peak flow among grain and animal workers during the workday (8), and these workers are also at increased risk

of developing chronic airway disease, such as obstructive lung disease (chronic bronchitis) as first reported in cross-sectional studies (23) and as is now suggested by the findings of longitudinal studies (23,24).

### Other Components

Other substances, including gases such as ammonia, may be carried by dust particles and may lead to worker exposure. Ammonia exposure is especially problematic in swine confinement buildings (10), where it emanates from the animal waste as it settles in large tanks underneath the buildings. Ammonia gas then disperses and adsorbs onto dust particles, allowing it to travel longer distances, and the gas can be inhaled at distant locations. Ammonia causes respiratory tract irritation (16) and is associated with the development of sinusitis and chronic obstructive lung disease (16). Ammonia levels inside the buildings may increase during the winter months because of decreased ventilation; levels may exceed the OSHA permissible exposure limits (PELs) for ammonia [50 ppm with a short-term exposure limit (STEL) of 35 ppm (25)]. Based on observed cross-shift declines in forced expiratory volume in 1 second ( $\text{FEV}_1$ ), some have recommended that the PEL be reduced to 7.5 ppm (4). Other known toxic components of CAFO environments, such as hydrogen sulfide ( $\text{H}_2\text{S}$ ) and  $\text{NO}_2$ , have not been shown conclusively to associate with dust particles.

Insect parts and pesticides may also be found in agricultural dusts. Disintegrated insect parts tend to contribute to the particle phase of dust but may also be involved in triggering allergic responses (19). In general, pesticides do not cause chronic lung disease. It is true that chemical pneumonitis is occasionally seen after exposure to herbicides such as glyphosate, and acute bronchospasm can occur upon exposure to organophosphate pesticides (16). An important exception to this rule is the herbicide paraquat, which can cause pulmonary fibrosis (16).

### AIRWAY RESPONSE TO INHALED DUSTS

The airway and lung response to inhaled grain dust is an inflammatory process, as demonstrated by increased neutrophils and tumor necrosis factor alpha ( $\text{TNF-}\alpha$ ) in bronchoalveolar lavage (BAL) fluid; this inflammation leads to decreases in  $\text{FEV}_1$  (26), the primary measure of lung function. This response is not dependent on allergic mechanisms, even in cases of chronic exposure (27). However, individuals with pre-existing asthma are more susceptible to the bronchoconstricting effects of exposure to grain dusts (28). Many factors, including particle size, appear to be important in the airway response to dust. However, endotoxin on the dust rather than the dust itself (29–32) seems to be a major factor causing many of the above findings.

## Evidence for Endotoxin as a Pathogenic Factor in Agricultural Dust

The evidence for endotoxin as a causative agent in agricultural dust-related airway diseases is strong and based upon the dose-response relationship between inhalation of endotoxin and the resulting increase in obstructive airway physiology. Several studies have shown that even in healthy persons, the concentration of inhaled endotoxin is directly associated with an acute decrease in lung function as measured by the FEV<sub>1</sub> (15). In addition, increases in markers of inflammation [neutrophils and interleukin (IL)-6] that would not be seen with dust exposure alone have been detected in those exposed to endotoxin (15).

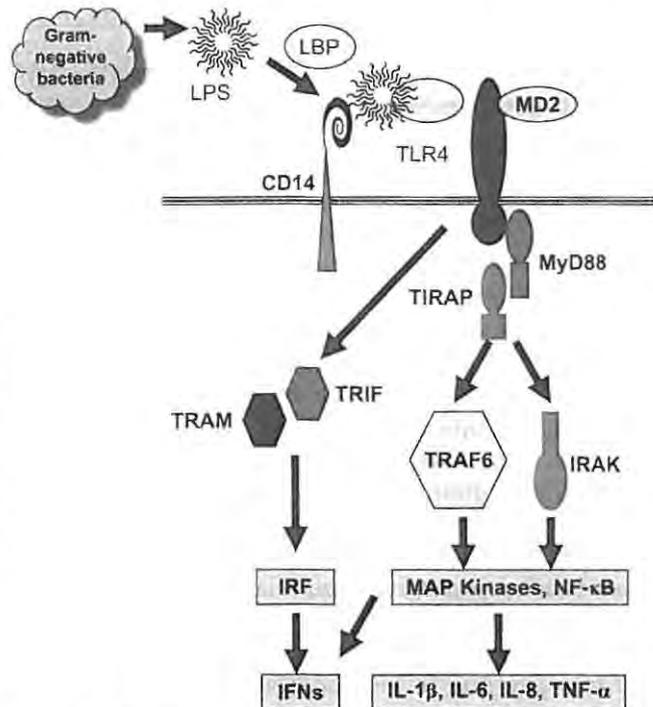
Both endotoxin and dust from animal confinements have similar physiologic and inflammatory effects. Healthy volunteers exposed to endotoxin-laden corn dust extract or endotoxin at low and high concentrations experienced similar degrees of productive cough, chest tightness, and shortness of breath after exposure to corn dust extract or endotoxin alone in the same concentration. Furthermore, a dose-response effect was seen between endotoxin concentration inhaled and airflow obstruction as well as inflammatory markers in BAL fluid (29).

Endotoxin-producing bacteria are common in agricultural environments and include *Pseudomonas*, *Pasteurella*, and *Enterobacter* species (16). Endotoxin is common in the agricultural and rural environment, and it is closely associated with dust and the dust-producing procedures common at grain elevators, livestock facilities, potato farms, poultry farms, and animal feed-producing operations (1). The farming practices leading to the greatest exposures to dusts occur during cleaning of silos, where the median levels are 63 mg per m<sup>3</sup> for dust and 650 ng per m<sup>3</sup> for endotoxin (22). Other common practices such as tilling of fields, manipulation and transfer of feed and grain, cleaning animal housing areas, unloading grain storage facilities, haying, and harvest also lead to human exposure (16). Similarly, inside animal confinement buildings, the dust levels vary according to the type of activity occurring in each building. Because there are no legal limits for agricultural dust exposure, some authorities have recommended using the OSHA PELs for nuisance dust (currently 15 mg per m<sup>3</sup> total dust, 5 mg per m<sup>3</sup> respirable dust, and 10 mg per m<sup>3</sup> for grain dusts) (16). However, there is documented evidence of respiratory disease in humans even at lower levels of dust exposure: Based upon post-workshift changes in measures of FEV<sub>1</sub> in exposed individuals, some have proposed new TLVs for total organic dust at 2.5 mg per m<sup>3</sup> (16,33).

The amounts of endotoxin in agricultural dust vary according to both type of animal and type of work, as well as the species of bacteria (16), and can be very high. The actual concentration of endotoxin needed to cause a response in a particular human may be difficult to know

and may vary among individuals. However, studies have shown that even low levels of inhalation exposure do cause measurable effects in humans. Endotoxin levels of 20 to 50 ng per m<sup>3</sup> (200 to 500 EU per m<sup>3</sup>) have been associated with mucous membrane irritation (19) and levels of 100 to 200 ng per m<sup>3</sup> have been associated with bronchoconstriction as seen by a cross-shift decline in FEV<sub>1</sub> (16,34). Chest tightness has been reported to occur at 300 to 500 ng per m<sup>3</sup>, and fever has been reported at 500 to 1,000 ng per m<sup>3</sup> (34,35). At higher levels (1,000 to 2,000 ng per m<sup>3</sup>), endotoxin causes other diseases, including the organic dust toxic syndrome (16). While there are no OSHA PELs for endotoxin, some have recommended 100 EU per m<sup>3</sup> as the upper limit for those chronically exposed in swine confinement facilities (4). Although the reported no-effect level for endotoxin has ranged from 50 to several hundred EU per m<sup>3</sup> (14), the feasibility of achieving these low levels in agriculture is unknown.

Recently, research has begun to reveal the molecular basis of the human response to inhalation of endotoxin (Fig. 36.1). There is a family of transmembrane receptors



**Figure 36.1** Lipopolysaccharide (LPS), from the cell wall of Gram-negative bacteria, is bound to LPS-binding protein (LBP); this complex interacts with CD14, which, with the regulatory protein MD2, facilitates recognition and signaling by TLR-4. TLR-4 acts through Myeloid differentiation response gene 88 (MyD88)-dependent and -independent routes to induce transcription of inflammatory cytokines. CD, IFNs, Interferons; IL, interleukin; IRAK, IL-1 receptor-associated kinase; IRF, Interferon regulatory factor; MAP, mitogen-activated protein; MD, MyD, myeloid differentiation; NF-κB, nuclear factor κB; TIRAP, toll- and IL-1 receptor protein adaptor protein; TLR, toll-like receptor; TNF, tumor necrosis factor; TRAF, TNF-receptor activated factor; TRAM, TRIF-related adaptor molecule; TRIF, toll-interleukin-1 receptor inducing interferon-β factor.

known as Tolllike receptors (TLRs) that mediate this response. One member of this family, TLR-4, is thought to be the main human receptor for bacterial endotoxin (36–39). The evidence for its involvement resides in several lines of investigation. *In vitro* studies show that a single amino acid substitution in TLR-4 leads to decreased signaling after endotoxin exposure (40,41), suggesting that TLR-4 mediates the response to endotoxin. Studies using TLR-4–knockout mice, which do not respond to endotoxin, confirmed its importance in this signaling pathway (42). Genetic polymorphisms in the genes for TLR-4 may affect the prevalence and severity of asthma in the setting of endotoxin exposure, but there is controversy as to whether or not TLR-4 polymorphisms are related to interindividual responses to endotoxin exposure (39,41,43–45). Although all details of endotoxin-triggered signaling through TLRs are not yet known, and some of the research has been conducted in mice, it is likely that continued research will lead to better understanding of the relation between endotoxin exposure and human lung disease.

## AIRWAY DISEASES

The most common respiratory condition caused by agricultural dust exposure is a nasopharynx-laryngeal mucous membrane irritation syndrome. It does not lead to severe clinical disease or permanent disability. It represents an inflammatory process and has been linked to the same components of agricultural dust that cause lung disease, including endotoxin, fungi, thermophilic bacteria, silicates, and grain dust (19). It will not be discussed further except to mention that it has been estimated to occur in 20% to 50% of workers (16).

Another condition, asthmalike syndrome, is clinically similar to asthma but is a nonallergic inflammatory process leading to recurrent episodes of bronchospasm (19). It differs from true work-related asthma in that it tends to subside during the work week despite ongoing occupational exposure (19,46). Few studies of this entity exist, but it is thought to be related to inhalation of endotoxin and possibly other components of grain dust (19).

## ASTHMA CAUSED BY AGRICULTURAL EXPOSURES

Asthma may be either caused or exacerbated by specific exposures to agents in the agricultural environment. In both cases, asthma caused by agricultural exposures is characterized by variable and intermittent airflow obstruction. The objective signs of airflow obstruction are often associated with symptoms of chest tightness, wheezing, coughing, and dyspnea. Because both

immediate and delayed (up to 12 hours) airway responses may occur following these exposures, the specific agent causing the onset of airflow obstruction may not always be apparent.

## Epidemiology

Defined broadly, occupational asthma is estimated to account for between 5% and 15% of the patients who are diagnosed with asthma (47,48). The prevalence of asthma caused by agricultural exposure has been difficult to determine, probably due to the “healthy worker effect.” One study of Swedish farmers determined that 10.5% had been diagnosed with asthma by a physician, whereas only 6% of the general population had been similarly diagnosed (49). One European study that defined asthma as “bronchial hyperresponsiveness, asthma symptoms, or use of asthma medication” found that farmers had the highest odds ratio (OR), 2.6, for having asthma among all occupations; among all agricultural workers, the OR was 1.8 (50). Part of the problem in determining the true prevalence of agriculture-related asthma is that not all studies use the same criteria to define asthma, and some define asthma based on the self-reporting of any symptoms that are consistent with asthma. Self-reports of asthma among Swedish male farmers are 179 per million per year versus a crude rate of 80 per million per year (51). Based on several recent studies, the prevalence of asthma among farmers has been estimated as 10.3% to 15.4% (52–54).

Regardless of the actual prevalence, self-reported wheezing among agricultural workers is dose-related (55,56) and appears to be influenced by host factors including atopy (55). There is an increased risk of wheezing among workers who have higher frequency of exposure and who are exposed to more farm animals (55). Interestingly, some studies indicate more or less likelihood of symptoms in relation to some specific animals. For example, swine have been shown to be more likely to be associated with asthma symptoms or wheezing in some studies (57) but not in others (55). In addition to these factors, differences in specific products or processing are likely to account for seasonal and geographic differences in the prevalence of asthma among agricultural workers.

The FEV<sub>1</sub> in healthy nonsmoking persons normally declines by 25 to 30 mL per year starting at age 25 to 30 (22). In smokers, this rate of decline is accelerated. Recent data show accelerated declines in lung function among agricultural workers as well. Swine confinement workers had an excess loss of 26 mL per year and grain farmers lost an excess of 16 mL per year compared to nonfarmer controls (23). Other researchers found that persistent wheezing among grain elevator workers was associated with an excess decline in FEV<sub>1</sub> of 28 mL per year (58).

## Exposures

### Plant-derived Material

The largest and perhaps the most clinically relevant category of agents known to cause asthma in the agricultural setting are plant-derived materials. Grain dust (59), cotton dust (60), and dusts generated from teas (61), tobacco (62), mushrooms (63), chicory (64), and vegetable gums (65) all represent a complex mixture of vegetable particles and fragments, feed additives including fish meal and antibiotics, avian and rodent proteins, and pesticides. The specific agents most likely to cause or exacerbate asthma from these plant products are high-molecular weight proteins that can act as allergens. However, other agents in these dusts, such as tannins, mycotoxins, endotoxin, pollens, and insect parts, may also contribute to the development of asthma in these individuals.

### Animal-derived Material

Animal-derived proteins can cause asthma in agricultural workers (15,19). This form of asthma is much more common in atopic individuals who are capable of developing an immunoglobulin E (IgE) response to specific aerosolized animal proteins. Animal handlers, especially in sale barns and confinement units, may be intermittently exposed to high concentrations of animal-derived proteins and are at particularly high risk of developing asthma (66,67). Arthropod-derived material from grain mites (68), honeybees (69), barn mites (70), and other insects have been clearly shown to cause or exacerbate asthma in exposed populations. There is new evidence that pests living in or on the grain are responsible for some cases of occupational asthma. One study found that a majority of participants had positive skin prick tests to flour derived from grain that had been infested with *Eurygaster*, and negative results when tested using uninfested flour (71). Because these are IgE-mediated responses, a period of sensitization is needed, and upon re-exposure, onset of wheezing is usually immediate and often accompanied by rhinitis and other allergic symptoms.

### Irritants

Chemicals common to the agricultural environment including solvents, ammonia vapors, welding fumes, pesticides, herbicides, and fertilizers may contribute to the exacerbation of airflow obstruction in individuals with pre-existing asthma. Low concentrations of irritants may result in airflow obstruction in workers with underlying asthma but do not usually cause asthma in healthy workers.

An extreme form of irritant-induced asthma may very rarely occur following inhalation of high concentrations of fumes or vapors in the agricultural setting. In particular, noxious gases such as ammonia or H<sub>2</sub>S may acutely

cause extensive airway injury and severe bronchospasm, and after recovery there may be recurrent episodes of nonspecific bronchial hyperreactivity upon exposure to any of a variety of irritants for months to years afterward. This phenomenon is known as *reactive airways dysfunction syndrome* (RADS). One case report of this in the literature describes an otherwise healthy farmer who did not have pre-existing asthma but who developed new bronchial hyperreactivity after exposure to H<sub>2</sub>S and ammonia gas inside a swine confinement building (72). RADS is considered a subset of irritant-induced asthma and by definition would apply only to individuals without pre-existing asthma (73).

Characteristically, irritant-induced asthma occurs only after an overwhelming exposure to irritating gases. The worker should be able to recall a specific event when he or she was exposed to a high concentration of fumes that resulted in an acute respiratory illness. However, such exposures can also acutely cause airway and alveolar injury resulting in acute lung injury or acute respiratory distress syndrome (ARDS).

Acute chemical pneumonitis resembles and must be differentiated from RADS. Toxic gas exposure can also cause an acute lung injury characterized by airway epithelial or alveolar cell injury (74) leading to pulmonary edema, and if severe, diffuse alveolar damage and respiratory failure as seen in ARDS (74). Apart from the higher incidence of respiratory failure in acute chemical pneumonitis, these two disease processes can be best differentiated by their exposure history.

### Pharmacologic Agents

Two agents thought to cause asthma through pharmacologic mechanisms are organophosphate insecticides (75) and vegetable dusts containing histamine (76). Since a report published in 1992 (77), asthma has also been linked to cholinesterase-inhibiting pesticides. Organophosphates disrupt the cholinergic regulation of bronchial responsiveness and potentiate bronchoconstriction in guinea pigs, and they appear to do this without inhibiting acetylcholinesterases as was previously thought (78). Cotton dust and other vegetable dusts contain histamine, which can promote an allergic-inflammatory response in the airway, and this may be responsible for the development of asthma following inhalation of such dusts.

Farm workers who were otherwise healthy and free of respiratory disease and whose work involved application of insecticides to livestock reported more wheezing after exposure to agricultural dusts (79). In a cohort of 52,000 farmers, those responding to a survey reported wheezing in association with exposure to different pesticides; wheezing was associated with use of 11 of 40 different pesticides (80). Wheezing after exposure to individual pesticides was not related to grains or the type of crop or animal.

## CHRONIC AIRWAY DISEASE

Agricultural workers are at excess risk of developing obstructive airway diseases such as chronic bronchitis and chronic obstructive lung disease, as demonstrated by accelerated declines in airflow over a single work shift as well as over time. This decline is directly related to the concentration of dust and endotoxin in agricultural bioaerosols. As described above, humans normally experience a decline in their pulmonary function over time, and the decline is quicker in smokers. However, grain workers and swine confinement workers have been shown to have an accelerated rate of decline in FEV<sub>1</sub> even after controlling for smoking; if the FEV<sub>1</sub> decreases enough, subjects will develop shortness of breath (23). A study of Danish farmers over 7 years revealed faster decline over time in FEV<sub>1</sub> for pig farmers when compared with dairy farmers; during this time, forced vital capacity (FVC) declined at similar rates in both groups (24). These declines in lung function result in obstructive lung disease similar to that seen in smokers.

A cross-sectional study of workers in 14 countries showed an increased risk for chronic bronchitis in agricultural workers, and this risk was higher in smokers (81). Moreover, agricultural workers may have a higher mortality from chronic pulmonary diseases than workers from other industrial sectors, although there is contradictory evidence supporting both increased and decreased mortality from lung disease among agricultural workers (19,82–85).

Members of social or ethnic minorities working in agriculture in the United States appear to be at increased risk of developing work-related obstructive lung disease. Among Mexican Americans, the highest percentage of attributable cases of work-related obstructive lung disease (32%) were linked to agriculture; among African Americans, it was 10.8%—these numbers are heavily dependent on the demographics of employment of these groups of individuals (86).

### Occurrence

Chronic exposure to agricultural dusts can cause irreversible and progressive airway disease. Epidemiologic studies performed in North America (31,87–90), Scandinavia (91), the United Kingdom (68), Egypt (92), and South Africa (93) demonstrate that workers chronically exposed to agricultural dust are at increased risk of developing chronic cough, phlegm production, wheeze, and dyspnea irrespective of smoking habits. Also, long-term follow-up studies have shown that grain workers (94) and others working in agriculture (17,34,95,96) have accelerated declines in airflow over time that are directly related to the concentration of dust or duration of exposure. Although short-term experimental (97) or occupational (98) exposure to grain dust results in

reversible airway symptoms and airflow obstruction, long-term occupational exposure to either grain dust (99) or cotton dust (100) causes irreversible and progressive airway disease. A cohort of nearly 11,000 Scandinavian farmers revealed a two- to threefold increase in the risk for chronic bronchitis that increased to sixfold if they smoked cigarettes (91).

Epidemiologic studies have shown that the acute airway response to grain dust and other organic dusts is predictive of the chronic airway response to these agents. Several epidemiologic studies have shown that the acute workshift-related declines in airflow are independently associated with accelerated longitudinal declines in lung function among grain handlers (27,94,101), cotton workers (95), and agricultural workers (96). Also, some groups of farmers have been shown to have accelerated declines in lung function over time (23,24,96,102–104). Other studies have shown that the prevalence of chronic bronchitis is increased in persons exposed to swine confinements (34). Although a workshift response to organic dust may simply identify a cohort of individuals with a high intrinsic risk of airway disease, it is equally possible that the acute physiologic and biologic responses to inhaled organic dusts place workers at higher risk of developing progressive airway disease. In a human autopsy report of three grain workers (105), the pathologic findings included peribronchiolar fibrosis without bronchiectasis, patchy emphysema, and interstitial fibrosis; however, the smoking histories for these individuals were not reported. Among cotton workers (106), chronic pathologic findings attributable to cotton dust include bronchitis and bronchiolitis with mucous gland hyperplasia and goblet-cell metaplasia. In aggregate, these findings indicate that agricultural workers chronically exposed to organic dust are at risk for developing chronic airway disease involving progressive airflow obstruction, persistent airway and alveolar inflammation, and remodeling of the airway architecture.

### Pathogenesis

Animal inhalation studies demonstrate that inhalation of grain dust and other organic dusts causes acute and chronic inflammatory lesions, primarily focusing on the airway and involving macrophages, neutrophils, and specific proinflammatory cytokines. Inhalation studies in mice (97,107,108) have shown that following a single exposure to grain dust, neutrophils are rapidly recruited to the lung and proinflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , and IL-6) and chemokines [macrophage inflammatory proteins (MIP)-2] are produced and released for up to 48 hours (97). Swiss mice exposed to grain dust for 16 weeks demonstrated increased neutrophils in the walls and lumen of small bronchi and clusters of neutrophils and macrophages in the acini (109). Similarly,

in rats exposed to grain dust for 8 weeks, histologic changes included subepithelial neutrophils in the bronchi and bronchioli and dilated respiratory and alveolar ducts (110). In guinea pigs, chronic exposure to cotton dust for 1 year resulted in airflow obstruction (111), anatomic changes of the small airways consisting of hyperplasia of bronchiolar epithelium and type II cells, and thickening of the alveolar ducts and alveolar septa (112,113). Six-week intratracheal dosing of hamsters with either cotton dust or endotoxin can cause mild centrilobular emphysema (114). The pathogenic mechanisms that result in chronic inflammation, irreversible airflow obstruction, and permanent airway remodeling are detailed previously.

### Clinical Features

The diagnosis of chronic obstructive pulmonary disease (COPD), of which chronic bronchitis is one manifestation, is based on the physiologic assessment of airflow. Patients with COPD have a reduced FEV<sub>1</sub> and a reduced FEV<sub>1</sub>/FVC ratio. Although most patients with COPD improve with bronchodilators, improvement in FEV<sub>1</sub> is usually less than 15%, and the spirometric measures of airflow, by definition, do not normalize. In addition, lung volumes may reveal air trapping, and the diffusing capacity may identify those patients with emphysema.

### Natural History

The key unanswered question is whether effective control of the acute inflammatory response to inhaled agricultural dusts will prevent the development of chronic airway disease. Studies have not been conducted to address this question. However, there is increasing evidence that in people with asthma, control of the acute inflammatory response substantially improves airflow and chronic airway inflammation (115–117). A randomized trial of healthy volunteers exposed to corn dust extract (with controlled endotoxin levels) and pretreated with either inhaled or intravenous corticosteroids demonstrated a modest protective effect for FEV<sub>1</sub> with the steroids (118). Prolonged treatment of newly diagnosed mild asthmatics with inhaled corticosteroids resulted in significant improvement in airflow. Our recommendations currently include removal of the affected individual from exposure or, if this is not possible, reducing the concentration of inhaled dusts through use of a two-strap respirator and using inhaled corticosteroids in individuals with recurrent episodes of agricultural dust-induced airflow obstruction. In a study of healthy volunteers, across-shift declines in FEV<sub>1</sub> seen during exposure to the air in a swine confinement were prevented by use of a two-strap N95 respirator along with a nose clip (72). This suggests that many of the potential long-term respiratory effects of dust exposure

seen in susceptible individuals may be prevented by either removal from exposure or use of respiratory protection.

## INTERSTITIAL LUNG DISEASE

### Exposures

Agricultural workers are exposed to a wide variety of inorganic and organic dusts, depending on both their occupational tasks and local geography. Occupational dust exposure has been linked to increased rates of interstitial lung disease such as pulmonary fibrosis (119). In one important study of 40 patients with idiopathic pulmonary fibrosis (IPF), there was a significant association between IPF and work with cattle, leading to an increased risk with an OR of 10.89 relative to age- and sex-matched controls (120). Other studies have supported an increased risk of pulmonary fibrosis among farm and livestock workers, with OR of 1.6 and 2.7, respectively (121). Inorganic dusts, especially those made up of silicates, have been implicated in the genesis of interstitial lung disease. As noted above, most soils contain a significant proportion of quartz and other silicate compounds, which become aerosolized during normal farming practices.

Although more commonly considered a hazard in indoor situations, asbestos is also a factor in some isolated agricultural environments, although little evidence exists to implicate asbestos as a significant exposure in general agriculture. A study of Bulgarian workers showed an increased incidence of asbestosis exposure among those working in the tobacco farming industry near an asbestos mine, suggesting that the exposure arose from asbestos-containing rocks in the ground where the tobacco was grown rather than mine-related contamination of the ambient air (122).

In patients with COPD, the deposition of particles is higher than in nondiseased lungs; there may be localized areas of more intense collections of particles. The mechanisms leading to pulmonary toxicity and interstitial lung disease may also be related to the generation of reactive oxygen species from the particles or from macrophages and polymorphonuclear cells activated by the particles. Also, the toxicity of silica dust particles is regulated at least partially by genetic mechanisms (20).

Organic dust exposures can lead to immunologic mediated interstitial lung disease such as extrinsic allergic alveolitis, which is also known as *hypersensitivity pneumonitis* (HP). One specific form of HP, farmer's lung disease, is a group of disorders varying in chronicity and severity depending on many factors. The etiologic agents for HP are found in moldy plant materials such as hay and are typically thermophilic members of the

*Actinomyces* species, fungi including certain *Aspergillus* species (50) and *Saccharopolyspora rectivirgula* (46). Although early in the course of the disease airway and parenchymal changes may be reversible and cause no clinically recognizable respiratory symptoms, chronic and recurrent exposure can lead to the combination of reduced lung volumes and inefficient gas exchange characteristic of pulmonary interstitial fibrosis.

Normal farming activity causes significant particulate suspension (123) and is made worse by factors such as erosion, flooding, and absence of ground cover. Raising livestock is also associated with significant dust exposure; this occurs because of both disruption of the soil surface and contamination of livestock feed with inorganic dusts. In addition, silicosis may result from inhalation of biogenic silica. A number of plants are known to produce silica-containing fibers, including sugar cane and grains (124,125); ingestion of these plants is associated with the development of esophageal carcinoma, but no studies have demonstrated silicosis caused by inhalation of these fibers.

### Pathogenesis

The immunopathogenesis of agricultural dust-associated interstitial lung disease remains unclear, as do the causes of IPF in the general population. Current studies that focus on familial pulmonary fibrosis may provide insights that are relevant to the pulmonary fibrotic response that is seen in many diseases (126). There is evidence of involvement of Th2-mediated processes leading to interstitial lung disease similar to the responses seen in asthma (20). Immunologic mediated interstitial disease also occurs after exposure to agricultural dusts, as in HP, which typically results from ongoing exposure to organic dusts in the farm environment. These responses appear to be Th1-centered.

### Occurrence

Although the relationship between many occupations and pulmonary fibrosis has been closely studied, the association between agricultural exposure and pulmonary fibrosis has not been as well-examined. Although most studies in agricultural settings have focused on the contribution of silicates (124,125,127) to the later development of pulmonary fibrosis, there have been no major outbreaks of silicosis among agricultural workers. Indeed, it is well-recognized that other exposures, such as asbestos (122) and aflatoxin inhalation (128), can also lead to pulmonary fibrosis. There are case reports (129–131) of mixed-dust pneumoconiosis in farmers (17), including one study from Russia that identified silicosis among 11 of 82 tractor operators who worked in sandy soils (129). Current exposure limits for silica have been set using mining and industrial

exposures as benchmarks; the relevance of these limits for agricultural workers has not been established.

## AGRICULTURAL DUST-RELATED INFECTIOUS DISEASES

Evidence exists that exposure to agricultural dust is associated with transmission of infection to humans. This is not unexpected, because there are a number of diseases whose reservoirs exist in animal populations, including pigs. Two viral diseases are of particular clinical importance both because of their severity and their prevalence: influenza and Hantavirus. Swine confinement workers are reported to be at increased risk of influenza (121), and with concerns of worldwide pandemics involving poultry populations, poultry farming and processing provides an important potential at-risk population for the human transmission of avian influenza.

Cases of Hantavirus pulmonary syndrome have been related to grain farming and cleaning of animal care areas; rodents are common inhabitants of farm buildings, and exposure was thought to have resulted after aerosolization of dried rodent urine, feces, and saliva in agricultural facilities (16,132–134). Hantavirus pulmonary syndrome is now known to occur throughout the United States as well as elsewhere in the Americas; it has a fatality rate greater than 30% (15). Antibody positivity for Hantavirus is higher among agricultural workers (135).

Human cases of tuberculosis caused by *Mycobacterium bovis* are an occasional problem among certain workers, including those exposed to livestock. *M. bovis* is known to be endemic in wild and domestic animals; since the introduction of pasteurization, *M. bovis* has become less important as a cause of human tuberculosis. However, it recently caused an outbreak of active human tuberculosis infections among workers exposed to an infected domesticated elk herd in Alberta (19).

The first documented case of Q fever in North Dakota arose in a grain and sheep farmer who developed a dry cough along with fever along with constitutional symptoms. Q fever is spread by the aerosolized bacterium *Coxiella burnetii*. Because of increasing prevalence of *C. burnetii* infection among sheep farmers, Q fever is now a reportable disease in North Dakota; indeed, five more cases have been reported to the North Dakota State Health Department since the initial report (136).

## SUMMARY

Despite having one of the lowest rates of smoking among all occupations, farm workers have a disproportionate risk of developing lung disease. The recognition of agricultural dust exposure as a significant contributor

to work-related respiratory disease illuminates the need to use measures to control workers' exposure. Agricultural dusts are heterogeneous and known to cause several types of disease, including obstructive lung disease. In severe cases or with ongoing exposure, irreversible and severe respiratory symptoms may result. The agents in agricultural dusts linked to disease include the dust particles themselves along with substances carried on or associated with the dust. Other manifestations of dust exposure include interstitial lung disease and infectious diseases. The study of agricultural dusts and their effects on humans is an active area of research and an area in which there is ample opportunity for improvement in the collective health of agricultural workers in the developed and developing world.

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# Environmental and Occupational Medicine

**FOURTH EDITION**

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